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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 for 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

Adapting Enhanced Recovery After Surgery for hepatobiliary and pancreatic surgery: a Korean perspective

Sang Hyun Shin

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In the previous issue, Hong et al. [1] presented Korean-adapted Enhanced Recovery After Surgery (ERAS) guidelines for hepatobiliary and pancreatic (HBP) surgery. ERAS has evolved substantially since the study group was founded in London in 2001, and the first colorectal guideline was published in 2005 [2]. International ERAS guidelines are now available for both pancreatoduodenectomy and hepatectomy [3,4]. However, anyone who has tried to apply them in the Korean context recognizes the considerable gap between theory and practice. Our patients tend to be leaner, our hospital stays are structured differently, and certain perioperative practices reflect traditional habits rather than evidence-based recommendations. A protocol developed around European cohorts does not always translate well to Korea, which is why a Korean adaptation was long overdue.

What is most notable about these guidelines is the process used to develop them. Rather than beginning with a simple literature review, the committee referred to a prior survey of Korean HBP surgeons to identify areas of genuine disagreement in clinical practice [5]. They then focused specifically on those controversial issues. This is a pragmatic strategy, and it is clearly reflected in the final recommendations. Among the 12 key questions, several recommendations directly challenge long-standing practices: avoiding routine drainage after uncomplicated hepatectomy [6], not using nasogastric tubes after pancreaticoduodenectomy [7], and applying a risk-stratified strategy for perianastomotic drain management based on the Fistula Risk Score and postoperative day 1 amylase levels [8]. The evidence supporting these recommendations is strong. However, whether they will truly change everyday practice in the ward setting is another question.

For readers of this journal, the nutritional aspects also deserve closer attention. Patients scheduled for pancreatic surgery often present in a malnourished state, with weight loss due to the tumor itself, decreased oral intake caused by biliary obstruction, and sometimes several weeks of reduced appetite that may not have been properly documented. The guidelines recommend screening with the Nutrition Risk Screening 2002 or the Patient-Generated Subjective Global Assessment and initiating nutritional support, which contributes to reduced postoperative complications and shorter hospital stays [9,10]. These measures may sound straightforward, but in real-world clinical settings, they require close coordination among surgeons, dietitians, and sometimes gastroenterologists, and many multidisciplinary teams have not yet fully established such collaboration. Despite these challenges, proper nutritional support before surgery is just as important as the surgery itself.

Once published, guidelines can easily remain on paper. The real work, including building multidisciplinary teams, auditing compliance, and providing feedback to frontline clinicians, begins only afterward. The Korean ERAS guidelines for HBP surgery provide a credible and locally relevant

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framework. Ultimately, their impact depends on how effectively we put them into practice.

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Authors' contribution

All work was done by Sang Hyun Shin.

Conflict of interest

Sang Hyun Shin has served as the editor of the *Annals of Clinical Nutrition and Metabolism* since 2021. However, he was not involved in the peer review process or decision-making regarding publication. Otherwise, no potential conflict of interest relevant to this article was reported.

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Guideline

A practical guide for enteral nutrition from the Korean Society for Parenteral and Enteral Nutrition: Part III. preparation of enteral nutrition formulas

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Abstract

Purpose: This guideline was developed to provide evidence-based recommendations for the safe preparation and handling of enteral nutrition (EN) formulas in order to improve patient safety and promote standardized clinical practice in Korea.

Methods: The key questions addressed the selection of open versus closed feeding systems, the safe preparation and handling of EN formulas, precautions related to blenderized tube feeding (BTF), and essential labeling requirements. Recommendations were drafted and refined through multidisciplinary expert consensus under the auspices of the Korean Society for Parenteral and Enteral Nutrition (KSPEN).

Results: The choice of feeding system should be determined according to the patient's condition, risk of infection, and anticipated dura-

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tion of feeding. Closed feeding systems are recommended because they reduce contamination risk and nursing workload, whereas open feeding systems require strict adherence to aseptic technique. For open or reconstituted EN formulas, hang time at room temperature should not exceed 4 hours, whereas closed feeding systems should follow the manufacturer's recommended hang time. For BTF, administration time should be limited to 2 hours to minimize bacterial growth, and their use is contraindicated in medically unstable or immunocompromised patients. Accurate labeling, including patient identifiers, formula information, administration route, and hang time, is essential to prevent administration errors.

Conclusion: These guidelines provide a practical framework for the safe preparation and management of EN formulas. Adherence to standardized preparation protocols, including appropriate feeding system selection and strict hygiene practices, is essential for reducing complications and improving the safety of EN therapy.

Keywords: Consensus; Enteral nutrition; Food safety; Nutrition support; Patient safety

Introduction

Following Part I, which addressed enteral nutrition (EN) prescription, and Part II, which focused on feeding route selection and EN initiation, Part III presents recommendations for the safe preparation and handling of EN formulas. Appropriate preparation practices are essential for ensuring patient safety and effective nutritional support, because improper preparation, storage, or handling may result in microbial contamination, administration errors, and adverse clinical outcomes.

In clinical practice, the preparation and delivery of EN formulas are influenced by the type of feeding system used, the characteristics of the formula, and the care setting. Appropriate selection between open and closed feeding systems, careful adherence to aseptic preparation techniques, and compliance with recommended storage conditions and administration times are all critical for minimizing contamination risk. In particular, powdered EN formulas require meticulous attention during reconstitution to maintain microbiological safety.

Additional caution is required when blenderized tube feeding (BTF) is used, because these preparations carry an increased risk of bacterial contamination if they are not properly managed. Safe use depends on strict control of preparation methods, storage conditions, and administration time, and BTF should be restricted in selected patient populations. Accurate and standardized labeling of EN preparations is also essential for preventing administration errors and maintaining traceability in clinical practice.

Part III summarizes practical, evidence-based recommendations to help healthcare professionals select appropriate feeding systems, safely prepare and handle EN formulas, apply necessary precautions when using BTF, and implement standardized labeling practices to improve patient safety.

Methods

The methodology used for Part III was identical to that described in Parts I and II. This guideline was developed to provide standardized recommendations for the safe preparation and handling of EN formulas in clinical practice and to reduce the risk of contamination and administration errors. The target population includes adult and pediatric patients receiving EN in hospital settings.

The Enteral Nutrition Committee of the Korean Society for Parenteral and Enteral Nutrition (KSPEN) identified key clinical questions related to the safe preparation and handling of EN formulas and organized them into four areas: (1) selection of open versus closed feeding systems; (2) safe preparation and handling of EN formulas; (3) precautions for BTF; and (4) labeling requirements for preventing administration errors.

This guideline was developed through an expert consensus process that adapted existing international guidelines, particularly the 2017 ASPEN Safe Practices for Enteral Nutrition Therapy, to the clinical environment in South Korea. Relevant literature was reviewed using PubMed, Embase, and the Cochrane Library with search terms including "enteral nutrition," "tube feeding," and "blenderized tube feeding." International guidelines from the European Society for Clinical Nutrition and Metabolism, the American Society for Parenteral and Enteral Nutrition, and the Society of Critical Care Medicine were also reviewed.

Recommendations were formulated through multidisciplinary expert consensus on the basis of available evidence and clinical applicability. Draft recommendations underwent internal review and cross-disciplinary peer review and were then approved by the KSPEN Guideline Committee. The structure of Part III follows the same format as the preceding parts and consists of key questions, practice recommendations, and supporting rationales.

Practice guide

Selection criteria for open and closed feeding systems

Key question 1. What factors should be considered when selecting between open and closed feeding systems?

Practice recommendation

Although the choice of feeding system depends on institutional resources and clinical circumstances, closed feeding systems should be preferred whenever feasible, especially for patients at increased risk of contamination or infection.

- Cost

  Closed feeding systems may reduce nursing workload and lower the risk of infection, which may in turn contribute to cost savings.
- Safety

  Open feeding systems require strict compliance with standardized handling procedures. Healthcare professionals should perform proper hand hygiene, prepare and administer EN formulas and feeding sets appropriately, and adhere to the recommended hang times.

Rationale

Open feeding systems are those that require manual transfer, decanting, or reconstitution of EN formulas before administration. In contrast, closed feeding systems use prefilled sterile containers that can be connected directly to the feeding set with minimal handling.

Commercially prepared EN formulas are sterile at the time of manufacture; however, contamination may occur during preparation or administration after opening. Contaminated enteral formulas have been associated with gastrointestinal complications, such as abdominal distension and diarrhea, as well as systemic infections, including bacteremia [1-4]. Several studies have shown that open feeding systems are more vulnerable to microbial contamination because they involve multiple handling steps, including decanting and formula reconstitution [1-4]. By contrast, closed feeding systems require minimal manipulation and have been shown to reduce microbial contamination and infection rates significantly. These advantages may also lessen nursing workload and shorten preparation time, thereby contributing to cost savings in clinical practice [1-4].

Nevertheless, open feeding systems can also be used safely if healthcare professionals follow aseptic techniques rigorously, including appropriate hand hygiene and standardized handling procedures [1-4]. Recommended hang time varies according to the feeding system and the type of formula. In open feeding systems using commercially prepared formulas, administration is generally limited to 4 hours, whereas blenderized or reconstituted formulas require shorter hang times because of the greater risk of microbial growth. Closed feeding systems should follow the manufacturer's recommended hang time.

In Korean healthcare institutions, commercially prepared liquid EN formulas are widely used in routine practice. However, powdered formulas are sometimes prepared in open feeding systems for specific patient groups, such as preterm infants or pediatric patients, when suitable sterile liquid alternatives are not readily available. In pediatric practice, the powdered formulas commonly used in open feeding systems are not sterile. Therefore, powdered formulas should be avoided in immunocompromised infants whenever sterile liquid formulas delivered through closed feeding systems are available [5]. Although some international guidelines mention pasteurized donor human milk as a possible alternative when a mother's own breast milk is unavailable, donor milk use remains limited in the Korean clinical setting and may not be broadly applicable in domestic practice.

Safe preparation of EN formulas

Key question 2. What are the essential requirements for the safe preparation of powdered EN formulas and the decanting of EN solutions?

Practice recommendations

- Preparation of EN formulas should be carried out by trained personnel using aseptic techniques.
- When powdered EN formulas are prepared, the preparation method should be selected according to the patient's level of risk.
  1. For high-risk neonates or immunocompromised infants, powdered formulas should be reconstituted using water at ≥70 °C to reduce microbial contamination.
  2. For adult patients using modular powders or powdered enteral formulas, reconstitution should be performed with sterile water under strict aseptic conditions, and the prepared formula should be administered within 4 hours at room temperature.
- Prepared EN formulas should be refrigerated immediately after preparation and used within 24 hours. Any unused prepared formula should be discarded promptly.
- Prepared EN formulas should not be kept at room temperature for longer than 4 hours and should be discarded thereafter.

Rationale

The following recommendations apply only to open feeding systems involving powdered formulas or circumstances in which EN formulas require modification. Preparation of EN formulas may involve reconstitution, dilution, mixing with single-nutrient modular supplements, and transfer into feeding containers. When sterile liquid EN is decanted into an open feeding container, the transfer should be performed by trained personnel using aseptic technique in a clean preparation area, and the allowable hang time should follow the limits for open systems. These handling steps may increase the risk of contamination not only of feeding sets but also of commercially prepared sterile liquid EN formulas. Water used for formula preparation may itself become a source of contamination. Accordingly, for pediatric and neonatal patients, EN formulas should be prepared using boiled and cooled water or sterile water [6,7]. In high-risk neonates, reconstitution with hot water (≥70 °C) may further reduce the risk of *Cronobacter* and other microbial contamination. In adult patients, particularly those at high risk of infection, sterile water should also be considered for formula preparation [6].

Precautions when using BTF

Key question 3. What precautions should be considered when using BTF?

Practice recommendations

- BTF is contraindicated in medically unstable or immunocompromised patients and should not be used in patients who cannot tolerate bolus feeding or in those whose gastrostomy site has not fully matured.
- BTF should be administered only through gastrostomy tubes with a diameter of 14 French (Fr) or greater.
- The administration time for BTF should be limited to 2 hours.
- Food safety and hygiene standards for preparation equipment and ingredients should be followed strictly. Prepared BTF should be used immediately or refrigerated, and any unused feeding should be discarded if it is not used within 24 hours.

Rationale

Commercial EN formulas have been widely available since the 1970s and are now used as the standard method of EN support in many countries. In Korea, commercially prepared EN formulas have been available and widely used in hospital settings since the 1990s. However, according to a 2018 international survey, BTF continues to be used in selected situations, particularly in pediatric patients, because of intolerance or allergic reactions to commercial formulas [8-10]. BTF is prepared by blending whole foods to facilitate administration through enteral feeding tubes and may be provided either alone or in combination with commercial formulas.

Evidence regarding the safety and efficacy of BTF in patients receiving home EN remains limited [11-13]. Because of the potential risks of cross-contamination and foodborne illness, BTF is contraindicated in medically unstable or immunocompromised patients and in those with an immature gastrostomy site [8,13,14]. In addition, it is generally recommended to administer BTF as bolus feeding rather than continuous infusion [8,13,14]. Therefore, its use may be inappropriate in patients who require restricted feeding volumes or who are intolerant to bolus feeding (Table 1).

Because of its high viscosity, BTF is associated with an increased risk of tube occlusion [11,13]. Blenderized formulas contain intact food particles and dietary fiber, resulting in greater viscosity and particle density than commercial enteral formulas. Even when high-performance blenders are used, these particles may increase flow resistance in narrow feeding tubes. Accordingly, the use of gastrostomy tubes with a diameter of at least 14 Fr is recommended to reduce the risk of tube occlusion and to ensure adequate flow during administration [11,13,14].

Table 1. Situations in which BTF may be considered and those in which it is not recommended

Situations in which BTF may be considered	Situations in which BTF is not recommended
Medically stable patients; in children and adolescents, stable growth status	Acute illness or immunocompromised state (increased risk of infection)
Enteral feeding tube with a diameter of 14 Fr or larger	Fluid restriction (difficulty meeting nutrient requirements)
Bolus feeding	Situations requiring prolonged feeding (increased risk of infection)
Family support	
Availability of appropriate resources and equipment (e.g., high-performance blender, refrigerator, electricity, clean water and food, and storage containers)	
Access to healthcare professionals with relevant knowledge and expertise	

BTF, blenderized tube feeding; Fr, French.

When BTF is prepared at home, strict attention should be given to food safety and hygiene, including equipment cleanliness, water quality, and ingredient safety, in order to prevent cross-contamination [13-16]. To minimize bacterial growth, prepared BTF should not remain at room temperature for more than 2 hours and should instead be refrigerated (e.g., ≤7 °C). Even under refrigeration, BTF should be discarded if it is not used within 24 hours of preparation [14].

Several studies have reported that BTF may be nutritionally inadequate, with deficiencies in macro- and micronutrients and lower energy density relative to prescribed volumes, highlighting the potential risk of nutritional imbalance [11,17]. Therefore, ongoing nutritional monitoring is essential whenever BTF is used. Nutritional intake, body weight, and clinical status should be assessed regularly to ensure adequate nutrient delivery. In addition, the nutrition support team, with an especially important role for clinical dietitians, should routinely evaluate whether BTF recipes meet the patient's age-appropriate requirements for energy, protein, micronutrients, and electrolytes and should modify formulations as clinically indicated [11-13]. As individualized, patient-centered care is increasingly emphasized, multidisciplinary nutrition support teams should maintain adequate knowledge of BTF and ensure that it is used appropriately in clinical practice [13].

Essential labeling requirements for safe EN administration

Key question 4. What essential information should be included on labels to ensure safe administration of EN?

Practice recommendations

- EN labels should contain essential information from the EN prescription whenever possible.
  Essential items: Patient name, registration number, ward and room number, date and time of preparation, prescribed EN formula or diet name, and administration information (total daily or per-meal amount: _____ kcal/_____ mL, route of administration, and method of administration).
- EN labels should use clear and accurate wording, and precautionary statements should be included whenever possible.
  Examples: "Maximum rate ___," "Maximum volume ___," "Use within ___ hours after opening," and "Not for intravenous use."
- Labels for human milk stored in hospital settings should include the following information whenever possible:
  Contents of the container, infant's name and registration number, date and time of milk expression, maternal medications, added fortifiers, frozen status of the milk, date and time of thawing, and the appropriate discard date.
  (Optional) To improve identification, barcodes, special colors, or symbols may be used for human milk labeling.

Rationale

Standardized labeling should be applied to all EN formulas provided to patients in order to improve safety and reduce administration errors [15,18]. Verification of standardized labels before EN administration provides a final opportunity to check the formula against the physician's prescription, thereby improving both medication and nutrition safety [18,19]. Whenever possible, each label should include four essential elements: patient information, type of EN formula, route of administration, and method of administration (Table 2).

In neonatal and pediatric settings, human milk administered enterally requires additional labeling elements beyond those used for standard EN formulas.

When labeling human milk, additional information be-

Table 2. Components of enteral nutrition labels

Enteral nutrition label	Human milk label
Patient name, registration number, ward/room	Infant's name
Prescribed enteral formula, volume, and energy density	Registration number
Date and time of administration	Dosing weight
Administration information	Date and time of milk expression
-Route of administration	Maternal medications or supplements
-Method and rate of administration (e.g., mL/hr × 24 hr, or "Max rate _____", or "Max volume _____")	Freezing status of milk
	Date and time of thawing (for frozen milk)
Expiration date (or discard date/time)	Appropriate discard date (considering milk storage conditions)
-Statement: "Not for intravenous use"	Statement: "Not for intravenous use"
	For fortified human milk:
	- Fortifier name, concentration, and date/time of preparation

yond standard EN labeling is recommended, including the date and time of milk preparation and other relevant preparation-related details, in order to ensure traceability and safe handling [5,20,21].

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Authors' contribution

Conceptualization: JMS. Formal analysis: JMS. Supervision: all authors. Methodology: JMS. Project administration: JMS. Writing–original draft: ISL. Writing–review & editing: all authors. All authors read and approved the final manuscript.

Conflict of interest

Ye Rim Chang has served as the editor of the *Annals of Clinical Nutrition and Metabolism* since 2024. However, she was not involved in the peer review process or decision-making regarding publication. Otherwise, no potential conflict of interest relevant to this article was reported.

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Supplementary materials

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Review

Bedside support for neurologically impaired patients via nutritional evaluations, swallowing function assessments, and gastrointestinal function tests: a narrative review

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Abstract

Purpose: Neurologically impaired patients often experience complex challenges in respiratory and nutritional management that may necessitate surgical intervention. Furthermore, some patients admitted to specialized facilities for neurologically impaired individuals do not receive adequate postoperative follow-up after being transferred. Kurume University Hospital has established a system of continuous routine rounds at such facilities. This review aims to describe the rationale, methods, and outcomes of multidisciplinary bedside support, with particular emphasis on nutritional evaluation, swallowing function assessment, and gastrointestinal function testing.

Current concept: Routine collaboration between pediatric surgeons and facility-based pediatricians enables continuous perioperative management. Preoperatively, patient background, nutritional status, and family preferences are recorded through structured communication and shared decision-making tools, such as the Ottawa Personal Decision Guide. During hospitalization, multidisciplinary evaluations include bioelectrical impedance analysis for nutritional assessment, endoscopic and pH impedance testing for swallowing function, and multichannel intraluminal impedance monitoring for gastroesophageal reflux. Postoperatively, periodic facility rounds ensure ongoing evaluation, with repeated assessments guiding nutritional optimization, early complication detection, and timely surgical consultation. This approach provides families and healthcare teams with detailed information on functional outcomes, strengthens trust, and enhances continuity of care. Sustained bedside engagement at facilities for neurologically impaired patients improves pre- and postoperative monitoring, promotes seamless collaboration between institutions, and ensures individualized evaluation of nutrition, swallowing, and gastrointestinal function.

Conclusion: By providing actionable data to families and multidisciplinary teams, this model strengthens shared decision-making and supports long-term outcomes. The system may serve as a framework for integrated perioperative care in similar high-risk patient populations.

Keywords: Child; Deglutition; Gastroesophageal reflux; Nutrition assessment; Perioperative care

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This study was presented at the 60th Annual Meeting of the Japanese Society for Surgical Metabolism and Nutrition, held on July 7, 2023, in Tokyo, Japan.

Introduction

Background

Patients with Severe Motor and Intellectual Disabilities (SMID) have a shortened life expectancy and suffer from numerous complications, including respiratory and gastrointestinal disorders. They are regarded as high-risk due to their need for continuous medical care and the presence of multiple comorbidities. The number of SMID patients nationwide is estimated to be approximately 47,000, with about 70% residing in facilities for children and adults with SMID (hereinafter referred to as SMID facilities) [1]. As of April 2022, there were 135 public corporation–run facilities (13,903 beds), 75 wards for children with SMID under the National Hospital Organization (8,148 beds), and one ward at the National Center for Advanced and Specialized Medical Care (60 beds) [2].

The recent increase in the number of SMID residents in such facilities is attributed to several factors, including a rise in patients requiring advanced medical care such as ventilator and gastrostomy management [3], the aging of caregivers; an increased caregiving burden related to environmental factors such as the limited capacity for therapeutic education [4,5]; and challenges in transitioning long-term patients from the NICU (neonatal intensive care unit) and pediatric wards to home care [6,7]. Additionally, it has been reported that approximately 20,000 children under 20 years of age nationwide require ongoing medical care [8]. As a result, pediatric surgeons are increasingly being consulted regarding surgical management.

However, among cases admitted to SMID facilities, postoperative functional evaluation is sometimes insufficient after transfer. Before our hospital began conducting regular rounds at these facilities, we often lacked comprehensive understanding of patients' preoperative backgrounds and postoperative progress.

At SMID facilities, pediatricians routinely assess respiratory, mental, and physical functions. In general, pediatric surgeons are more likely to intervene surgically in conditions related to the respiratory system, gastrointestinal tract, and nutrition. As the number of patients requiring surgical intervention grows and postoperative recovery periods extend, requests for additional consultations from families and SMID facilities have also increased. To address these issues, we established a system of regular medical rounds at SMID facilities.

Objectives

This paper introduces the ongoing efforts of the Department of Pediatric Surgery at Kurume University Hospital, which continuously evaluates the nutritional status, swallowing function, and gastrointestinal function of SMID patients in daily practice—from preadmission to postdischarge.

Medical care at SMID facilities and trends in referred patients

Kurume University Hospital is located in the southern part of Fukuoka Prefecture, with five SMID facilities situated within a 30 km radius. Since 2012, pediatric surgeons from our hospital have conducted rounds once or twice a month at four of these facilities. Medical care provided during these visits includes replacement of nutritional tubes such as gastrostomy tubes, elemental diet tubes, and gastrojejunostomy tubes, as well as tracheostomy cannula replacement. We also consult with facility physicians regarding nutritional content, medication prescriptions, and the necessity of surgical intervention. For patients who have undergone surgery at our hospital, regular inpatient evaluations are performed to assess postoperative function, as described later. The number of patients referred to our hospital was 10 before the initiation of rounds in 2012, but has steadily increased since the program's introduction (Fig. 1).

Collaborative medical system between SMID facilities and Kurume University Hospital

Surgical procedures commonly performed on patients referred to our hospital include gastrostomy for nutritional supplementation, fundoplication for gastroesophageal reflux disease (GERD), and tracheostomy or laryngotracheal separation for swallowing disorders and pharyngolaryngeal reflux. Since the start of regular rounds, a collaborative system has been established in which pediatricians at SMID facilities and pediatric surgeons at our hospital coordinate care from the preoperative stage onward. After transfer to our hospital, pediatric surgeons conduct preoperative evaluations, while pediatricians provide perioperative support for underlying conditions. Following postoperative transfer back to the SMID facilities, pediatricians at the facilities continue observation, and our pediatric surgeons perform regular rounds to assess the patient's status. This arrangement has established a truly collaborative system of care (Fig. 2). The following sections describe our initiatives from the preoperative through postoperative periods since the introduction of this system.

Efforts at SMID facilities (preoperative)

Preoperatively, we collect detailed patient information—

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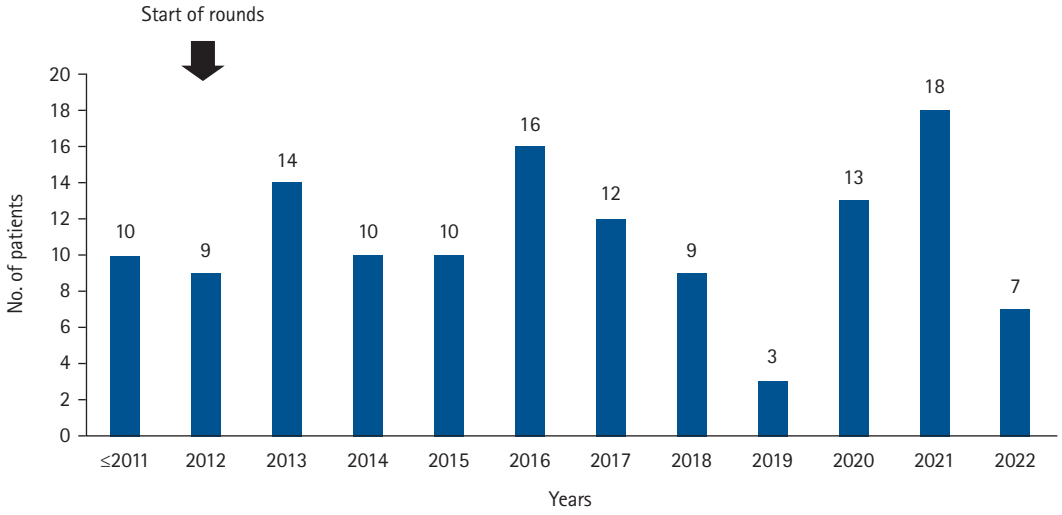

Fig. 1. Trends in the number of patients referred from facilities for neurologically impaired patients to our hospital. Before the start of regular rounds in 2012, the total number of patients was about 10. After the start of rounds, the number of referrals gradually increased.

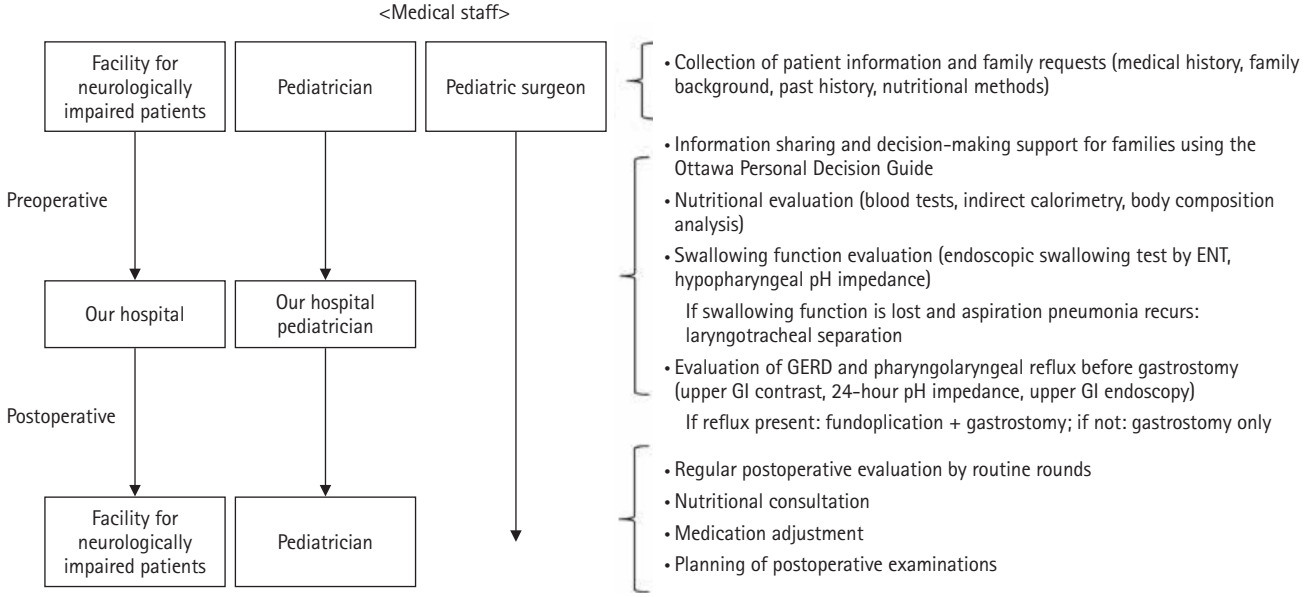

Fig. 2. Medical collaboration system between facilities and our hospital. After the start of rounds, seamless care is provided for patients requiring respiratory and nutritional management. From the preoperative stage, pediatricians at the facility and pediatric surgeons at our hospital collaborate, and after transfer, pediatric surgeons perform preoperative evaluation and pediatricians provide perioperative support for underlying diseases. GERD, gastroesophageal reflux disease; GI, gastrointestinal.

including medical history, past history, family background, and nutritional methods—at SMID facilities and listen carefully to the wishes of the patient's family to fully understand the patient's condition before admission. Since the initiation of regular rounds, communication with the primary physicians at SMID facilities has become more detailed and effective. Furthermore, by explaining the content of preoperative examinations and anticipated treatments to the patient's family before transfer to our hospital, we have been able to establish trusting relationships even before admission.

Efforts at the hospital (during hospitalization)

Information sharing and decision-making support for families using the Ottawa Personal Decision Guide

For SMID patients who are unable to express their own

wishes, decision-making regarding treatment is typically delegated to their families. Our hospital employs the Ottawa Personal Decision Guide developed by Dr. O'Connor and colleagues at the University of Ottawa [9]. Nurses use this guide to help families clarify their values, understand their emotional state, and receive the information necessary to make informed decisions. Unlike traditional informed consent, this structured approach facilitates mutual understanding of family perspectives regarding examinations and treatments, thereby fostering more meaningful communication and trust.

Nutritional evaluation

Nutritional assessments are performed using blood tests, indirect calorimetry, and bioelectrical impedance analysis (BIA) to quantify nutritional status and guide perioperative management.

Swallowing function tests

Swallowing endoscopy conducted by an otolaryngologist and hypopharyngeal pH impedance testing are performed to evaluate swallowing function. In cases of recurrent aspiration pneumonia, laryngotracheal separation is performed to prevent further respiratory complications.

Pre-gastrostomy evaluation for GERD and pharyngolaryngeal reflux

To assess for GERD and pharyngolaryngeal reflux prior to gastrostomy, patients undergo an upper gastrointestinal contrast study, 24-hour esophageal pH impedance monitoring (multichannel intraluminal impedance–pH monitoring [MII-pH]), and upper gastrointestinal endoscopy. When severe GERD is identified, both fundoplication and gastrostomy are performed; if no reflux is observed, only gastrostomy is carried out.

Efforts at SMID facilities (postoperative)

In addition to regular rounds for postoperative assessment, nutritional consultation, and medication management, postoperative examinations are scheduled as necessary to ensure continuous follow-up and optimization of care.

Examinations for status evaluation and clinical research achievements

Nutritional evaluation

In a study examining the relationship between phase angle (PhA) measured by BIA and serum albumin levels, it was shown that PhA in SMID patients is lower than in healthy individuals and that SMID patients with hypoalbuminemia (serum albumin <3.5 g/dL) have significantly lower PhA values than normal cases [10]. In another study evaluating resting energy expenditure (REE), fat-free mass (FFM), and fat mass in SMID patients, a significant correlation was found between FFM and REE. The predictive formula for REE (kcal/day)=550.6+166.6×FFM (kg) was established [11]. Appropriate nutritional management during hospitalization before surgery contributes to improved perioperative nutritional control in SMID patients.

Swallowing function evaluation

According to the Swallowing Disorder Clinical Practice Guidelines, swallowing endoscopy is a valuable and essential tool for evaluating swallowing function [12]. In SMID patients, videofluoroscopic swallowing studies pose a high risk of aspiration; therefore, our hospital employs swallowing endoscopy and hypopharyngeal pH impedance testing instead. Swallowing endoscopy is scored using the Hyodo system, which assesses saliva retention, laryngeal sensation, elicitation of the swallowing reflex, pharyngeal clearance, and the degree of aspiration. Hypopharyngeal pH impedance testing enables evaluation not only of reflux reaching the hypopharynx but also of impedance values around the pyriform sinus. Because impedance values decrease when fluid accumulates, we reported that the Hyodo score and pharyngeal baseline impedance are negatively correlated, and that a low hypopharyngeal impedance value indicates saliva retention (Fig. 3) [13], with a cutoff value of 1,552 Ω. While swallowing endoscopy allows assessment of saliva retention and glottic penetration, SMID patients often cannot follow instructions. Therefore, for patients with hyperactivity or strong muscle tone, hypopharyngeal pH impedance testing is considered particularly useful. In the past, when SMID facilities consulted us regarding tracheostomy or laryngotracheal separation, there was often a gap between the family's understanding and the patient's actual condition. Since the introduction of regular rounds, however, we have been able to provide families with more accurate information based on accumulated test results and direct examinations. This approach has enabled us to better understand patients' current conditions and to explain both the necessity of surgery and the expected postoperative course.

Gastrointestinal function tests

In our department, MII-pH testing is performed before and after fundoplication in SMID patients with GERD. We reported that each measured parameter showed significant improvement following surgery (Fig. 4) [14]. Furthermore,

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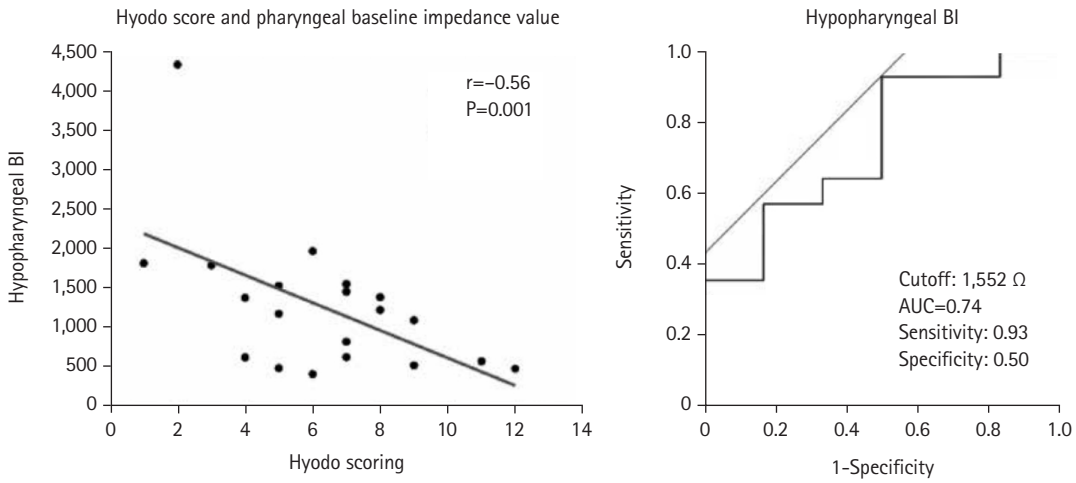

Fig. 3. Swallowing function evaluation using hypopharyngeal pH impedance test. The negative correlation between Hyodo score and baseline pharyngeal impedance value suggests that low hypopharyngeal impedance indicates saliva retention. BI, baseline impedance; AUC, area under the curve. Adapted from Masui et al. [13].

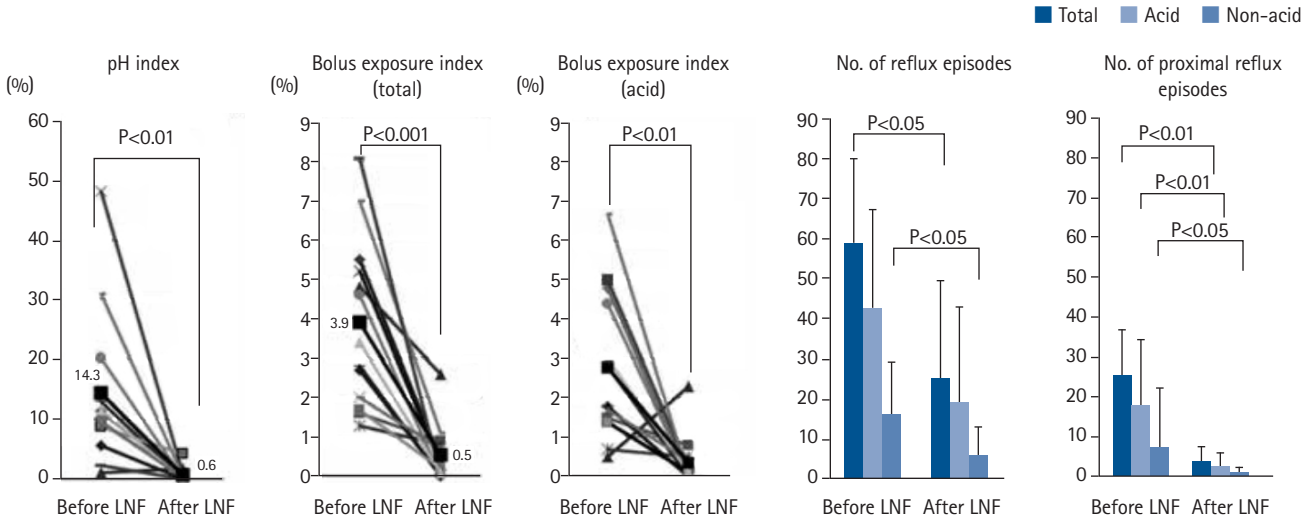

Fig. 4. 24-Hour pH impedance test: pre- and post-fundoplication evaluation. Each parameter showed significant improvement after surgery. LNF, laparoscopic Nissen fundoplication. Adapted from Fukahori et al., with permission of Elsevier [14].

we demonstrated that 70 reflux episodes identified by MII-pH testing correspond to a pH index of 9% and a baseline impedance value of approximately 1,000 Ω, and that these thresholds can serve as useful indicators for performing fundoplication [15]. Based on these findings, we have established a treatment flowchart for GERD management in our department (Fig. 5) [16]. In a separate evaluation of MII-pH testing before and after gastrostomy, we found no significant differences in parameters between pre- and postoperative assessments. However, we experienced one case—a 3-year-old girl—in whom fundoplication was performed 3 years after gastrostomy. This patient showed a tendency toward a high number of reflux episodes before the initial surgery, and we consider such cases to require special attention (Fig. 6) [16]. As with swallowing function testing, gastrointestinal function testing enables us to provide families with clear and objective information. Conducting treatment with the family's understanding and continuing careful postoperative observation fosters stronger trust between the medical team and the family.

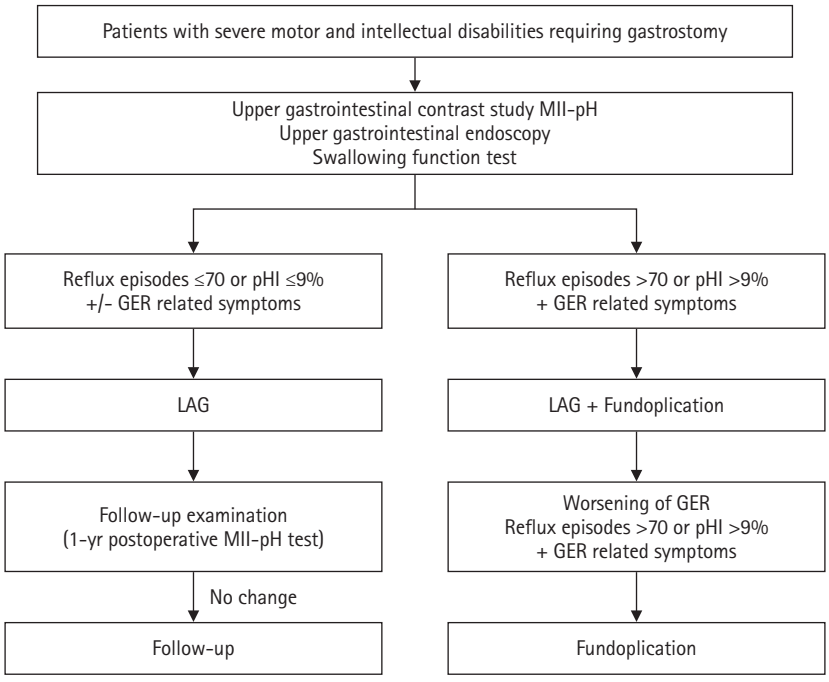

Fig. 5. Flowchart for surgical decision-making. A flowchart has been created to determine whether to perform LAG alone or in combination with fundoplication for neurologically impaired patients requiring gastrostomy. MII-pH, multichannel intraluminal impedance–pH monitoring; GER, gastroesophageal reflux; LAG, laparoscopy-aided gastrostomy. Reprinted from Masui et al., with permission of Springer Nature [16].

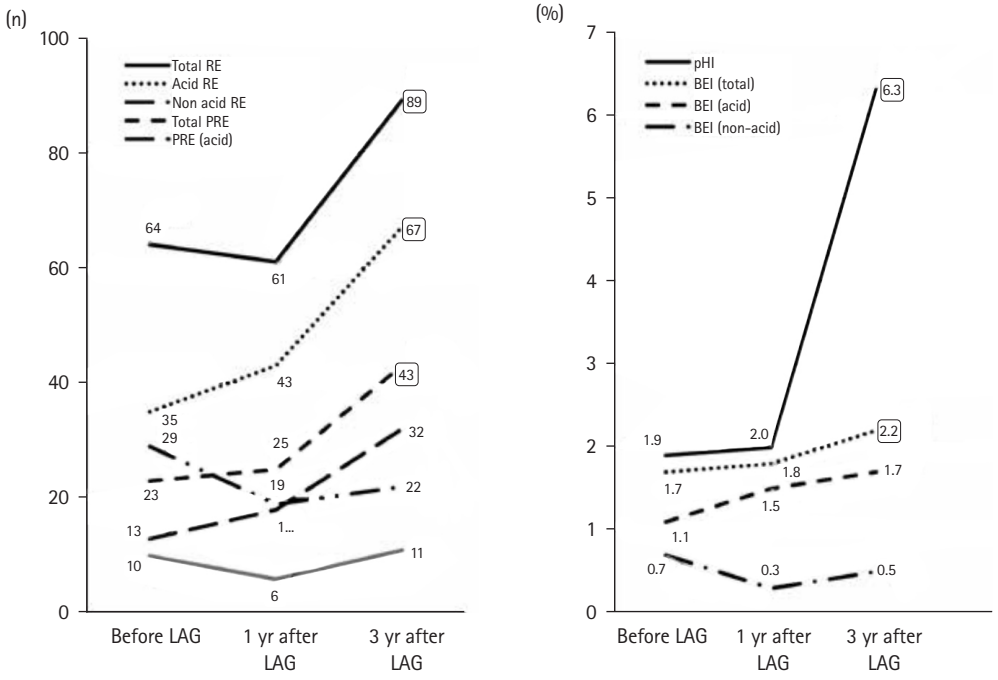

Fig. 6. Comparison of MII-pH parameters before and after laparoscopy-aided gastrostomy. In one case (a 3-year-old girl), fundoplication was added 3 years after gastrostomy due to worsening parameters. Patients with a high number of reflux episodes before surgery should be carefully monitored. RE, reflux episodes; PRE, proximal reflux episodes; BEI, bolus exposure index; MII-pH, multichannel intraluminal impedance–pH monitoring; LAG, laparoscopy-aided gastrostomy. Reprinted from Masui et al., with permission of Springer Nature [16].

Current status and issues from the start of rounds to the present

Children requiring home medical care can be continuously monitored for postoperative function because they regularly visit outpatient clinics for tracheostomy site observation and gastrostomy tube replacement. However, in cases where patients are transferred to SMID facilities after surgery, there are currently no formal reports from the surgical facility regarding the implementation of rounds or the content of postoperative evaluations. According to 2018 data, the number of children using ventilators was reported to be 4,178, and the total number of children requiring medical care has doubled in the past 10 years, while the number requiring ventilator management has increased more than tenfold. The increase is particularly notable among children aged 0–4 years [17], suggesting that the number of children requiring medical care in SMID facilities will continue to grow. At our hospital, the current system allows us to assess each patient's condition in advance through preoperative rounds, enabling information sharing with hospital physicians prior to admission. In addition, based on accumulated test results, we can now provide more detailed explanations to key persons (typically the patient's family). Surgical policies can be determined more clearly using objective functional assessments, and by directly observing patients' postoperative progress, not only physicians at SMID facilities but also nurses can offer more specific explanations to families, fostering a deeper understanding of both disease and treatment.

For pediatric surgeons, it is also advantageous to monitor postoperative conditions closely and to verify the appropriateness and effectiveness of surgical procedures. However, after transfer to a facility, there are cases where marked weight gain is observed. One possible explanation is that tracheostomy or laryngotracheal separation, performed in patients who previously required substantial respiratory effort, reduces the energy expenditure needed for breathing, thereby increasing available calories for weight gain. Continuing regular rounds enables early recognition and management of such issues.

Moreover, since the introduction of rounds, an environment has been created in which consultations are more readily initiated. Face-to-face contact between facility pediatricians and hospital surgeons has facilitated smoother communication and is thought to have contributed to the increased number of referrals. Ongoing rounds before and after surgery, combined with active medical collaboration, have had a positive impact on SMID patients, their families, and healthcare providers. We believe this system could serve as a model for medical systems.

Conclusion

We have described initiatives aimed at providing continuous, integrated medical care for SMID patients. Through the implementation of regular rounds, it has become possible to observe both preoperative and postoperative conditions systematically and to maintain effective collaboration with SMID facilities, thereby strengthening continuity and quality of care.

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Authors' contribution

Conceptualization: DM, TK (Tatsuru Kaji). Data curation: DM. Formal analysis: DM, NH (Naoki Hashizume), YK. Investigation: DM, TA, HE, HY, ST (Shotaro Taki). Methodology: DM, TK (Tomohiro Kurahachi), ST (Shiori Tsuruhisa). Project administration: DM, NH (Naoki Hashizume). Supervision: NH (Naoki Hashizume), TK (Tatsuru Kaji). Validation: DM, YK. Visualization: NH (Naruki Higashidate), TK (Tomohiro Kurahachi). Writing–original draft: DM, NH (Naoki Hashizume). Writing–review & editing: KH, HE, HY, ST (Shiori Tsuruhisa), TA, TK (Tomohiro Kurahachi), ST (Shotaro Taki), NH (Naruki Higashidate), TK (Tatsuru Kaji). 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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Review

Effectiveness of perioperative rehabilitation and nutrition in esophageal cancer: a narrative review

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Abstract

Purpose: Esophageal cancer surgery requires robust perioperative management to reduce its high rate of complications. This review evaluates the clinical utility of comprehensive exercise and nutritional therapy, with a specific focus on initiatives led by the multidisciplinary Hamamatsu Perioperative Care Team (HOPE), established at Hamamatsu University Hospital to optimize patient safety and postoperative recovery outcomes.

Current concept: The HOPE protocol involves a diverse team, including surgeons, nurses, pharmacists, and dietitians, who collaboratively implement a multifaceted perioperative care bundle. These interventions include strict smoking cessation, intensive oral care, and immunonutrition incorporating n-3 fatty acids. A distinctive feature of this program is the integration of patient-reported treatment diaries and wearable fitness tracking devices (WFTs) to visualize daily activity, thereby helping to sustain patient motivation. Preoperative rehabilitation focuses on preventing sarcopenia through combined aerobic and resistance training, while postoperative care emphasizes immediate enteral nutrition and early mobilization. Retrospective analyses demonstrated that HOPE implementation reduced Clavien-Dindo grade III or higher infectious complications, pneumonia and surgical site infections, compared with historical controls. In addition, a propensity score–matched analysis showed that WFT users experienced lower pneumonia rates, shorter hospital stays, and better preservation of nutritional markers, including albumin and transthyretin, during the recovery phase compared with non-users.

Conclusion: The HOPE strategy illustrates that combining standard nutritional support and exercise therapy with digital tools enables individualized rehabilitation. This integrated approach reduces morbidity and preserves function, strongly suggesting that incorporation of wearable technology into established surgical care protocols represents a strategy for improving long-term outcomes in high-risk cancer patients.

Keywords: Enteral nutrition; Esophageal neoplasms; Immunonutrition diet; Postoperative care; Preoperative exercise

Introduction

Background

Esophageal cancer is associated with a poor prognosis and ranks as the sixth leading cause of cancer-related death worldwide [1]. The standard surgical procedure for esophageal cancer is subtotal esophagectomy, which involves operative manipulation of three anatomical regions: the cervical,

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thoracic, and abdominal areas. Consequently, the degree of surgical invasiveness is substantial, and the incidence of postoperative complications is higher than that observed in other gastrointestinal surgeries. To promote rapid postoperative recovery and prevent complications, the concept of Enhanced Recovery After Surgery (ERAS), also referred to as fast-track surgery, has been introduced and widely established in surgical practice. The ERAS protocol was proposed by the ERAS group of the European Society for Clinical Nutrition and Metabolism and aims to prevent postoperative complications, shorten hospital stay, and improve patient safety through the comprehensive implementation of recovery-enhancing measures [2]. Among these components, exercise therapy recommends muscle strength training and respiratory rehabilitation beginning in the preoperative period, along with early mobilization after surgery. In recent years, the usefulness of these interventions has been increasingly recognized, as reflected by their approval for reimbursement within medical fee systems. With respect to nutritional therapy, systematic nutritional assessment and early intervention starting in the preoperative period are required, and early postoperative enteral nutrition has been shown to reduce the incidence of postoperative complications.

Objectives

In this paper, we outline the usefulness of perioperative exercise and nutritional therapy in esophageal cancer surgery and describe the specific efforts undertaken by our perioperative management team to implement these interventions in clinical practice.

Perioperative team medicine

Changes in the perioperative management team

The usefulness of perioperative management teams has been widely reported as a means of achieving safer perioperative care by enabling multidisciplinary medical staff to apply the specific strengths of each profession while sharing patient information across organizational boundaries. Shirakawa et al. [3] established the Perioperative Management Center (PERiO) in 2008. For patients with esophageal cancer, PERiO provides a comprehensive range of services, including preoperative smoking cessation guidance; assessment of physical function and general condition before and after surgery; exercise therapy; oral care delivered by the dental department; postoperative eating and swallowing rehabilitation; respiratory physical therapy; and assistance with basic movement (Table 1) [3]. Following the introduction of PERiO, reductions were reported in both the time to postoperative ambulation and the length of postoperative hospital stay among patients undergoing esophageal cancer surgery. Additionally, the incidence of adverse events during preoperative chemotherapy was reported to have significantly decreased after PERiO implementation [4].

Watanabe et al. [5] established a Perioperative Team at the Cancer Institute Hospital (PeriCan) in 2013. This team provides preoperative guidance on abstinence from alcohol and smoking, oral care, early postoperative mobilization, rehabilitation, assessment of swallowing function, and dietary guidance (Table 1). In a comparison of short-term outcomes before and after the introduction of PeriCan in 113 patients who underwent esophagectomy, postoperative complications, particularly postoperative pneumonia, were reported to be significantly reduced [5]. Furthermore, even among patients who developed postoperative recurrent laryngeal nerve palsy, the incidence of postoperative pneumonia was significantly lower after the introduction of PeriCan [5]. In Japan, the Ministry of Health, Labour and Welfare actively promotes team-based medical care to enhance the quality of healthcare delivery and improve efficiency through the effective utilization of specialized professionals and strengthened interprofessional collaboration. In line with this policy, numerous reports on perioperative management teams have been published (Table 1) [6-10].

Establishment of the perioperative management team HOPE

At our hospital, beginning in April 2017, we launched the Hamamatsu Perioperative Care Team (HOPE), which consists of doctors, nurses (outpatient, ward, intensive care unit [ICU], and operating room), the rehabilitation department, pharmacists, registered dietitians, the dental department, the infection control team, and the palliative care team. This multidisciplinary team aims to implement safe perioperative management while improving long-term prognosis and enhancing patients' long-term quality of life. The perioperative management bundle implemented by HOPE is described below.

Preoperative intensive exercise and nutritional therapy

For esophageal cancer patients scheduled for surgery, HOPE staff intervene beginning at the first outpatient visit. After the physician explains the medical condition, the outpatient nurse provides psychological support and lifestyle guidance to the patient. In our department, all esophageal cancer patients are instructed to abstain from smoking and drinking for more than 1 month (Fig. 1). In the dental

Table 1. Perioperative management teams

Perioperative management team	Author	Preoperative	Postoperative	Outcome
PERiO	Shirakawa et al. (2019) [3] Shirakawa et al. (2021) [4]	Smoking cessation guidance, physical ability assessment, exercise therapy, oral care	Physical ability assessment, respiratory physiotherapy, basic movement assistance, eating/swallowing rehabilitation	Fewer days to postoperative ambulation, shortened hospital stay, reduced adverse events during preoperative chemotherapy
PeriCan	Watanabe et al. (2016) [5]	Alcohol and smoking cessation guidance, oral care	Early mobilization, rehabilitation, swallowing function assessment, dietary guidance	Reduced pneumonia
Perioperative Center	Ochiai (2018) [6]	Patient orientation, oral care, medication adjustment, deep vein thrombosis prevention	Postoperative pain control, oral care	Shortened average hospital stay
PMT	Yamamoto and Sakakibara (2023) [7]	Smoking/alcohol cessation guidance, respiratory rehabilitation, nutritional guidance, oral care, skin protection, consultation for use of economic/social resources (post-discharge life support, nursing care, etc.)	Continued postoperative nursing, discharge support, utilization of social resources	Reduced surgery postponement, optimized hospital stays, prevention of complications
PMT	Yokoyama (2021) [8]	Physical and social background, patient/family acceptance of surgery, swallowing function assessment, risk of postoperative nausea/vomiting, preoperative pain management plan	Treatment course, evaluation of future PMT interventions, coordination with each committee	Identification of high-risk patients for swallowing disorders
Tobu Hospital Patient Support Center	Ishida (2023) [9]	Assessment of dietary intake, nutritional guidance, grip strength/body measurement, calculation of nutritional indices, body composition measurement, prehabilitation (aerobic exercise, resistance exercise, stretching, respiratory training), oral care	Nutritional management, rehabilitation	Increased walking distance, improved sit-and-reach, increased skeletal muscle mass
HOPE	Current study (2017)	Physical fitness measurement (rehabilitation), respiratory/physical therapy, sputum discharge guidance, dietary intake assessment/nutritional guidance, lifestyle guidance, psychological care, comorbidity/medication assessment, oral care by dental department, MRSA screening, enteral nutrition (nasal feeding tube, gastrostomy, etc.)	Practice of safe minimally invasive surgery, surgery without recurrent laryngeal nerve palsy, SSI prevention, early mobilization/respiratory physiotherapy, pain control, delirium/insomnia prevention, deep vein thrombosis prevention, early enteral nutrition therapy, dietary form based on swallowing evaluation, management of diarrhea, post-discharge lifestyle guidance	Reduced incidence of atrial fibrillation, reduced pneumonia, increased skeletal muscle mass

PERiO, Perioperative Management Center; PeriCan, Perioperative Team at the Cancer Institute Hospital; PMT, Perioperative Management Team; MRSA, methicillin-resistant *Staphylococcus aureus*; SSI, surgical site infection.

department, oral evaluation and oral care are performed, while rehabilitation specialists measure baseline physical function, including walking speed, grip strength, and knee extension muscle strength. They also conduct cardiopulmonary exercise testing and provide individualized aerobic and resistance exercise guidance for preoperative rehabilitation to prevent sarcopenia (Fig. 1). At the same time, respiratory physical therapy using an incentive spirometer is initiated, and guidance on sputum expectoration is provided.

In addition, registered dietitians conduct a detailed interview regarding the patient's dietary intake, measure upper arm circumference, triceps skinfold thickness, upper arm muscle circumference, and lower limb circumference, and perform body composition analysis using InBody to comprehensively evaluate preoperative nutritional status (Fig. 1). In preoperative nutritional management, previous reports have shown that administration of n-3 fatty acid–enriched nutritional supplements from the preoperative period significantly shortens ICU stay and the duration of systemic inflammatory response syndrome and reduces postoperative infectious complications [11]. According to parenteral and enteral nutrition guidelines, enteral nutrition should be con-

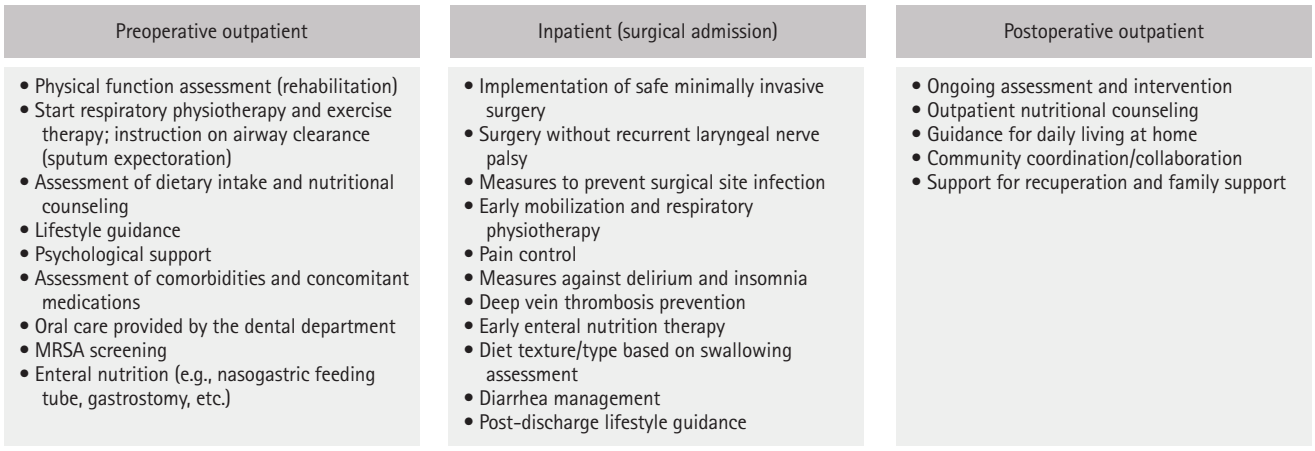

Fig. 1. Hamamatsu Perioperative Care Team esophageal cancer perioperative management bundle. MRSA, methicillin-resistant *Staphylococcus aureus* [12].

sidered first as the route of nutritional administration. If oral intake is possible, semi-digested enteral nutrition is administered orally as oral nutritional support (ONS). When severe tumor-related stenosis is present, a nasogastric feeding tube or percutaneous endoscopic gastrostomy is performed to provide enteral nutrition (Fig. 1).

A HOPE conference is held once a week to share information regarding required nutritional intake, actual dietary intake, rehabilitation progress, and gastrointestinal symptoms such as vomiting and diarrhea. This process enables risk visualization and promotes information sharing among multiple professions. Since 2019, to encourage active patient participation in preoperative rehabilitation, a treatment diary has been provided. Patients record daily dietary intake, exercise volume, the number of respiratory rehabilitation sessions, tooth brushing frequency, and subjective symptoms (Fig. 2). In addition, patients wear a wearable fitness tracking device (WFT; Fitbit) to record heart rate, step count, physical activity, calories burned, and sleep duration. By visualizing physical activity using the WFT, the outcomes of perioperative rehabilitation become more apparent, and patient motivation is expected to improve. Patients are admitted 5 days before surgery, consume ONS orally, and receive daily rehabilitation interventions to implement intensive preoperative nutritional and exercise therapy.

In all cases, nasal screening for methicillin-resistant *Staphylococcus aureus* (MRSA) is performed. When results are positive, mupirocin calcium ointment, chlorhexidine disinfection, and perioperative anti-MRSA agents are administered to prevent postoperative pneumonia and surgical site infection (Fig. 1).

Early postoperative exercise therapy and early enteral nutrition therapy

Surgery is performed with the aim of achieving safe and minimally invasive treatment, including the use of robot-assisted surgery when appropriate, with careful attention to avoiding recurrent laryngeal nerve palsy. Prolonged bed rest after surgery leads to the progression of respiratory dysfunction induced during the surgical procedure. In addition, the accumulation of airway secretions, exudate, and blood causes peripheral airway obstruction in the lower lungs, resulting in decreased alveolar ventilation and, ultimately, alveolar collapse. Furthermore, reduced physical activity associated with prolonged postoperative bed rest is known to cause secondary complications, including muscle atrophy, bone atrophy, orthostatic hypotension, and pressure ulcers. Therefore, provided there are no problems with the general condition, particularly respiratory and circulatory dynamics, early mobilization beginning on the first postoperative day is strongly recommended [13].

In addition to preventing disuse of the limbs through standing and walking, early mobilization improves ventilation–perfusion imbalance, increases respiratory airflow, and allows exercise-induced bronchial dilation, which is expected to promote sputum clearance. In our department, pain control is managed in consultation with anesthesiologists, and both early mobilization and early initiation of respiratory physical therapy are actively promoted (Fig. 1). Postoperative rehabilitation protocols are prepared for each hospital day, and patient progress is recorded in accordance with these protocols (Fig. 3). The minimum rehabilitation goals include ambulation by postoperative day 3, walking within the ward by postoperative week 1, and initiation of aerobic exercise, such as ergometer training, by postoperative week 2.

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We provide preoperative outpatient respiratory rehabilitation and guidance on home self-training.

Respiratory Rehabilitation

After surgery, anesthesia and pain can cause shallow breathing, reducing oxygen delivery to all areas of the lungs. Also, sputum becomes harder to expel and may accumulate deep in the lungs, increasing the risk of pneumonia and delaying recovery.

① **Breathing Techniques**
② **Sputum Clearance**
③ **Respiratory Function Training**

When appropriate, your attending physician may recommend purchasing training devices and continuing supervised and self-training.

Do this daily for at least 1 week (ideally 2+ weeks) before surgery to improve lung function.

Benefits

Improved pulmonary function (vital capacity and FEV1)

Shorter hospital stay (3–7 days shorter)

Lower incidence of postoperative pneumonia

Can be continued after surgery to further improve respiratory function

Keep up your self-training for a faster recovery!

Smoking Cessation Before Surgery

Complete smoking cessation is required before surgery.
For patients undergoing esophageal surgery, complete cessation for at least **1 month** is mandatory.

Why you must quit

Smoking increases sputum production
↓
Mechanical ventilation further increases sputum
↓
Post-surgery: Shallow breathing & difficulty coughing
↓
Accumulated sputum → **Pneumonia**, **Suffocation**

Risks of Continuing Smoking

Surgical Site Infection **1.5 - 3x**

Respiratory Complications **3 - 10x**

By Quitting Smoking

You can reduce the risk of overall complications by:
30 - 40%

Additional Risk
Smoking also raises the risk of surgical site infections.

It's not too late. Quit now!
For a safe and early recovery

Please measure and record your body temperature and weight daily at a fixed time.

Date (Month/Day)	Temp (°C)	Weight (kg)	Rehabilitation	Oral nutritional support
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Fig. 2. Treatment diary example.

Esophageal Resection Post-surgery Rehabilitation Progress Protocol

Name _____ ID _____ Date of surgery _____

Mobility level	Coach 2: maximum inspiratory volume (preoperative: ___)															Target mobilization level Step-up permitted as appropriate depending on the patient's condition
11	Cycle ergometer (preoperative ATL level)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	4
10	Cycle ergometer ≥20 minutes	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Sitting at bedside or wheelchair use ≥2 hours each in the morning and in the afternoon
9	Cycle ergometer <20 minutes	•	•	•	•	•	•	•	•	•	•	•	•	•	•	3
8	Walking 300 m (3 laps of the ward)	•	•	•	•	•	•	•	•	•	•	•	•	•	★	
7	Walking 200 m (2 laps of the ward)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Sitting at bedside or wheelchair use ≥3 hours
6	Walking 100 m (1 lap of the ward)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
5	Walking (1 lap of the nurse station)	•	•	•	•	•	•	★	•	•	•	•	•	•	•	2
4	Walking (to the toilet, 20 m)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Sitting at bedside or wheelchair use ≥1 hour
3	Standing position/ stepping in place	•	•	★	•	•	•	•	•	•	•	•	•	•	•	
2	Sitting at the edge of the bed	•	•	•	•	•	•	•	•	•	•	•	•	•	•	1
1	Bed up (in bed)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Bed up for ≥1–3 hours
	Days after surgery	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
	Date															

Fig. 3. Rehabilitation protocol after esophagectomy.

In addition, early initiation of enteral nutrition has been reported to be effective in suppressing postoperative weight loss and preventing postoperative pneumonia [14]. In our department, a gastrointestinal fistula, either a gastric tube fistula or jejunostomy, is created in all cases, and early enteral nutrition is initiated on the day of surgery. Enteral nutrition is started with continuous administration of elemental nutrition at a rate of 10 kcal per hour, and the infusion rate is increased daily while carefully monitoring for abdominal symptoms, with a target of 50 kcal per hour by postoperative day 5. To prevent essential fatty acid deficiency, the enteral nutrition formula is switched to a semi-digested preparation rich in n-3 fatty acids around postoperative day 7. During enteral nutrition therapy, bowel movement frequency, consistency, and volume are monitored, and if diarrhea occurs, adjustments to the infusion rate, stool culture testing, and the use of probiotics or antidiarrheal agents are considered as appropriate (Fig. 1) [12].

Before initiating oral intake, swallowing function is evaluated in all cases by rehabilitation specialists using swallowing videofluorography and swallowing endoscopy, and the form of the diet is adjusted and introduced according to swallowing function (Fig. 4). In addition, guidance on eating posture is provided to ensure safe oral intake and prevent aspiration. The amount of enteral nutrition is gradually reduced in accordance with increases in oral intake; however, when oral intake, including ONS, remains insufficient at discharge, enteral nutrition is continued at home after discharge.

With the aging of the population, the average age of patients undergoing esophageal cancer surgery in our department has also increased. For older patients, discharge directly to home after surgery is often difficult, and therefore, in the future, it will be necessary to strengthen inter-hospital cooperation to facilitate home discharge through structured rehabilitation at convalescent hospitals.

Team intervention at outpatient visits after discharge

Even after discharge, follow-up is continued in cooperation with rehabilitation specialists during outpatient visits. Specifically, physical fitness measurements and evaluations of physical function are conducted at 1, 3, 6, and 12 months after surgery. At the same time, registered dietitians provide outpatient nutritional counseling, assess nutritional intake in the home setting, and offer guidance on oral intake, introduction of ONS products, and enteral nutrition management tailored to individual lifestyles. The treatment diary and WFT are used continuously from the start of intervention until 1 month after discharge.

Results and future issues of perioperative team medicine

We compared short-term outcomes among 137 patients who underwent esophagectomy with gastric tube recon-

Oral Intake Initiation Criteria Table
(Esophageal Cancer Postoperative Pattern) ID: Name:

[Principles for Aspiration Prevention]
- Do not initiate oral intake if arousal or alertness is insufficient.
- If occluding molars or dentures are not worn, do not provide meals that require prolonged oral intake (≥5 minutes).
- Confirm eating behavior in patients who tend to swallow food whole or stuff food into the mouth.

[Discontinuation Criteria]
If any of the following are observed, report to the physician and confirm whether oral intake should be continued.
- Fever ≥37.5 °C or signs of inflammation
- Worsening respiratory status (especially if SpO_2 decreases by ≥3% during meals, suspect silent aspiration)
- Decreased level of consciousness or drowsiness

Water Swallow Test
10 mL × 3 trials
- Score ≥4: Proceed to oral intake
- Score ≤3: Perform swallowing training in the rehabilitation room

Date	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N	/ M D N
Food texture	Dysphagia 2-1	Dysphagia 2-2	Dysphagia 3	Dysphagia 4	Post-minced rice diet (rice porridge)			Post-soft diet (rice porridge or regular rice)				
Staple food	Blended rice porridge 100 g	Blended rice porridge 150 g	Rice porridge 150 g	Rice porridge 150 g	Rice porridge 200 g (currently handled by comment entry)			Rice porridge 200 g (for regular rice, handled by comment entry)				
Supplement	None				Provided (standard: morning = Premil corn soup; lunch = Hemul coffee)							
Fluids	Thickened				Not thickened							
Posture	45°, neck flexed forward					60°		Seated position				

Fig. 4. Hamamatsu Perioperative Care Team oral intake protocol.

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struction at our hospital between January 2015 and October 2019. Patients were categorized into three groups: before HOPE introduction (n=43), early HOPE period (until April 2018, n=40), and late HOPE period (from April 2018 to October 2019, n=54). When comparing the incidence of infectious complications classified as Clavien-Dindo (C-D) grade III or higher, including anastomotic leakage, pneumonia, and wound infection, no significant difference was observed between the pre-HOPE group and the early HOPE period (18.6% vs. 15.0%). In contrast, the incidence was significantly lower in the late HOPE period compared with the pre-HOPE group (18.6% vs. 5.6%; P=0.001) (Fig. 5). In addition, rates of postoperative weight loss at 1, 3, and 6 months after surgery were significantly improved in both the early and late HOPE periods compared with the pre-HOPE period (Fig. 6) [15].

To examine the effects of using a treatment diary and WFT, 62 patients were selected by propensity score matching from 94 patients who underwent subtotal esophagectomy between 2019 and 2021. Outcomes were compared between the WFT group (n=31) and the non-WFT group (n=31) [12]. The average WFT wearing rate was 91.8%. The incidence of postoperative complications of C-D grade II or higher was significantly lower in the WFT group, and in particular, the incidence of postoperative pneumonia of C-D grade II or higher was significantly reduced (WFT group 16.1% vs. non-WFT group 38.7%; P=0.043) (Table 2) [12]. Postoperative hospital stay was also significantly shorter in the WFT group (median, 22 days vs. 29 days; P=0.012) (Table 2).

Regarding nutritional indicators at 1 month after surgery, serum albumin levels (median, WFT group 3.9 g/dL vs. non-WFT group 3.6 g/dL; P=0.013), serum transthyretin levels (median, WFT group 24.4 mg/dL vs. non-WFT group 19.4 mg/dL; P=0.001), and the prognostic nutritional index (PNI) (median, WFT group 46.2 vs. non-WFT group 42.6; P=0.034) were all significantly higher in the WFT group (Table 2) [16].

Currently, we are conducting a randomized, non-blinded, controlled trial to evaluate the effects of our institution's preoperative short-term nutrition and exercise therapy program,

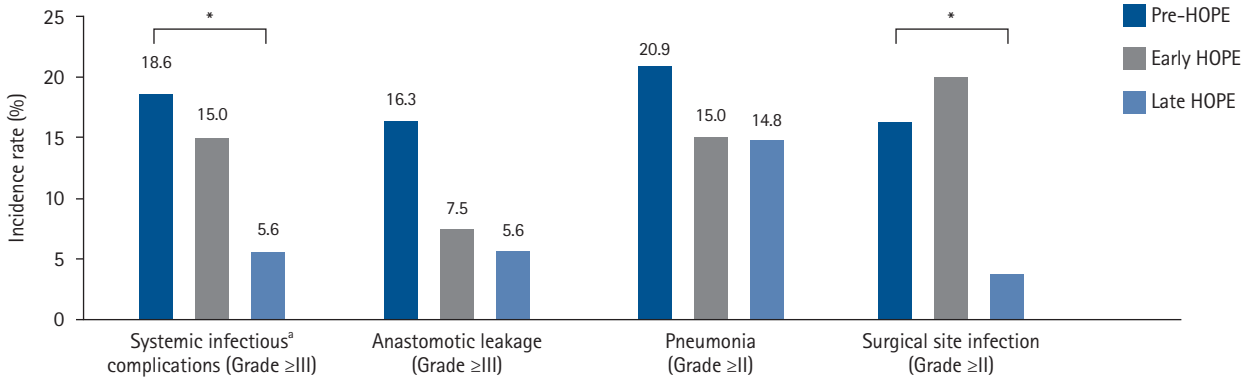

Fig. 5. Postoperative complications. Bar graph or table showing the incidence of Clavien-Dindo grade III or higher infectious complications (anastomotic leakage, pneumonia, wound infection) before and after Hamamatsu Perioperative Care Team (HOPE) introduction. [a]All complications had been evaluated by Clavien-Dindo classification. *P<0.05.

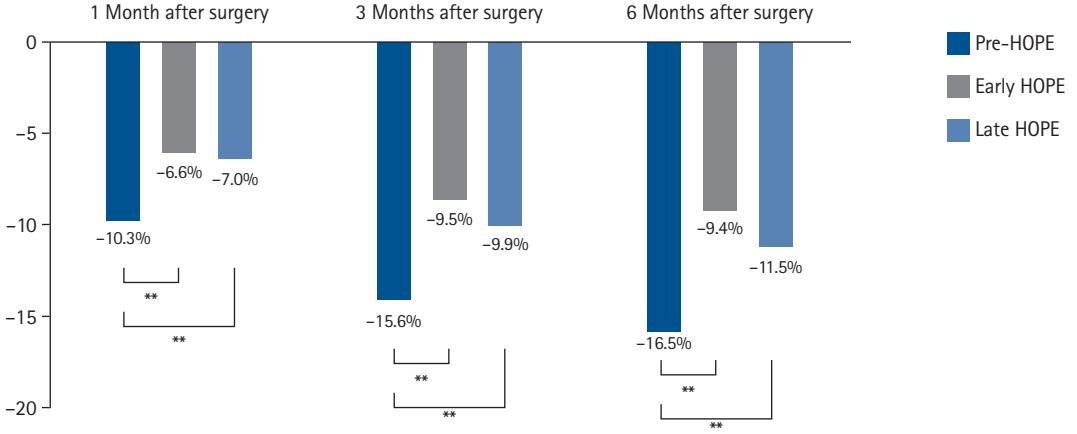

Fig. 6. Postoperative weight changes. Line graph or table comparing the percentage of weight loss at 1, 3, and 6 months postoperatively between pre-Hamamatsu Perioperative Care Team (HOPE), early HOPE, and late HOPE groups [15]. **P<0.01.

Table 2. Comparison of short-term outcomes by use of WFTs

	WFT use (n=31)	No WFT use (n=31)	P-value
All complications, No. (%)			
C-D grade II or higher	5 (16.1)	12 (38.7)	0.043
Anastomotic leakage	3 (9.7)	2 (6.5)	0.500
Pneumonia	0	7 (22.6)	0.005
Postoperative hospital stay (day), median (range)	22 (20–29)	29 (24–36)	0.012
Blood test results at 1 month after surgery, median (range)			
Prognostic nutritional index	46.2 (40.8–49.7)	42.6 (37.8–45.9)	0.034
Albumin (g/dL)	3.9 (3.6–4.1)	3.6 (3.2–3.9)	0.013
Transthyretin (mg/dL)	24.4 (21.5–26.0)	19.4 (15.0–22.9)	0.001
CRP (mg/dL)	0.14 (0.09–0.31)	0.35 (0.15–1.60)	0.018

WFTs, wearable fitness tracking devices; C-D, Clavien-Dindo classification; CRP, C-reactive protein.

referred to as the STEP-NEXT (Preoperative Short-Term Program for Nutrition and Exercise Trial), on postoperative nutritional status and physical function following esophagectomy.

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Authors' contribution

Conceptualization: HT. Data curation: YS, KS, TM (Tomohiro Murakami), EB, TM (Tomohiro Matsumoto), HK, YH. Methodology/formal analysis/validation: YS, KS, TM (Tomohiro Murakami), EB, TM (Tomohiro Matsumoto), HK, YH. Project administration: HT. Writing–original draft: RH. Writing–review & editing: RH, YS, KS, TM (Tomohiro Murakami), EB, TM (Tomohiro Matsumoto), HK, YH, HT. 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

Epigallocatechin gallate increases fatty acid oxidation but not 24-hour survival in lipopolysaccharide-induced endotoxic shock in mice

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Abstract

Purpose: This study aimed to explore the effects of epigallocatechin gallate (EGCG) in critically ill patients using a mouse model.
Methods: C57BL/6 mice were divided into control and EGCG groups (n=8 per group). The EGCG group received a 0.1% EGCG solution for 2 weeks, after which the mice were intraperitoneally injected with a lethal dose of lipopolysaccharide to induce acute endotoxic shock. Indirect calorimetry was performed for 24 hours. Changes in body weight, epididymal fat weight, and survival were measured, together with serum lipid levels, interleukin-6 (IL-6), and superoxide dismutase (SOD) concentrations. The expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) was determined using quantitative real-time polymerase chain reaction, and its serum concentration was subsequently measured.
Results: Indirect calorimetry showed a significant increase in fatty acid oxidation (P<0.0001) in the EGCG group, along with significant decreases in body weight and epididymal fat weight (P<0.01 and P<0.05, respectively). Survival did not differ significantly between groups (P=0.197). Serum lipid levels, IL-6, and SOD showed numerical differences, although these differences were not statistically significant. Furthermore, hepatic PGC-1α expression showed a tendency toward upregulation, and serum PGC-1α levels were significantly higher (P<0.05).
Conclusion: EGCG stimulates endogenous lipid metabolism through PGC-1α activation and may suppress inflammatory responses; therefore, it may represent a potentially useful nutrient for acute nutritional therapy.

Keywords: Critical illness; Epigallocatechin gallate; Fatty acids; Lipid metabolism; Survival

Introduction

Background

The importance of acute nutritional therapy for critically ill patients who have experienced severe trauma or sepsis is widely recognized, and various clinical guidelines have been developed to support evidence-based practice [1,2]. Among these recommendations, the use of indirect calorimetry to estimate energy expenditure is recommended with a GRADE 2B level of evidence in the latest Japanese guidelines [3]. We have previously shown that metabolism shifts from carbohydrate-dominant to lipid-dominant metabolism during physiological stress and that therapeutic interventions targeting lipid metabolism may be effective [4]. Specifically,

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peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which plays a critical role in mitochondrial biogenesis and fatty acid β-oxidation [5], is activated by interventions such as low-intensity exercise and neuromuscular electrical stimulation, leading to enhanced lipid metabolism and improved survival outcomes [6,7]. However, evidence regarding effective nutrients for acute nutritional therapy in critically ill patients remains limited. Although n-3 fatty acids and glutamine were previously considered potential immunomodulatory nutrients, large-scale clinical trials have reported negative results, and their use is no longer recommended [8,9]. Conversely, hydroxymethylbutyrate has shown some promise as a pharmaconutrient, particularly in enhancing recovery from exercise-induced muscle damage [10].

Tea catechins are water-soluble polyphenols with a flavanol structure that are abundant in green tea, which is widely consumed in Japan and other Asian countries. Tea leaves contain approximately 30%–42% catechins by dry weight, with epigallocatechin gallate (EGCG) accounting for 50%–70% of the total catechin content. EGCG has been reported to exert antioxidant, anti-inflammatory, anticancer, and antibacterial effects and has also been associated with weight loss and anti-aging effects. This broad biological activity profile suggests potential utility not only in the management of chronic conditions but also in acute care settings, where inflammation and metabolic dysregulation are prominent. However, its effects in humans, particularly under acute stress conditions, remain unclear [11]. Several studies have suggested that EGCG can activate PGC-1α [12,13]; however, its effects in conditions such as sepsis have not been thoroughly investigated. In addition, the potential of EGCG to influence mitochondrial function, modulate immune responses, and enhance metabolic flexibility makes it a promising candidate for therapeutic investigation in critical care settings.

Objectives

This study aimed to investigate the potential role of EGCG in acute nutritional therapy for critically ill patients, with a particular focus on its effects on metabolic regulation and clinical outcomes under conditions of physiological stress.

Methods

Ethics statement

This study adhered to the ethical guidelines of the Aichi Medical University Animal Experimentation Committee (approval number: 2024-38) and complied fully with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Study design

EGCG feeding protocol

Eleven-week-old male C57BL/6 mice (Japan SLC) were used in this study. According to company data, the mice were produced under controlled conditions based on established production management standards, and no differences in body weight or biochemical characteristics were observed between individuals. The animals were acclimated in individual cages under a 12-hour light–dark cycle (light phase: 07:30–19:30 hours; dark phase: 19:30–07:30 hours) at a constant temperature (22±1 °C). Standard laboratory chow (Oriental Yeast) was provided *ad libitum*. All animals were monitored daily for general health, food and water intake, and activity levels to ensure consistent baseline conditions before the intervention. Environmental enrichment was provided to minimize stress and maintain physiological stability throughout the experimental period. On day 1, the mice were randomly assigned to control or EGCG groups (n=8 per group). Tap water or a 0.1% EGCG solution was provided *ad libitum* for 2 weeks. This concentration was calculated based on a report indicating that the non-toxic dose in mice is 500–750 mg/kg/day [14] and that the average daily drinking volume in mice is approximately 5 mL/day [15].

Body weight, epididymal fat weight, and serum lipid levels

Changes in body weight were measured after 2 weeks of EGCG intake. The mice were then sacrificed and dissected, and epididymal fat weight was measured. Liver and plasma samples were collected for analysis. To evaluate serum lipid levels, the concentration of non-esterified fatty acids (NEFA) was measured using a Wako spectrophotometry kit according to the manufacturer's instructions.

Serum inflammatory cytokine and oxidative stress marker levels

To evaluate serum inflammatory cytokine and oxidative stress markers, plasma concentrations of interleukin-6 (IL-6) and superoxide dismutase (SOD) were measured using Quantikine enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems) according to the manufacturer's instructions.

Liver and serum PGC-1α levels

Quantitative real-time polymerase chain reaction was performed to evaluate PGC-1α messenger RNA (mRNA) expression in the liver. Total RNA was extracted from liver tissue using TriPure Isolation Reagent (Roche Diagnostics)

and reverse-transcribed into complementary DNA. Real-time polymerase chain reaction was performed using the TaqMan probe method with a LightCycler system (Roche Diagnostics). Hypoxanthine-guanine phosphoribosyltransferase served as the internal control. The primer sequences used were as follows: *pgc1a*, TGTGGAACTCTCTGGAACTGC (forward) and AGGGTTATCTTGGTTGGCTTTA (reverse); and *hprt*, TCCTCCTCAGACCGCTTTT (forward) and CCTGGTTCATCATCGCTAATC (reverse). Serum PGC-1α concentration was also measured using a Quantikine ELISA kit according to the manufacturer's instructions.

Acute endotoxic shock mouse model

After 2 weeks of EGCG or tap-water intake, mice in both groups were intraperitoneally injected with a lethal dose of lipopolysaccharide (LPS) (20 mg/kg; *Escherichia coli* O55:B5, L-2880; Sigma-Aldrich) diluted in normal saline (10 mL/kg) to induce acute endotoxic shock. Food was withheld during the 24-hour metabolic assessment, whereas water was available *ad libitum*.

Indirect calorimetry and survival probability

Nutritional metabolism was assessed using indirect calorimetry for 24 hours after LPS administration using a mass spectrometer for respiratory gas analysis and a bioprocess monitoring system (ARCO-2000; Arco System Inc.). The system operated under controlled conditions of constant temperature (25±2 °C) and humidity (60%±10%). Data were collected every 10 minutes, and fatty acid oxidation (FAO) was calculated using the Frayn formula [16]:

$FAO=1.67\times VO_2-1.67\times VCO_2$.

Survival was monitored for 24 hours after LPS administration.

Statistical analysis

All values are presented as mean±standard error of the mean. Data between the two groups were analyzed using the Mann-Whitney U test. FAO data were analyzed using two-way analysis of variance with Sidak's *post hoc* test. Survival data were analyzed using the Kaplan-Meier method with the log-rank test. Statistical analyses were performed using GraphPad Prism 9 software (GraphPad Inc.), and statistical significance was defined as P<0.05.

Results

Body weight, epididymal fat weight, and serum lipid level

The mean EGCG intake was 193.5±4.5 mg/kg/day, which was well below the reported toxic dose. Body weight and epididymal fat weight were significantly lower in the EGCG group than in the control group (P=0.004 and P=0.029, respectively). Serum NEFA levels did not significantly differ between the groups (P=0.64). These findings suggest enhanced lipid utilization in the EGCG group (Fig. 1).

Serum IL-6 and oxidative stress marker levels

Serum IL-6 levels tended to be lower in the EGCG group than in the control group (P=0.098). Serum SOD levels also tended to be lower in the EGCG group (P=0.114). These findings suggest that EGCG may exert mild anti-inflammatory and antioxidant effects. The reductions in IL-6 and SOD levels, although not statistically significant, were consistent with previous reports describing the immunomodulatory properties of EGCG (Fig. 2).

Liver and serum PGC-1α levels

Compared with the control group, the EGCG group showed a higher hepatic PGC-1α mRNA expression (P=0.99) and significantly higher serum PGC-1α levels (P=0.045). These findings are consistent with the hypothesis that EGCG activates PGC-1α signaling pathways, potentially enhancing mitochondrial biogenesis and FAO (Fig. 3).

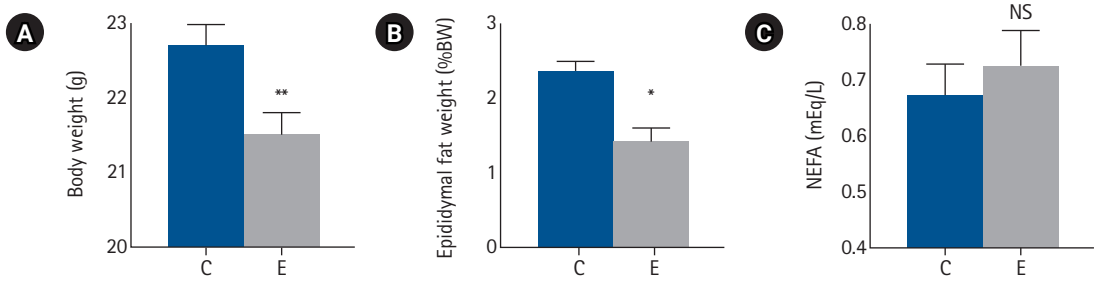

Fig. 1. Effects of EGCG on metabolic parameters. (A) Body weight, (B) epididymal fat weight, and (C) serum NEFA levels. Values are presented as mean±standard error of the mean (n=8 per group) and were analyzed using the Mann-Whitney U test. C, control group; E, epigallocatechin gallate (EGCG) group; NS, not significant; NEFA, non-esterified fatty acid. *P<0.05, **P<0.01 vs. C.

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Indirect calorimetry

Indirect calorimetry showed that FAO was significantly higher in the EGCG group than in the control group (P=0.0001, P=0.006, and P=0.031 at 0, 4, and 8 hours after LPS administration, respectively) (Fig. 4).

Survival proportions

Survival did not differ significantly between the groups (P=0.197) (Fig. 5).

Discussion

Key results

In this study, we investigated the effects of EGCG in a mouse model intended to reflect acute critical illness. Fig. 6 illustrates the proposed mechanism underlying the effects of EGCG observed in this study. EGCG intake increased PGC-1α levels and endogenous lipid metabolism and suppressed oxidative stress and inflammation, but it did not significantly improve survival.

Interpretation/comparison with previous studies

These findings are consistent with the hypothesis that EGCG may act as a metabolic modulator during acute physiological stress. Indirect calorimetry is useful for assessing individual metabolic changes under stress conditions and for applying these data to acute nutritional therapy; accordingly, studies evaluating its clinical utility are increasing [17]. This method may be important for precision medicine and personalized nutrition therapy [18,19], both of which have received increasing attention in intensive care. By tailoring nutritional interventions to a patient's real-time metabolic

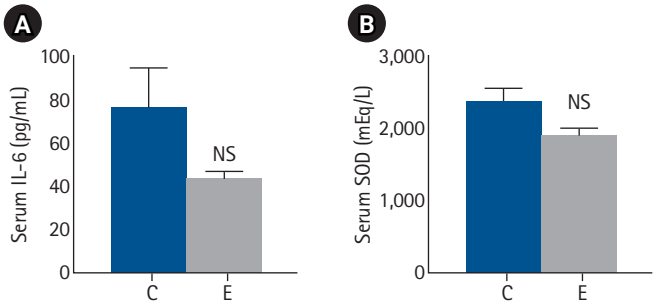

Fig. 2. Serum inflammatory response markers. (A) Serum IL-6 and (B) SOD levels. Values are presented as mean±standard error of the mean (n=8 per group for IL-6 and n=4 per group for SOD) and were analyzed using the Mann-Whitney U test. IL-6, interleukin-6; SOD, superoxide dismutase; C, control group; E, epigallocatechin gallate (EGCG) group; NS, not significant.

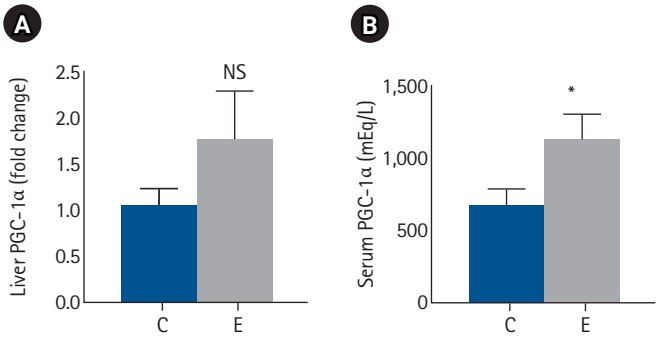

Fig. 3. PGC-1α levels in liver and serum. (A) Liver PGC-1α levels. (B) Serum PGC-1α levels. Values are presented as mean±standard error of the mean (n=8 per group) and were analyzed using the Mann-Whitney U test. PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; mRNA, messenger RNA; C, control group; E, epigallocatechin gallate (EGCG) group; NS, not significant. *P <0.05 vs. C.

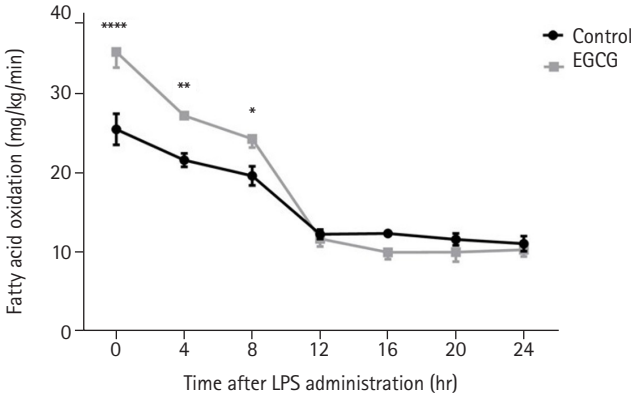

Fig. 4. Indirect calorimetry. Values are presented as mean±standard error of the mean (n=8 per group). Fatty acid oxidation was analyzed using two-way analysis of variance with Sidak *post hoc* test. EGCG, epigallocatechin gallate; LPS, lipopolysaccharide. *P<0.05, **P<0.01, ****P<0.0001 vs. control.

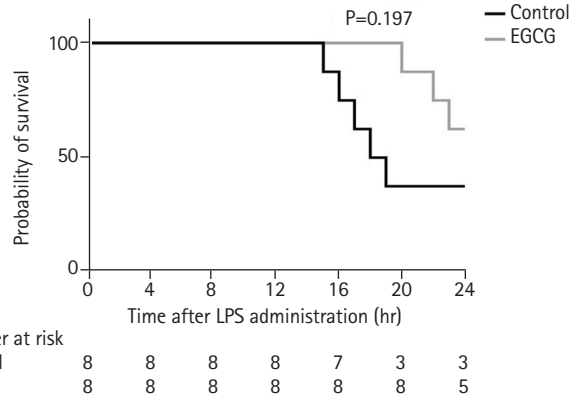

Fig. 5. Survival proportions. Survival proportions were analyzed using the Kaplan-Meier method and the log-rank test. EGCG, epigallocatechin gallate; LPS, lipopolysaccharide.

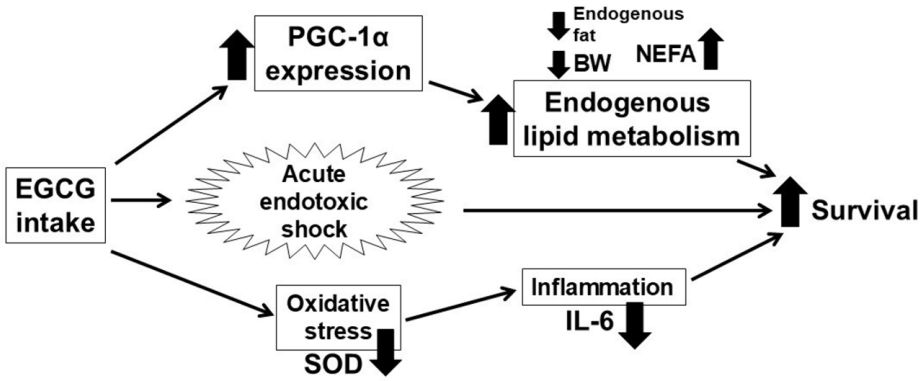

Fig. 6. Proposed mechanism of EGCG intake in acute endotoxic shock. EGCG, epigallocatechin gallate; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; SOD, superoxide dismutase; BW, body weight; NEFA, non-esterified fatty acid; IL-6, interleukin-6.

status, clinicians may be able to optimize recovery and reduce complications.

PGC-1α plays an important role in energy metabolism and is thought to improve lipid metabolism. Exercise, fasting, and cold exposure activate PGC-1α [20]. We have previously shown that low-intensity exercise during the acute phase affects PGC-1α and lipid metabolism and improves survival [9]. In addition, specific neuromuscular electrical stimulation conditions increase PGC-1α and lipid metabolism, suppress inflammation, and improve survival [10]. These interventions may be applicable to critically ill patients with hemodynamic instability. However, nutritional components with similar effects have not been adequately investigated. This gap underscores the importance of exploring bioactive nutrients such as EGCG, which may offer similar benefits without requiring physical exertion, which is often not feasible in critically ill patients.

Tea catechins are distinctive bioactive compounds found in green tea, and EGCG in particular is believed to have several beneficial effects, including anti-inflammatory, antioxidant, and fat-reducing effects. EGCG has been reported to reduce body fat after long-term intake in humans [21] and to exert antioxidant and antibacterial effects [22,23]. On this basis, we considered it a potentially useful nutrient for acute nutritional therapy in critically ill patients. Its natural origin and widespread dietary use make green tea an attractive candidate for integration into clinical nutritional protocols, particularly in regions where green tea consumption is culturally prevalent.

The findings of this study suggest that EGCG may exert metabolic regulatory effects in acute endotoxic shock by increasing endogenous lipid metabolism through PGC-1α activation and by suppressing inflammatory responses. Here, "metabolic resuscitation" refers to improvement in outcomes through recovery from metabolic dysfunction during severe stress, such as sepsis. EGCG may be a useful nutrient during early enteral nutrition in critically ill patients. This approach may be particularly helpful for patients who cannot tolerate physical interventions such as exercise or neuromuscular electrical stimulation, because it may provide a noninvasive means of stimulating metabolic recovery and potentially enhancing the efficacy of early nutritional support, which is already known to be beneficial in critical care. Moreover, the compatibility of EGCG with enteral nutrition formulations makes it a practical candidate for incorporation into existing intensive care unit protocols.

Limitations

First, this study was conducted in a mouse model, and the optimal dose in humans remains unknown. In our mouse experiment, the administered intake was below the reported toxic dose; however, liver injury and other adverse effects have been reported in humans [24]. Therefore, careful attention should be paid to the dose administered in humans. In addition, the pharmacokinetics and bioavailability of EGCG in critically ill patients may differ substantially from those in healthy individuals, necessitating careful clinical evaluation. Second, in this study, EGCG was administered before LPS administration, not after the onset of acute endotoxic shock. Forced administration of a fixed amount of EGCG to mice after LPS administration was not feasible because the procedure itself caused substantial stress and increased mortality. In the clinical setting, whether similar effects would occur when EGCG is administered after hospital arrival, that is, after disease onset, remains unclear. Finally, because of the short duration of the experiment, the effects on long-term outcomes remain unknown. Future studies should investigate the therapeutic window, optimal dosing strategies, and long-term safety and effects of EGCG in humans.

Conclusion

EGCG may be a useful nutrient for acute nutritional therapy in critically ill patients. Our findings suggest that EGCG may serve as a novel adjunctive therapy in critical care, particularly during the early phase of enteral nutrition. Further clinical studies are required to determine its effects in humans, including the optimal dose, timing, and delivery method, as well as its long-term safety and efficacy. If validated, EGCG could be incorporated into personalized nutritional strategies to support metabolic recovery and improve outcomes in critically ill patients.

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Authors' contribution

Conceptualization: RK, DO, TT. Formal analysis: TI, MMI, US, SM, RA. Investigation: TI, MMI, US, SM, RA. Supervision: EW. Writing–original draft: TI, RK, DO, TT. Writing–review & editing: all authors. 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

Contact the corresponding author for research data availability.

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Supplementary materials

None.

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Original Article

Association of soy oil-based lipid injectable emulsion with early body weight loss after minimally invasive esophagectomy in Japan: a retrospective cohort study

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ABSTRACT

Purpose: Postoperative body weight loss (PBWL) is associated with poor long-term outcomes following esophagectomy for esophageal cancer, underscoring the critical importance of perioperative nutritional management. Although minimally invasive procedures, such as robot-assisted radical transmediastinal esophagectomy (RA-TME), have become increasingly prevalent, perioperative nutritional strategies have received comparatively limited attention. This study evaluated the impact of soy oil-based injectable lipid emulsion (SO-ILE) on PBWL in patients undergoing RA-TME.

Methods: We retrospectively analyzed 155 patients who underwent RA-TME for esophageal or esophagogastric junction cancer at our hospital between 2011 and 2022. Patients were divided into two groups: the lipid (+) group (n=33), which received SO-ILE between postoperative days 1 and 6, and the lipid (–) group (n=122), which did not receive SO-ILE. Oral or enteral nutrition was withheld until postoperative day 6. Nutrient intake, postoperative outcomes, and nutritional status were compared between the two groups.

Results: Patient backgrounds, surgical outcomes, and postoperative complication rates were similar between the two groups. However, patients in the lipid (+) group received significantly greater total energy and nutrient intake. PBWL at 2 weeks after surgery was significantly lower in the lipid (+) group than in the lipid (–) group (5.8% vs. 7.4%; P=0.027). Univariate analysis showed that absence of SO-ILE administration was the only significant risk factor for PBWL greater than 5% at 2 weeks after RA-TME (P=0.038).

Conclusion: SO-ILE may have the potential to mitigate early PBWL after RA-TME.

Keywords: Enteral nutrition; Esophageal neoplasms; Esophagectomy; Lipids; Treatment outcome

Introduction

Background

Esophageal cancer is the 10th most common malignancy worldwide and has the sixth poorest prognosis among all cancers [1]. Multidisciplinary treatment approaches, including surgery, radiation therapy, and chemotherapy, play essential roles in its management. Among these modalities, esophagectomy remains the standard treatment for esophageal cancer. However, it is a highly catabolic procedure and is associated with substantial risks of postoperative body weight loss (PBWL), severe complications, and hospital mortality.

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Moreover, pronounced PBWL has been linked to poor long-term outcomes following esophagectomy [2-4]. Accordingly, various strategies have been implemented to reduce surgical stress, including advances in minimally invasive techniques, maintenance of adequate nutritional status, and enhanced postoperative recovery protocols [5-7].

We developed robot-assisted radical transmediastinal esophagectomy (RA-TME), a nontransthoracic esophagectomy with radical mediastinal lymphadenectomy that combines a robotic transhiatal approach with a video-assisted cervical approach, to reduce surgical invasiveness. This technique has been employed at our institution since 2011. In our previous studies, we demonstrated that RA-TME shortens hospital stay, reduces pulmonary morbidity, and provides superior postoperative quality of life compared with conventional transthoracic esophagectomy [8,9].

Because RA-TME is considerably less invasive than conventional open thoracic surgery, most patients are discharged without major complications at approximately postoperative day (POD) 17. As a result, our current standard clinical pathway does not include the creation of a feeding jejunostomy or placement of a central venous catheter (CVC). Instead, patients are maintained on peripheral parenteral nutrition (PPN) alone until oral intake is initiated. While this approach avoids CVC- and jejunostomy-related complications that were previously encountered, it also restricts total caloric delivery due to insufficient lipid and amino acid provision. Consequently, patients may experience an early postoperative negative energy balance.

In Japan, perioperative parenteral nutrition formulations that contain large amounts of glucose as the primary energy substrate have traditionally been prescribed, whereas lipid calories are often minimized because of safety concerns. Early intensive care unit studies reported associations between high-dose soy oil-based injectable lipid emulsions (SO-ILEs) and exacerbated systemic inflammation, cholestasis, and liver disease [10-13]. Nevertheless, SO-ILEs provide essential fatty acids and energy-dense calories. Because fish oil-based lipid emulsion products have not yet been introduced into routine clinical practice in Japan, SO-ILEs remain the only intravenously administered lipid products commercially available.

Several previous studies have evaluated the role of SO-ILEs in postoperative nutritional management. Some reports have suggested that SO-ILEs contribute to maintaining energy balance and preventing excessive catabolism after major surgery, whereas others have raised concerns regarding inflammatory or hepatic adverse effects, particularly with high-dose administration [14,15]. However, the clinical impact of low-dose SO-ILE administration after minimally invasive esophagectomy has not been clearly established.

Objectives

The aim of this study was to determine whether the addition of SO-ILE to parenteral nutrition influences short- or long-term clinical outcomes in patients undergoing a minimally invasive esophagectomy procedure, specifically RA-TME.

Methods

Ethics statement

This study was approved by the Ethics Committee of the University of Tokyo Hospital (approval No. 3962). Written informed consent was waived by the institutional review board because of the retrospective nature of the study.

Study design

This was a retrospective cohort study with a single-center, nonrandomized, exposure-based comparative design.

Setting

Electronic medical records were reviewed for patients who underwent RA-TME with gastric conduit reconstruction for esophageal or esophagogastric junction cancer at the University of Tokyo Hospital between January 2011 and December 2022. All included patients received neither oral nutrition nor enteral nutrition prior to POD 6.

Surgical methods

RA-TME with two- or three-field lymphadenectomy was performed in three stages, with all procedures conducted while the patient was in the supine position [16]. In the first stage, lymph node dissections in the cervical and abdominal fields were performed simultaneously by two surgical teams. The cervical procedure was carried out via a collar incision under mediastinoscopic guidance, whereas the abdominal procedure was performed laparoscopically. In the second stage, a robotic surgical system, either the da Vinci S or Xi (Intuitive Surgical), was used to perform the transhiatal robotic procedure through the abdominal ports. During the combined cervical collar incision and transhiatal da Vinci procedures, the entire esophagus and the dissected mediastinal lymph nodes were mobilized and freed from surrounding adhesions and attachments. After completion of mediastinal dissection, the da Vinci S or Xi robotic system was withdrawn from the operative field. The final stage included retrieval of the surgical specimens, reconstruction using a gastric tube conduit, and creation of a cervical anastomosis.

Postoperative nutrition protocol

Postoperative nutritional management followed a standardized prescription. All patients began taking ice on POD 3, and drinking water was initiated on POD 7. On POD 7, patients started a clear liquid diet and gradually advanced to pureed food and subsequently to regular meals. Patients consumed only hospital-provided food during the postoperative period. The timing of initiation and advancement of oral intake could be adjusted according to the patient's clinical condition and the attending physician's judgment. Until oral intake was initiated, patients received intravenous infusions only. The composition of these infusions, including the inclusion of lipid injectable emulsions or amino acids, was determined by the attending physicians.

Participants

Among the target population, patients with residual tumors after surgery were excluded from the present study. Eligible patients were classified into two groups: the lipid (+) group (n=33), who received SO-ILE between POD 1 and POD 6, and the lipid (–) group (n=122), who did not receive SO-ILE.

Variables

The exposure variable was administration of SO-ILE at least once during POD 1 through POD 6. The primary outcome was PBWL at 2 weeks, calculated as the percentage change from baseline body weight. Secondary outcomes included serial measurements of body weight, body composition, and hematological parameters at the preoperative baseline and at POD 6–8, 12–16, and 25–35; postoperative complications graded according to the Clavien-Dindo classification by POD 14; and overall survival (OS) and relapse-free survival (RFS) at 2 years. Covariates included age, sex, body mass index, skeletal muscle index, Short Physical Performance Battery (SPPB) score, American Society of Anesthesiologists Physical Status class, and the presence of sarcopenia.

Data sources/measurements

Data were extracted from the institutional database and electronic medical records. Hematological parameters and body weight were assessed at four time points: preoperatively, and at 1 week (POD 6–8), 2 weeks (POD 12–16), and 4 weeks (POD 25–35) postoperatively. Physical performance was assessed using the SPPB, and perioperative risk was evaluated using the American Society of Anesthesiologists Physical Status classification. Sarcopenia was defined by the presence of both low physical performance (SPPB ≤9) and low skeletal muscle mass, with skeletal muscle index thresholds of <7.0 kg/m^2 for men and <5.0 kg/m^2 for women, as measured by bioelectrical impedance analysis. Postoperative changes in body weight, hematological parameters, muscle strength, and body composition were recorded. Pathological findings were classified according to the 8th edition of the TNM classification published by the Union for International Cancer Control [17]. Postoperative complications were recorded on POD 14, and their severity during hospitalization was graded using the Clavien-Dindo classification [18]. Long-term outcomes included OS and RFS at 2 years. Details of postoperative nutritional intake were calculated based on prescribed intravenous infusions and the types and quantities of hospital-provided food from POD 1 through POD 14. Nutritional intake was additionally normalized by body weight to allow comparisons among individuals with differing body sizes.

Bias

This retrospective, single-center study is subject to potential selection bias and confounding by indication, as the decision to administer SO-ILE was made by attending physicians without a standardized nutritional protocol. In addition, baseline group imbalances and temporal changes in clinical practice over the study period may have influenced the results. To minimize information bias, predefined variables were extracted from electronic medical records using standardized definitions, including the Clavien-Dindo classification.

Study size

No a priori sample size calculation was performed. The study population consisted of all eligible RA-TME patients treated between 2011 and 2022 who received no oral or enteral nutrition by POD 6 (n=155), including 33 patients in the lipid (+) group and 122 in the lipid (–) group.

Statistical methods

Categorical variables are presented as numbers (percentages). Normally distributed continuous variables are expressed as mean±standard deviation, whereas non-normally distributed variables are reported as median (interquartile range). The Student t test was used to compare normally distributed continuous variables, and the Mann-Whitney U test was applied to non-normally distributed continuous variables. Categorical variables were compared using the chi-square test, with the Fisher exact test applied when any expected cell count was less than 10. Longitudinal changes in body weight, body composition, and hematological parameters were analyzed using linear mixed-effects models. Results

of logistic regression analyses are presented as odds ratios with 95% confidence intervals. OS and RFS were compared between groups using the log-rank test. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using JMP Pro version 17 (SAS Institute) for Windows.

Results

Patient characteristics

Fig. 1 presents the flowchart of patient enrollment. Overall, 262 patients underwent RA-TME for esophageal or esophagogastric junction cancer at our hospital between 2011 and 2022. Among these patients, 155 who received only intravenous infusions prior to POD 6, without oral or enteral nutrition, were included in the analysis. Patients were divided into two groups: a lipid (+) group (n=33), who received intravenous infusions containing SO-ILE at least once between surgery and POD 6, and a lipid (–) group (n=122), who were not prescribed SO-ILE during this period. Table 1 summarizes preoperative patient characteristics. Significant differences were observed in aspartate aminotransferase (AST) levels, which were higher in the lipid (+) group than in the lipid (–) group. However, values in both groups remained within the normal reference range.

Surgical and postoperative outcomes

There were no significant differences between the two groups in intraoperative parameters, including operative time, intraoperative blood loss, or reconstruction route (Table 2). Postoperative outcomes are shown in Table 3. No significant differences were observed between the two groups

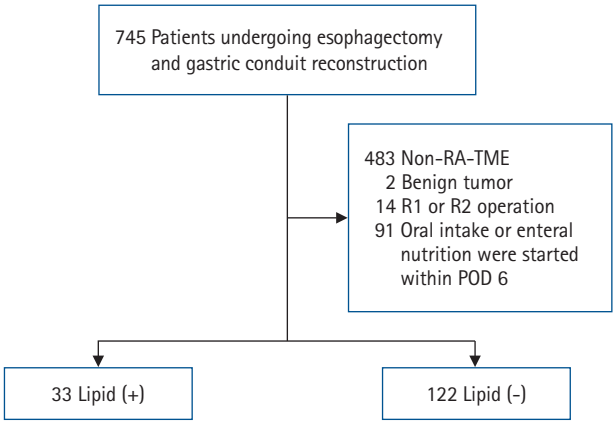

Fig. 1. Flow diagram of patient enrollment. Among 262 patients who underwent robot-assisted radical transmediastinal esophagectomy (RA-TME), 155 who received neither oral nor enteral nutrition by postoperative day (POD) 6 were included and classified according to whether they received peripheral parenteral nutrition with soy oil-based lipid injectable emulsion during this period.

Table 1. Patients' characteristics

Variable	Lipid (+) group (n=33)	Lipid (–) group (n=122)	P-value
Sex			0.246
Male	26 (78.8)	106 (86.9)	
Female	7 (21.2)	16 (13.1)	
Age (yr)	68.0 (61.0–74.0)	67.5 (60.0–73.0)	0.627
≥75	7 (21.2)	23 (18.9)	0.761
Height (cm)	165.2 (160.1–169.9)	166.5 (161.1–170.3)	0.820
Body weight (kg)	59.2 (53.6–66.1)	61.7 (53.9–67.9)	0.266
BMI (kg/m^2)	21.1 (19.4–23.8)	22.0 (20.1–23.8)	0.188
Obesity (≥25)	5 (15.2)	18 (14.8)	0.955
Underweight (≤18.5)	7 (21.2)	14 (11.5)	0.147
Muscle mass (kg)	45.1 (38.0–47.8)	46.5 (42.2–49.9)	0.118
Body fat percentage (%)	20.2 (14.7–25.6)	19.4 (15.8–23.4)	0.850
SPPB score	12 (12–12)	12 (11–12)	0.453
SPPB score			0.147
≤9 points	2 (7.7)	2 (2.0)	
≥10 points	24 (92.3)	96 (98.0)	
SMI (kg/m^2)	7.3 (6.3–7.8)	7.5 (6.8–8.1)	0.145
Low SMI	10 (30.3)	22 (18.0)	0.076
Sarcopenia	6 (23.1)	14 (13.7)	0.241
Preoperative chemotherapy	13 (39.4)	67 (54.9)	0.113
ASA-PS			0.485
I or II	29 (87.9)	112 (91.8)	
III	4 (12.1)	10 (8.2)	
White blood cells (/μL)	6,500 (5,000–8,050)	6,300 (5,000–7,725)	0.873
Neutrophils (/μL)	4,543 (3,231–6,232)	4,165 (3,239–5,201)	0.528
Lymphocytes (/μL)	1,341 (1,079–1,578)	1,477 (1,223–1,727)	0.101
Hemoglobin (g/dL)	11.3 (10.1–13.4)	12.4 (10.4–13.7)	0.211
Serum albumin (g/dL)	4.0 (3.6–4.3)	3.9 (3.7–4.1)	0.825
AST (U/L)	21.0 (17.5–26.5)	19.0 (16.0–22.0)	0.048
ALT (U/L)	13.0 (11.0–17.5)	14.0 (10.0–18.0)	0.948
γ-GTP (U/L)	33.5 (21.3–49.3)	26.0 (20.5–39.0)	0.215
Total bilirubin (mg/dL)	0.5 (0.4–0.7)	0.6 (0.4–0.7)	0.678
CRP (mg/dL)	0.09 (0.04–0.27)	0.07 (0.03–0.19)	0.226
NLR	3.3 (2.5–4.9)	2.8 (2.2–4.1)	0.053
PNI	45.9 (42.4–48.5)	46.9 (43.7–48.9)	0.417

Values are presented as number (%) or median (interquartile range).
SPPB scores and number of sarcopenia include missing values.
BMI, body mass index; SPPB, Short Physical Performance Battery; SMI, skeletal muscle index; ASA-PS, American Society of Anesthesiologists Physical Status classification; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

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in postoperative complications, length of hospital stay, or pathological outcomes. Linear mixed-effects model analyses demonstrated that the lipid (+) group had significantly higher overall postoperative levels of white blood cell count (WBC; P=0.033), neutrophils (P=0.007), C-reactive protein (CRP; P=0.002), and neutrophil-to-lymphocyte ratio (NLR; P=0.003) compared with the lipid (–) group (Table 4). These results indicate that patients who received SO-ILE exhibited higher systemic inflammatory markers across the postoperative course. Although contrast analyses showed no statistically significant differences at any specific postoperative time point, the overall longitudinal trends differed between groups. Hepatic markers, including AST, alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), and total bilirubin, did not differ significantly between the two groups, suggesting that SO-ILE administration was not associated with clinically relevant hepatic injury.

Table 2. Surgical outcomes

Variable	Lipid (+) group (n=33)	Lipid (–) group (n=122)	P-value
Operation time (min)	419 (365–458)	434 (383–482)	0.064
Intraoperative blood loss (mL)	160 (60–225)	180 (90–370)	0.057
Lymphadenectomy			0.194
Three fields	24 (72.7)	101 (82.8)	
Two fields	9 (27.3)	21 (17.2)	
Reconstruction route			0.643
Posterior mediastinal route	32 (97.0)	116 (95.1)	
Non-posterior mediastinal route	1 (3.0)	6 (4.9)	

Values are presented as median (interquartile range) or number (%).

Nutrition

Fig. 2 illustrates postoperative nutritional intake. In the lipid (+) group, not only fat intake but also total energy and amino acid administration during the observation periods were significantly higher than in the lipid (–) group. No significant differences were observed in intravenous fluid volume at any observational time point between the two groups.

Table 3. Postoperative short-term and pathological outcomes

Variable	Lipid (+) group (n=33)	Lipid (–) group (n=122)	P-value
Postoperative complications[a]			
CD grade ≥II	19 (57.6)	69 (56.6)	0.917
CD grade ≥III	10 (30.3)	31 (25.4)	0.572
Pneumonia	7 (21.2)	18 (14.8)	0.371
Anastomotic leakage	8 (24.2)	19 (15.6)	0.244
Superficial surgical site infection	3 (9.1)	6 (4.9)	0.363
Postoperative hospital stay (day)	22 (16–33)	18 (17–26)	0.774
Pathological T factor			0.672
pT1 or 2	22 (66.7)	86 (70.5)	
pT3 or 4	11 (33.3)	36 (29.5)	
Lymph node metastasis	20 (60.6)	56 (45.9)	0.134
Presence	13 (39.4)	66 (54.1)	
Absence			
Pathological stage			0.453
pStage I	9 (27.3)	47 (38.5)	
pStage II	5 (15.2)	24 (19.7)	
pStage III	15 (45.5)	40 (32.8)	
pStage IV	4 (12.1)	11 (9.0)	

Values are presented as number (%) or median (interquartile range).
[a]Clavien-Dindo classification (CD) reflects the highest-grade complication per patient.

Table 4. Linear mixed-effects models of postoperative hematological findings (lipid (–) group vs. lipid (+) group)

	Group main effect (95% CI)	P-value	Timexgroup interaction, F (df)	P-value	Time-point contrasts		
					Time-point	Estimate (95% CI)	P-value
White blood cells (/μL)	–398 (–764 to –33)	0.033	1.31 (3,430)	0.269			
Neutrophils (/μL)	–479 (–826 to –132)	0.007	1.04 (3,426)	0.375			
Lymphocytes (/μL)	51 (–19 to 122)	0.150	0.72 (3,419)	0.540			
Hemoglobin (g/dL)	0.1 (–0.2 to 0.3)	0.604	1.56 (3,423)	0.197			
Serum albumin (g/dL)	0.0 (–0.0 to 0.1)	0.248	1.31 (3,428)	0.268			
AST (U/L)	–0.1 (–1.8 to 1.7)	0.941	2.19 (3,425)	0.089	Week 1	1.5 (–0.6 to 3.6)	0.159
ALT (U/L)	0.9 (–3.2 to 5.0)	0.660	0.49 (3,427)	0.686			
γ-GTP (U/L)	–14 (–26 to –3)	0.180	2.35 (3,402)	0.072	Week 2	–11 (–22 to 0)	0.053
Total bilirubin (mg/dL)	–0.0 (–0.1 to 0.1)	0.862	0.58 (3,392)	0.630			
CRP (mg/dL)	–0.7 (–1.1 to –0.3)	0.002	2.78 (3,433)	0.041	Week 2	–0.5 (–1.0 to 0.0)	0.069
NLR	–1.1 (–1.8 to –0.4)	0.003	2.11 (3,425)	0.098	Week 1	–0.5 (–1.2 to 0.1)	0.086
PNI	0.6 (–0.2 to 1.3)	0.132	0.33 (3,426)	0.805			

CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

Body composition

PBWL at 2 weeks after surgery was significantly lower in the lipid (+) group than in the lipid (–) group (Fig. 3). In addition, absence of SO-ILE administration was identified as the only risk factor for PBWL greater than 5% at 2 weeks after RA-TME in univariate analysis (Table 5). However, no significant risk factors were identified in multivariate analyses (Table 6). Body composition parameters, including muscle mass and body fat percentage, assessed at 4 weeks after surgery did not differ significantly between the two groups (Supplement 1).

Long-term prognosis

Among patients with pathological Stage II disease (n=29), the 2-year RFS rate was 100% (5/5) in the lipid (+) group and 60.9% (14/23) in the lipid (–) group. However, this difference did not reach statistical significance (Fisher exact test, P=0.090; log-rank test, P=0.119). In the overall cohort, as well as among patients with pathological Stage I, III, or IV disease,

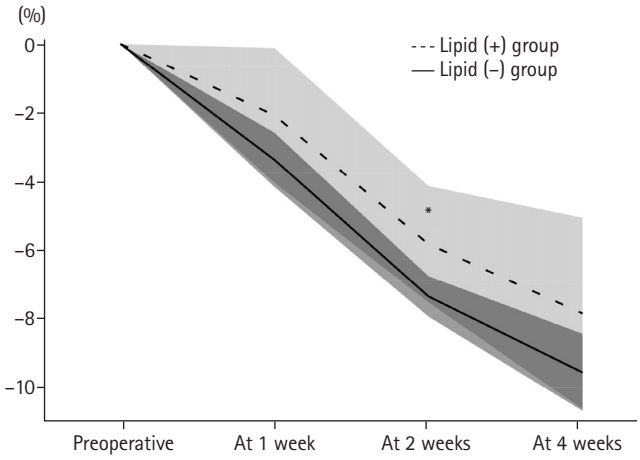

Fig. 3. Postoperative body weight change. Mean percentage change in body weight from baseline over time in the lipid (+) and lipid (–) groups, presented as mean±confidence interval. *P-values <0.05 compared with the lipid (–) group at each time point (linear mixed-effects models).

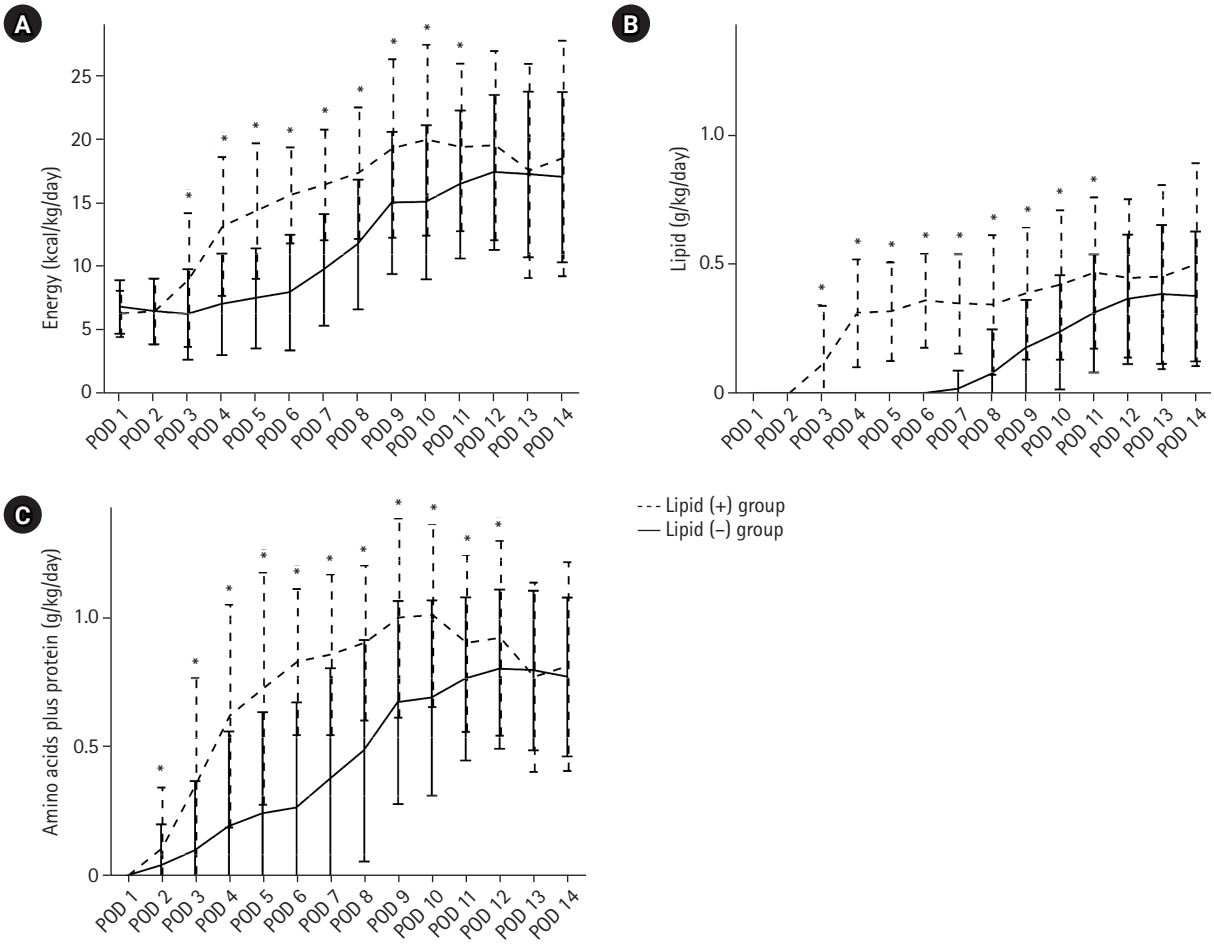

Fig. 2. Postoperative nutritional components. Total administered amounts of energy (A), lipid (B), and amino acids plus protein (C) were compared between the two groups from postoperative day (POD) 1 to POD 14. Data are presented as mean±standard deviation. *P-values <0.05 compared with the lipid (–) group at each time point (linear mixed-effects models).

no significant differences in OS or RFS were observed between the lipid (+) and lipid (–) groups.

Discussion

Key results

The most important finding of this study was that SO-ILE administration was associated with less PBWL at 2 weeks after RA-TME, without an increased risk of postoperative complications. However, this association does not necessarily indicate a direct causal effect of SO-ILE administration itself. In this study, addition of SO-ILE to PPN during the first postoperative week after RA-TME was associated with reduced early PBWL. Specifically, PBWL at 2 weeks was significantly lower in the lipid (+) group than in the lipid (–) group, and the proportion of patients with PBWL ≥5% at 2 weeks was also significantly lower in the lipid (+) group. To our knowledge, this study uniquely reports a short-term benefit of SO-ILE–supplemented PPN in esophageal cancer patients undergoing minimally invasive esophagectomy, with respect to maintenance of body weight.

Table 5. PBWL in the first 2 weeks after RA-TME

Variable	PBWL in 2 wk RA-TME, No. (%)		P-value
	≥5% (n=106)	<5% (n=31)	
Sex			0.093
Male	92 (86.8)	23 (74.2)	
Female	14 (13.2)	8 (25.8)	
Age ≥75 yr	20 (18.9)	9 (29.0)	0.223
BMI (kg/m^2)			
Obesity (≥25)	17 (16.0)	5 (16.1)	0.990
Underweight (≤18.5)	12 (11.3)	6 (19.4)	0.244
Preoperative chemotherapy	52 (49.1)	12 (38.7)	0.310
ASA-PS			0.059
I or II	100 (94.3)	26 (83.9)	
III	6 (5.7)	5 (16.1)	
Lymphadenectomy			0.327
Three fields	22 (20.8)	4 (12.9)	
Two fields	84 (79.2)	27 (87.1)	
Reconstruction route			0.218
Posterior mediastinal route	101 (95.3)	31 (100.0)	
Non-posterior mediastinal route	5 (4.7)	0	
Pneumonia	16 (15.1)	6 (19.4)	0.570
Anastomotic leakage	21 (19.8)	5 (16.1)	0.646
Superficial surgical site infection	7 (6.6)	2 (6.5)	0.976
Pathological T factor			0.785
pT1 or 2	30 (28.3)	8 (25.8)	
pT3 or 4	76 (71.7)	23 (74.2)	
Lymph node metastasis			0.349
Presence	48 (45.3)	17 (54.84)	
Absence	58 (54.7)	14 (45.16)	
Postoperative complications[a]			
CD grade ≥II	62 (58.5)	20 (64.5)	0.547
CD grade ≥III	29 (27.4)	10 (32.3)	0.595
Lipid use	19 (17.9)	11 (35.5)	0.038
Amino acid use	45 (42.5)	18 (58.1)	0.125
Total energy until POD 6 ≥3,000 kcal	34 (32.1)	14 (45.2)	0.179

PBWL, postoperative body weight loss; RA-TME, robot-assisted radical transmediastinal esophagectomy; BMI, body mass index; ASA-PS, the American Society of Anesthesiologists Physical Status classification; CD, Clavien-Dindo classification; POD, postoperative day.
[a]CD reflects the highest-grade complication per patient.

Interpretation/comparison with previous studies

The precise mechanism underlying prevention of PBWL in the lipid (+) group cannot be determined from the present study. Nevertheless, fat is essential for the synthesis of various structural components and mediators that regulate responses to surgical stress. In addition to glucose and amino acids, wound healing requires an adequate lipid supply. Accordingly, it is plausible that SO-ILE administration contributed, at least in part, to attenuation of early PBWL.

In Japan, intravenous lipid administration has traditionally been minimized because high-dose SO-ILE provision has been shown to cause severe inflammation, cholestasis, and liver disease [19]. Consistent with these historical concerns, our linear mixed-effects analyses demonstrated that inflammatory markers were generally higher in the lipid (+) group than in the lipid (–) group, as reflected by significantly elevated WBC counts, CRP levels, neutrophil counts, and NLR values across the postoperative course. However, no significant differences were observed at any individual postoperative time point, and liver-related parameters, including AST, ALT, γ-GTP, and total bilirubin, did not differ significantly between groups. These findings suggest that although SO-ILE administration may modestly elevate systemic inflammatory markers at the group level, the relatively low dose used in this

Table 6. Logistic regression analysis of risk factors for the rate of PBWL in 2 weeks after RA-TME ≥5%

	Multivariate analysis	
	OR (95% CI)	P-value
Lipid-free PN	2.22 (0.89–5.57)	0.088
Male sex	2.12 (0.76–5.88)	0.150
ASA ≤2	2.93 (0.78–10.97)	0.110

PBWL, postoperative body weight loss; RA-TME, robot-assisted radical transmediastinal esophagectomy; OR, odds ratio; CI, confidence interval; PN, parenteral nutrition; ASA, American Society of Anesthesiologists.

study did not induce clinically meaningful hepatic injury or overt inflammatory complications. Furthermore, SO-ILE administration was not associated with an increased incidence of postoperative complications in the lipid (+) group, possibly because the administered dose was relatively small, approximately 0.35 g of lipid per kilogram of body weight per day during PPN. This dosage falls within the generally accepted safe range for SO-ILE administration and is sufficient to supply essential fatty acids [20]. Previous studies have reported detrimental effects of higher SO-ILE doses, approximately 1 g/kg/day, including prolonged intensive care unit stays and excessive inflammation in critically ill patients [21,22]. In contrast, the lower SO-ILE dose used in the present study appears to be both safe and tolerable in patients exposed to surgical stress.

In addition, the contribution of increased total energy and amino acid provision to postoperative body weight maintenance in the lipid (+) group cannot be excluded. It remains unclear whether reduced PBWL was attributable to SO-ILE administration itself or to differences in overall energy or amino acid delivery. Although univariate analysis identified SO-ILE administration as a significant factor associated with reduced PBWL, this association was no longer significant in multivariate analysis. Accordingly, we cannot emphasize an independent effect of SO-ILE on postoperative body weight change. Conversely, because cumulative differences in total energy, fat, and amino acid intake increased progressively over time, these nutritional differences themselves may have contributed to the observed reduction in PBWL. Owing to the limited sample size, we were unable to perform analyses matched for total energy and amino acid provision between groups. Future studies with controlled and equivalent energy and amino acid delivery will be necessary to clarify the independent effect of SO-ILE administration.

Reduced PBWL was not associated with lower rates of postoperative complications or shorter hospital stays in the present study. Beyond its caloric contribution, lipid emulsion may exert biological effects. Polyunsaturated fatty acids have been shown to modulate inflammatory pathways and may attenuate postoperative catabolism [14]. Although the present study was not designed to investigate mechanistic pathways, these potential effects warrant further investigation. Because PBWL has been reported to adversely affect long-term survival after esophagectomy in cancer patients, PPN supplemented with SO-ILE may contribute to improved long-term outcomes [23]. Indeed, among patients with pathological Stage II disease, RFS at 2 years tended to be better in the lipid (+) group than in the lipid (–) group, although this difference did not reach statistical significance. Given the small sample size, further accumulation of cases will be required to evaluate this potential association.

Limitations

First, this study had a retrospective, single-center design with a relatively small sample size, which limits generalizability. The imbalance in group size (lipid [+] group, n=33; lipid [–] group, n=122) reduces statistical power and may have introduced bias. In particular, the number of patients with body composition measurements at 4 weeks was limited, as the first postoperative outpatient visit was not routinely scheduled at this time point. Second, the decision to administer SO-ILE was made by attending physicians in the absence of a standardized nutritional protocol. Some physicians may have paid closer attention to intravenous nutritional composition and prescribed SO-ILE, whereas others may not have prioritized nutritional management. Third, long-term outcomes were evaluated only up to 2 years after surgery. Fourth, because total energy and amino acid provision differed between groups, we cannot exclude the possibility that PBWL was influenced primarily by overall nutrient supply rather than by lipid administration per se. Finally, the present data suggest only a potential benefit of SO-ILE–supplemented PPN compared with SO-ILE–free PPN, and the optimal postoperative nutritional strategy following this newer esophagectomy procedure remains uncertain.

Conclusion

Although SO-ILE administration did not affect postoperative morbidity, it was associated with reduced body weight loss after RA-TME. While these findings should be interpreted cautiously in light of the study's limitations, SO-ILE may have the potential to mitigate early PBWL after less invasive RA-TME. Future prospective randomized controlled trials are warranted to confirm these findings and to define optimal perioperative nutritional strategies.

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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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None.

Supplementary materials

Supplementary materials can be found via https://doi.org/10.15747/ACNM.25.0030

Supplement 1. Body composition and muscle strength in 1 month after surgery.

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Original Article

Association between the calcium-to-phosphorus ratio and early hypophosphatemia in preterm infants receiving parenteral nutrition in Korea: a retrospective cohort study

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Abstract

Purpose: This study aimed to evaluate the association between the calcium-to-phosphorus (Ca/P) ratio and serum phosphate levels in preterm infants receiving total parenteral nutrition (TPN) and to explore Ca/P ratio ranges associated with hypophosphatemia.
Methods: We retrospectively reviewed the medical records of preterm infants admitted to the neonatal intensive care unit at Ajou University Hospital between January 2022 and June 2024. The review focused on TPN composition and serum electrolyte changes during the first week of life. Based on the cumulative Ca/P ratio during this period, infants were categorized into two groups: Ca/P-Low (mass ratio ≤1.3) and Ca/P-High (mass ratio >1.3).
Results: A total of 117 preterm infants were included in the analysis (Ca/P-Low group, n=46; Ca/P-High group, n=71). During the first week of life, the cumulative phosphorus deficit was significantly greater in the Ca/P-High group (61.4 mg/kg vs. 8.5 mg/kg; P<0.001). By day of life (DOL) 7, both hypophosphatemia and severe hypophosphatemia had increased markedly in the Ca/P-High group compared with DOL 3. In the Ca/P-High group, the incidence of hypophosphatemia increased from 44.4% on DOL 3 to 75.0% on DOL 7, while the incidence of severe hypophosphatemia increased from 4.8% to 23.1%.
Conclusion: These findings suggest that parenteral nutrition strategies may benefit from phase-adapted Ca/P ratios rather than a fixed ratio during the first week of life. A higher ratio may be considered during DOL 0–2, whereas a lower ratio may be considered during DOL 3–6, particularly when overall calcium and phosphorus supply is suboptimal.

Keywords: Calcium; Hypophosphatemia; Parenteral nutrition; Premature infants; Refeeding syndrome

Introduction

Background

Very low birth weight preterm infants, including those who are small for gestational age (SGA), often have inadequate nutrient stores as a result of prematurity, placental insufficiency, or impaired intrauterine growth [1,2]. Total parenteral nutrition (TPN) is essential to prevent nutrient deficiencies in very low birth weight preterm infants. However, early aggressive TPN may predispose physiologically immature and vulnerable infants to refeeding syndrome, which is characterized by hypophosphatemia during the first days of life [2-7].

When nutritional support is initiated after birth in undernourished infants, metabolism shifts toward cellular anabolism and is accompanied by increased insulin secretion. By stimulating ATPase activity, insulin enhances ATP produc-

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tion, which markedly increases cellular phosphate demand. If adequate phosphate is not supplied, this increased demand may lead to rapid depletion of intracellular and extracellular phosphate stores [1,2,8]. In the presence of intracellular phosphate deficiency, this transcellular shift can result in pronounced acute hypophosphatemia [6,9].

Phosphorus is essential for ATP synthesis, acid-base buffering, and the function of numerous enzymes [1,10,11]. Consequently, phosphorus deficiency may lead not only to critical cellular dysfunction but also to increased insulin resistance, sepsis, neurodevelopmental impairment, chronic lung disease, and mortality [1,3,4,6,7,11,12]. These risks are of particular concern in preterm infants, whose gastrointestinal and renal capacities for calcium and phosphate absorption are immature [7,13,14].

The ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommend supplying calcium at 32–80 mg/kg and phosphate at 31–62 mg/kg during the first days of life, with a molar calcium-to-phosphorus (Ca/P) ratio of 0.8–1.0 (equivalent to a mass ratio of 1.0–1.3) to prevent early hypophosphatemia [15]. However, fluid restriction is often required in preterm infants with cardiac or pulmonary conditions, making it difficult to provide adequate calcium and phosphate without precipitation [13].

Objectives

Therefore, this study aimed to evaluate the association between guideline-recommended Ca/P ratios and hypophosphatemia, particularly in clinical settings where calcium and phosphate intake is relatively suboptimal. We also examined the relationship between cumulative phosphorus deficit and serum phosphate levels and assessed potential threshold values associated with hypophosphatemia.

Methods

Ethics statement

Ethics approval for this study was obtained from the Institutional Review Board (IRB) of Ajou University Hospital, Suwon, Korea (No. IRB-DB-2024-367). The requirement for written informed consent was waived by the IRB.

Study design

This was a single-center retrospective cohort study with repeated outcome assessments during early life.

Setting

We retrospectively reviewed the medical records of preterm infants admitted to the neonatal intensive care unit at Ajou University Hospital between January 2022 and June 2024.

Nutrition protocol

TPN was initiated within 24–36 hours after birth. On the first day of TPN, only calcium was added to the TPN solution at a typical dose of 30–40 mg/kg/day, whereas other electrolytes were withheld. Calcium and phosphate were provided as 10% calcium gluconate and monobasic potassium phosphate, respectively. Because the phosphate preparation contains potassium, phosphate administration was restricted during day of life (DOL) 0–2 when elevated potassium levels or decreased ionized calcium levels were noted on capillary blood gas analysis. Enteral nutrition was initiated with breast milk or preterm formula at 10–20 mL/kg/day as tolerated, and TPN was discontinued once enteral nutrition provided 70%–80% of energy requirements.

Participants

Among infants who received TPN within 24–36 hours after birth, those with a gestational age of <32 weeks or a birth weight of <1,500 g were included in this study. Infants were excluded if they discontinued TPN within 72 hours after birth, died within the first week of life, received peripheral TPN, had major congenital anomalies, or required resuscitation at birth. Based on the cumulative parenteral supply of calcium and phosphate during the first week of life, the infants were divided into two groups: the Ca/P-Low group (mass ratio ≤1.3) and the Ca/P-High group (mass ratio >1.3).

Variables

The primary exposure variable was the Ca/P ratio in parenteral nutrition administered during the first week of life. Infants were categorized into two groups according to this ratio: those receiving a low ratio (≤1.3) and those receiving a high ratio (>1.3). The primary outcome variables were hypophosphatemia, defined as a serum phosphate level of <4.5 mg/dL, and severe hypophosphatemia, defined as a level of <3.0 mg/dL [9], measured on DOL 3 and DOL 7. Prespecified covariates included gestational age, birth weight, SGA, and the total amounts of calcium and phosphorus received from both parenteral and enteral nutrition during the first 3 days (DOL 0–2).

Data sources/measurement

Electrolytes were monitored daily using capillary blood gas analysis. On DOL 3 and DOL 7, however, comprehensive metabolic panels were performed instead. Because phosphate levels were measured only in the comprehensive

metabolic panels, total serum calcium levels were used for the analysis. Based on the capillary blood gas and comprehensive metabolic panel results obtained early each morning, TPN was revised and administered beginning at 2 p.m. on the same day. Accordingly, laboratory results on DOL 3 were assumed to reflect TPN administered during DOL 0–2, whereas results on DOL 7 were assumed to reflect TPN administered during DOL 3–6. Missing outcome data were primarily attributable to discontinuation of TPN before the relevant time point or to the absence of scheduled laboratory testing on that day. Analyses at each time point were therefore performed using a complete-case approach.

Phosphorus requirements were estimated using the following formula, which accounts for amino acid and calcium intake [10]:

P (mg/kg/day)=Ca (mg/kg/day)/2.15 + (amino acid [g/kg/day]–1.3)×0.8×12.3

The phosphorus deficit was calculated by subtracting the actual amount supplied via TPN from the estimated requirement derived from this formula. A positive value indicated a deficit, whereas a negative value indicated an excess.

Bias

To minimize selection bias, we included all eligible preterm infants who received parenteral nutrition within 24–36 hours after birth throughout the study period. Exposure and outcomes were defined a priori using standardized prescription records and laboratory assays. Confounding was mitigated through prespecified covariate adjustment.

Study size

The study size was determined by the number of infants who met the inclusion criteria within the predefined period; therefore, a formal a priori power calculation was not performed. To maximize precision, all eligible infants were included. The sample yielded a sufficient number of outcome events to support multivariable modeling (with at least 10 events per parameter) and subgroup analyses.

Statistical methods

Continuous variables were analyzed using the independent t-test or the Mann-Whitney U test, whereas categorical variables were analyzed using the chi-square test or Fisher exact test, as appropriate. Multivariable logistic regression was performed to identify factors associated with early hypophosphatemia on DOL 3. The model was adjusted for gestational age, birth weight, SGA, and total phosphorus and calcium intakes during DOL 0–2. Calcium and phosphorus intakes were entered separately rather than as the Ca/P ratio to avoid multicollinearity. Linear regression analysis was performed to evaluate the association between cumulative phosphorus deficit and serum calcium and phosphate levels. The predictive value of cumulative phosphorus deficit for hypophosphatemia occurring at any time during the first week of life was assessed using receiver operating characteristic (ROC) curve analysis. The association between severe hypophosphatemia and complications in preterm infants was evaluated using logistic regression analysis. All statistical analyses were performed using SPSS Statistics version 29.0.2.0 (IBM Corp.), and a P-value of <0.05 was considered statistically significant.

Results

Participants

A total of 166 preterm infants with a gestational age of <32 weeks or a birth weight of <1,500 g who received parenteral nutrition after birth were initially enrolled. Of these, 37 infants who received peripheral TPN, five who died within 7 days after birth, four who discontinued TPN within 72 hours after birth, and three who had congenital anomalies or required immediate resuscitation after birth were excluded. Thus, 117 infants were included in the final analysis and divided into two groups according to the Ca/P ratio: the Ca/P-Low group (mass ratio ≤1.3; n=46) and the Ca/P-High group (mass ratio >1.3; n=71) (Supplement 1). Although most variables did not differ significantly between the two groups, the Ca/P-Low group had a significantly higher proportion of SGA infants (15.2% vs. 5.6%; P=0.026) and a higher incidence of culture-proven sepsis (21.7% vs. 5.6%; P=0.009) than the Ca/P-High group (Table 1).

Association of the Ca/P ratio with phosphorus deficit and serum phosphate levels

We analyzed nutritional support provided through TPN and enteral nutrition during the first week of life by dividing the period into two phases: DOL 0–2 and DOL 3–6 (Table 2). Although enteral nutrition was administered concurrently, the Ca/P ratio of parenteral nutrition was selected as the primary exposure variable because the Ca/P ratio of enteral nutrition is fixed. There were no significant differences between the two groups in the amounts of fluid, calories, amino acids, glucose, or lipids administered during either phase. In the early phase (DOL 0–2), calcium intake was higher in the Ca/P-High group (36.0 mg/kg/day vs. 30.0 mg/kg/day; P=0.019), whereas phosphorus intake was minimal in both groups, resulting in substantial phosphorus deficits (20.8 mg/kg/day vs. 18.1 mg/kg/day; P=0.011). In the later phase (DOL 3–6),

Table 1. Demographic characteristics and neonatal outcomes

Variable	Ca/P-Low (n=46)	Ca/P-High (n=71)	P-value
Demographic characteristics			
Gestational age (wk)	28.5 (26.0–30.0)	28.0 (27.0–29.0)	0.966
Birth weight (g)	1,045 (820–1,380)	1,130 (1,003–1,385)	0.063
Male sex	32 (69.6)	40 (56.3)	0.151
SGA	7 (15.2)	4 (5.6)	0.026
Cesarean section	38 (82.6)	47 (66.2)	0.052
PROM	11 (23.9)	27 (38.0)	0.111
Antenatal steroids	28 (60.9)	52 (73.2)	0.160
Preeclampsia/eclampsia	14 (30.4)	14 (19.7)	0.185
Apgar score, 1 min	5 (3–6)	5 (4–6)	0.305
Apgar score, 5 min	7 (6–7)	7 (6–8)	0.450
Neonatal outcomes			
Duration of TPN (day)	17.5 (8.0–32.0)	11.0 (7.0–21.0)	0.065
Days needed to regain birth weight (day)	10.2±4.7	10.9±4.2	0.373
Mortality	5 (10.9)	3 (4.2)	0.260
Culture-proven sepsis	10 (21.7)	4 (5.6)	0.009
Moderate-to-severe BPD	10 (23.8)	20 (29.0)	0.311
IVH G3 and higher	3 (6.5)	5 (7.0)	>0.999
ROP with laser or anti-VEGF therapy	4 (9.8)	3 (4.3)	0.129
NEC G2 or higher	3 (6.5)	1 (1.4)	0.298
Rickets	16 (40.0)	30 (43.5)	0.107
Nephrocalcinosis	4 (9.1)	8 (11.6)	0.763

Values are presented as median (interquartile range), number (%), or mean±SD.
Ca/P, calcium-to-phosphorus; SGA, small for gestational age; PROM, premature rupture of membranes; TPN, total parenteral nutrition; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor; NEC, necrotizing enterocolitis; SD, standard deviation.
A P-value <0.05 was considered significant.

calcium intake remained higher in the Ca/P-High group (15.6 mg/kg/day vs. 6.0 mg/kg/day; P<0.001), whereas phosphorus intake was significantly greater in the Ca/P-Low group (24.8 mg/kg/day vs. 15.5 mg/kg/day; P<0.001). Accordingly, the phosphorus deficit declined to –3.7 mg/kg/day in the Ca/P-Low group and 6.2 mg/kg/day in the Ca/P-High group (P<0.001). Consequently, the cumulative phosphorus deficit during the first week of life was significantly greater in the Ca/P-High group than in the Ca/P-Low group (61.4 mg/kg vs. 8.5 mg/kg; P<0.001).

Of the 117 eligible infants, serum phosphate measurements were available for 102 on DOL 3 and 81 on DOL 7 (Table 3). On DOL 3, the Ca/P-Low group had a significantly lower mean serum phosphate level than the Ca/P-High group (3.7±1.4 mg/dL vs. 4.7±1.1 mg/dL; P<0.001), and the mean value in the Ca/P-Low group was within the hypophosphatemic range. Consistent with this finding, the incidences of both hypophosphatemia and severe hypophosphatemia were significantly higher in the Ca/P-Low group (79.5% vs. 44.4%; P=0.002 and 28.2% vs. 4.8%; P=0.003). On DOL 7, however, the mean serum phosphate level increased to 4.0 mg/dL in the Ca/P-Low group and decreased to 3.9 mg/dL in the Ca/P-High group, with no significant difference between the groups (P=0.965). Both values remained within the hypophosphatemic range. Compared with DOL 3, the incidence of hypophosphatemia decreased slightly in the Ca/P-Low group but increased markedly in the Ca/P-High group, with no significant between-group difference (65.5% vs. 75.0%; P=0.050). Although the incidence of severe hypophosphatemia remained higher in the Ca/P-Low group (34.5% vs. 23.1%; P=0.041), the increase over time was greater in the Ca/P-High group. Serum calcium and albumin levels measured on DOL 3 and DOL 7 did not differ significantly between the two groups.

Multivariable logistic regression analysis showed that higher early calcium intake and lower birth weight were associated with early hypophosphatemia on DOL 3. Gestational age, SGA, and phosphorus intake were not significantly associated with the outcome (Table 4).

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Table 2. Comparison of nutritional composition according to the Ca/P ratio

Variable	Ca/P-Low	Ca/P-High	P-value
Parenteral nutrition (DOL 0–2)			
Fluid (mL/kg/day)	70.0 (60.0 to 80.0)	70.0 (60.0 to 80.0)	0.847
Energy (kcal/kg/day)	53.7±9.4	51.3±10.7	0.053
Amino acids (g/kg/day)	2.0 (2.0 to 2.5)	2.0 (2.0 to 2.5)	0.126
Glucose (g/kg/day)	7.9 (7.2 to 8.6)	7.9 (7.2 to 8.6)	0.209
Lipid (g/kg/day)	1.5 (1.0 to 1.5)	1.0 (1.0 to 1.5)	0.455
Calcium (mg/kg/day)	30.0 (18.0 to 36.0)	36.0 (24.0 to 42.0)	0.019
Phosphate (mg/kg/day)	0 (0 to 15.5)	0 (0 to 0)	0.010
Parenteral nutrition (DOL 3–6)			
Fluid (mL/kg/day)	85.0 (65.0 to 95.4)	83.0 (70.0 to 97.5)	0.780
Energy (kcal/kg/day)	72.6±14.1	73.5±16.4	0.576
Amino acids (g/kg/day)	2.8 (2.5 to 3.0)	3.0 (2.5 to 3.0)	0.866
Glucose (g/kg/day)	10.1 (8.6 to 10.8)	10.1 (8.6 to 11.5)	0.494
Lipid (g/kg/day)	2.5 (2.0 to 2.5)	2.5 (2.0 to 3.0)	0.263
Calcium (mg/kg/day)	6.0 (0 to 18.0)	15.6 (6.0 to 24.0)	<0.001
Phosphate (mg/kg/day)	24.8 (15.5 to 31.0)	15.5 (12.4 to 15.5)	<0.001
Enteral nutrition (DOL 0–2)			
Fluid (mL/kg/day)	3.4 (0 to 9.3)	6.6 (0 to 14.5)	0.002
Energy (kcal/kg/day)	2.4 (0 to 6.5)	4.7 (0 to 9.9)	0.002
Amino acids (g/kg/day)	0.1 (0 to 0.2)	0.1 (0 to 0.3)	0.005
Calcium (mg/kg/day)	3.6 (0 to 10.1)	7.2 (0 to 15.4)	0.002
Phosphate (mg/kg/day)	1.9 (0 to 5.2)	3.7 (0 to 7.9)	0.002
Enteral nutrition (DOL 3–6)			
Fluid (mL/kg/day)	8.3 (0 to 31.2)	12.9 (0 to 30.4)	0.490
Energy (kcal/kg/day)	5.8 (0 to 21.6)	9.0 (0 to 21.3)	0.492
Amino acids (g/kg/day)	0.2 (0 to 0.6)	0.3 (0 to 0.6)	0.495
Calcium (mg/kg/day)	8.8 (0 to 31.9)	12.6 (0 to 31.2)	0.514
Phosphate (mg/kg/day)	4.5 (0 to 16.4)	6.5 (0 to 16.1)	0.500
Total intake (PN+EN, DOL 0–2)			
Calcium (mg/kg/day)	36.2 (23.2 to 43.2)	42.0 (34.6 to 49.0)	<0.001
Phosphate (mg/kg/day)	5.2 (0.0 to 18.7)	5.3 (0.3 to 15.5)	0.705
Total intake (PN+EN, DOL 3–6)			
Calcium (mg/kg/day)	24.4 (6.0 to 45.2)	33.0 (18.0 to 48.4)	0.004
Phosphate (mg/kg/day)	31.2 (20.1 to 46.5)	24.0 (15.5 to 34.4)	<0.001
Theoretical calculations for phosphorus intake (PN, DOL 0–2)			
Estimated phosphorus need (mg/kg/day)	22.3 (18.1 to 25.8)	23.6 (18.7 to 26.4)	0.126
Deficit of phosphorus intake (mg/kg/day)	18.1 (4.4 to 23.6)	20.8 (8.2 to 26.4)	0.011
Theoretical calculations for phosphorus intake (PN, DOL 3–6)			
Estimated phosphorus need (mg/kg/day)	18.8 (13.4 to 22.8)	21.6 (16.7 to 25.8)	<0.001
Deficit of phosphorus intake (mg/kg/day)	−3.7 (−15.5 to 3.9)	6.20 (−0.3 to 12.4)	<0.001
Theoretical calculations for phosphorus intake (PN, DOL 0–6)			
Estimated phosphorus need (mg/kg/day)	20.2 (15.3 to 25.1)	23.0 (17.4 to 26.4)	<0.001
Deficit of phosphorus intake (mg/kg/day)	2.1 (−9.3 to 11.1)	9.6 (2.6 to 19.5)	<0.001
Cumulative phosphorus deficit (mg/kg)	8.5±41.6	61.4±33.7	<0.001

Values are presented as median (interquartile range) or mean±SD.
Ca/P, calcium-to-phosphorus; DOL, day of life; PN, parenteral nutrition; EN, enteral nutrition; SD, standard deviation.
A P-value <0.05 was considered significant.

Relationship between cumulative phosphorus deficit and hypophosphatemia

The relationship between cumulative phosphorus deficit during the first week of life and serum calcium and phosphate levels was analyzed using linear regression (Fig. 1). Cumulative phosphorus deficit was positively correlated with serum calcium levels (r^2=0.204) and negatively correlated with serum phosphate levels (r^2=0.089), indicating that greater phosphorus deficits were associated with higher serum calcium and lower serum phosphate levels (both P<0.001).

Table 3. Serum biochemical parameters on DOL 3 and 7 according to the Ca/P ratio

Variable	Ca/P-Low	Ca/P-High	P-value
DOL 3 (n=102)			
Serum phosphate levels (mg/dL)	3.7±1.4	4.7±1.1	<0.001
Serum calcium levels (mg/dL)	9.7±0.9	9.5±1.0	0.233
Serum albumin (g/dL)	3.2±0.3	3.3±0.4	0.169
Hypophosphatemia[a]	31 (79.5)	28 (44.4)	0.002
Severe hypophosphatemia[b]	11 (28.2)	3 (4.8)	0.003
DOL 7 (n=81)			
Serum phosphate levels (mg/dL)	4.0 (2.4–4.8)	3.9 (3.0–4.5)	0.965
Serum calcium levels (mg/dL)	9.9±1.0	10.2±1.1	0.308
Serum albumin (g/dL)	3.1±0.5	3.3±0.6	0.127
Hypophosphatemia[a]	19 (65.5)	39 (75.0)	0.050
Severe hypophosphatemia[b]	10 (34.5)	12 (23.1)	0.041

Values are presented as mean±SD, number (%), or median (interquartile range).
DOL, day of life; Ca/P, calcium-to-phosphorus; SD, standard deviation.
[a]Hypophosphatemia: serum phosphate level <4.5 mg/dL.
[b]Severe hypophosphatemia: serum phosphate level <3.0 mg/dL.
A P-value <0.05 was considered significant.

To further illustrate the intake imbalance underlying these associations, the distribution of the Ca/P mass ratio cutoff used for group classification is shown in Supplement 2. ROC curve analysis of cumulative phosphorus deficit for hypophosphatemia during the first week of life yielded an area under the ROC curve (AUC) of 0.694 (95% confidence interval, 0.625–0.763; P<0.001). A cutoff value of 36.1 mg/kg was identified, with a sensitivity of 61.4% and a specificity of 74.2% (Fig. 2).

Clinical outcomes associated with hypophosphatemia

In this study, severe hypophosphatemia was associated with higher odds of culture-proven sepsis (odds ratio [OR]=3.95), intraventricular hemorrhage (IVH) (OR=4.60), and rickets (OR =2.99). No significant associations were observed with necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, nephrocalcinosis, or mortality (Table 5).

Table 4. Multivariable logistic regression for early hypophosphatemia on DOL 3

Variable	Adjusted OR (95% CI)	P-value
Gestational age	1.31 (0.89–1.94)	0.175
Birth weight	1.00 (0.99–1.00)	0.024
SGA	2.31 (0.18–29.51)	0.520
P (PN+EN, DOL 0–2)	0.98 (0.95–1.00)	0.089
Ca (PN+EN, DOL 0–2)	1.02 (1.00–1.04)	0.016

DOL, day of life; OR, odds ratio; CI, confidence interval; SGA, small for gestational age; P, phosphorus; PN, parenteral nutrition; EN, enteral nutrition; Ca, calcium.
The model was adjusted for gestational age, birth weight, SGA, total phosphorus and calcium intakes during DOL 0–2. Ca and phosphorus P intakes are expressed as mg/kg/day.

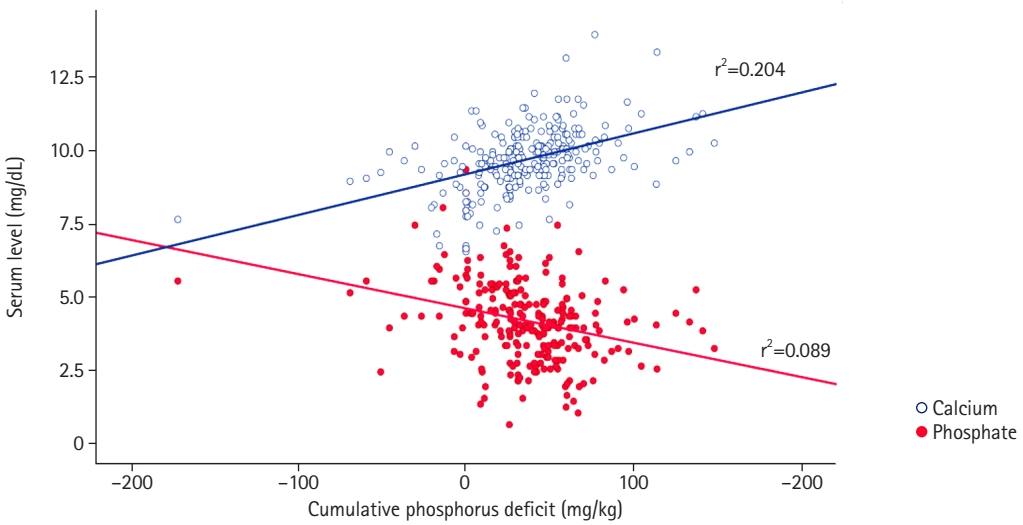

Fig. 1. Relationship between cumulative phosphorus deficit and serum calcium and phosphate levels. Serum calcium levels showed a positive correlation (r^2=0.204), whereas serum phosphate levels showed a negative correlation (r^2=0.089) with cumulative phosphorus deficit. Linear regression analysis was performed.

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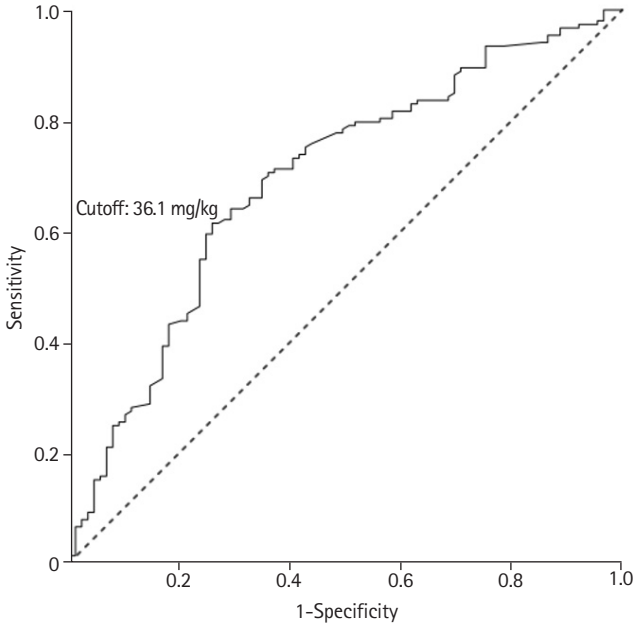

Fig. 2. Receiver operating characteristic (ROC) curve of cumulative phosphorus deficit for predicting hypophosphatemia during the first week of life. The optimal cutoff value was 36.1 mg/kg (sensitivity, 61.4%; specificity, 74.2%; accuracy, 66.1%). The area under the ROC curve was 0.694 (95% confidence interval [CI], 0.625–0.763; P<0.001). A P-value <0.05 was considered significant.

Table 5. Logistic regression analysis of the association between severe hypophosphatemia and neonatal morbidities

Morbidities	OR (95% CI)	P-value
Mortality	2.63 (0.62–11.21)	0.190
Culture-proven sepsis	3.95 (1.25–12.45)	0.019
Moderate-to-severe BPD	1.43 (0.58–3.54)	0.441
IVH G3 or higher	4.60 (1.03–20.46)	0.045
ROP with laser or anti-VEGF therapy	3.75 (0.79–17.86)	0.097
NEC G2 or higher	7.94 (0.80–79.20)	0.078
Rickets	2.99 (1.27–7.07)	0.013
Nephrocalcinosis	2.61 (0.78–8.77)	0.121

OR, odds ratio; CI, confidence interval; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor; NEC, necrotizing enterocolitis; Ca/P, calcium-to-phosphorus.
The Ca/P-Low group was used as the reference category. Estimates may be unstable due to limited events. A P-value <0.05 was considered significant.

Discussion

Key results

Infants in the Ca/P-High group experienced a significantly greater phosphorus deficit over time than those in the Ca/P-Low group (61.4 mg/kg vs. 8.5 mg/kg). By DOL 3, the Ca/P-Low group had a higher incidence of hypophosphatemia than the Ca/P-High group, with 79.5% affected versus 44.4%. Severe hypophosphatemia was also more prevalent in the Ca/P-Low group (28.2% vs. 4.8%). However, by DOL 7, this pattern had shifted in the Ca/P-High group, in which the prevalence of hypophosphatemia increased markedly to 75.0% and severe hypophosphatemia increased to 23.1%. A greater phosphorus deficit was associated with a corresponding decrease in serum phosphate levels. Severe hypophosphatemia was associated with culture-proven sepsis, IVH (grade ≥3), and rickets.

Interpretation/comparison with previous studies

In neonatal parenteral nutrition, calcium and phosphorus administration is constrained by solubility, such that increasing phosphorus provision often necessitates a reduction in calcium. However, because placental calcium transfer ceases at birth and hormonal regulation remains immature, preterm infants are susceptible to early hypocalcemia. Consequently, concerns regarding calcium homeostasis often lead to calcium-dominant supplementation during the early postnatal period, which limits phosphorus provision and results in a high Ca/P ratio, thereby increasing the risk of progressive phosphorus depletion [13,15].

Because baseline serum phosphate levels immediately after birth were not available, the potential influence of preexisting phosphate status on early hypophosphatemia cannot be completely excluded. Therefore, we evaluated factors associated with hypophosphatemia using the earliest available serum phosphate measurement on DOL 3. Lower birth weight was associated with early hypophosphatemia on DOL 3. However, although infants in the Ca/P-Low group tended to have lower birth weight and a higher frequency of SGA, these factors alone do not fully explain the higher incidence of hypophosphatemia. After adjustment for gestational age, birth weight, SGA, and phosphorus intake, higher early calcium intake remained associated with early hypophosphatemia. These findings suggest that relatively high calcium exposure during early life may contribute to phosphate depletion during the first days of life.

This temporal pattern may, in part, reflect clinical decision-making that prioritized phosphorus supplementation while relatively reducing calcium intake during DOL 3–6. The direction of the association differed by time point: the Ca/P-Low group showed lower phosphate levels on DOL 3, whereas the Ca/P-High group showed greater deterioration from DOL 3 to DOL 7, consistent with a larger cumulative deficit. Although the absolute incidence of severe hypophosphatemia on DOL 7 remained higher in the Ca/P-Low group, the increase

over time was more pronounced in the Ca/P-High group.

In the Ca/P-Low group, the mean serum phosphate level on DOL 3 was lower than that in the Ca/P-High group. However, with relatively greater phosphate intake (mass ratio, 0.24) during DOL 3–6, the Ca/P-Low group showed an increasing trend in serum phosphate levels by DOL 7, although the mean level remained within the hypophosphatemic range. Conversely, in the Ca/P-High group, calcium and phosphorus were administered at a mass ratio of 1.0 during DOL 3–6. As a result, serum phosphate levels, which were within the normal range on DOL 3, decreased to the hypophosphatemic range on DOL 7, accompanied by a marked increase in the incidence of both hypophosphatemia and severe hypophosphatemia.

In this study, among the total study population, the incidence of hypophosphatemia was 57.8% and that of severe hypophosphatemia was 13.7% on DOL 3; by DOL 7, these incidences had increased to 71.6% and 27.2%, respectively. These findings indicate a downward trend in serum phosphate levels between DOL 3 and DOL 7, which is consistent with previous reports. In the study by Pajak et al. [4], phosphate was administered via TPN, usually starting on DOL 3 (range, DOL 2–5), which was similar to the protocol used in our study. Among preterm infants who received parenteral nutrition for more than 3 days, 66% showed a downward trend in serum phosphate levels, and this decline was observed up to DOL 10 (median, DOL 6). These findings suggest that hypophosphatemia may occur frequently in preterm infants during the first week of life, highlighting the potential need for more aggressive phosphate supplementation during this period.

Greater cumulative phosphorus deficits were associated with lower serum phosphate levels, and deficits exceeding 36.1 mg/kg were associated with a higher risk of hypophosphatemia. This is consistent with the finding that the Ca/P-High group, which had a cumulative phosphorus deficit of 61.4 mg/kg during the first week of life, showed a decline in serum phosphate levels between DOL 3 and DOL 7, accompanied by a higher incidence of hypophosphatemia and severe hypophosphatemia.

Given the similar parenteral amino acid provision across groups, the cumulative phosphorus deficit in this cohort primarily reflected differences in calcium-phosphorus balance. However, amino acid intake remains an important determinant when estimating the Ca/P ratios required to maintain phosphorus balance. Assuming that the threshold value of 36.1 mg/kg was evenly distributed over the first week of life, we derived a daily phosphorus deficit limit of 5.2 mg/kg/day and used the formula described in the Methods to estimate the range of Ca/P ratios required to maintain phosphorus balance. With calcium supplementation of 30–40 mg/kg/day, the estimated Ca/P mass ratio ranged from 1.4 to 2.0 at an amino acid intake of 2 g/kg/day and decreased to 1.0–1.3 at 3 g/kg/day. However, when these estimates were applied to the actual nutritional intakes observed in this study during DOL 3–6 with an amino acid intake of 3 g/kg/day, the Ca/P ratio was calculated to be approximately 0.3–0.4 for the Ca/P-Low group (calcium, 6 mg/kg/day) and 0.6–0.8 for the Ca/P-High group (calcium, 15.6 mg/kg/day). These findings are consistent with the report by Spath et al. [16], which noted that a lower Ca/P ratio and a relatively higher phosphorus-to-amino acid ratio were associated with the prevention of severe hypophosphatemia. This interpretation is further supported by the observation that, during DOL 3–6, calcium and phosphorus were supplied at a mass ratio of 0.24 in the Ca/P-Low group, which was below the calculated theoretical ratio of 0.3–0.4, resulting in partial correction of serum phosphate levels by DOL 7. In contrast, in the Ca/P-High group, a higher ratio of 1.0, which exceeded the calculated theoretical ratio of 0.6–0.8, was supplied during the same period, leading to a decrease in serum phosphate levels by DOL 7.

Overall, a Ca/P mass ratio of approximately 1.4–2.0 may be appropriate during DOL 0–2, when amino acid intake remains relatively low, whereas a ratio of 1.0–1.3 may be considered during DOL 3–6 as amino acid intake increases. However, given the practical difficulty of providing sufficient calcium and phosphorus in preterm infants, a somewhat lower Ca/P ratio than 1.0–1.3 may be required to mitigate the risk of hypophosphatemia.

Consistent with previous reports, this study also found that severe hypophosphatemia was significantly associated with culture-proven sepsis, IVH (grade ≥3), and rickets. However, unlike some earlier studies, no significant associations were observed with moderate-to-severe bronchopulmonary dysplasia or mortality. Nevertheless, because this study did not account for long-term nutritional support or therapeutic interventions, these findings should be interpreted with caution when evaluating the relationships between severe hypophosphatemia and prematurity-related complications.

A major strength of this study is that it compared two groups with comparable supplies of energy sources, including amino acids. This design allowed evaluation of the association between the Ca/P ratio and serum phosphate levels with less confounding from other parenteral nutrition components. These findings suggest that adjusting the Ca/P ratio according to calcium intake may be associated with a reduced risk of hypophosphatemia, including severe hypophosphatemia, which may substantially affect clinical outcomes in preterm infants.

Limitations

First, this was a single-center retrospective study with a small sample size, which may limit the reliability and generalizability of the findings. In addition, although cumulative phosphorus deficit was associated with hypophosphatemia, it reflects underlying nutritional prescription patterns and showed only modest predictive performance (AUC=0.694); therefore, it should be interpreted as an exploratory rather than a definitive predictor. Likewise, the multivariable analysis, although conducted with at least 10 events per variable, may still have been affected by multicollinearity and should therefore be interpreted with caution. Consistent with previous reports by Pajak et al. [4] and Spath et al. [16], insufficient phosphorus intake contributes to the development of hypophosphatemia. In this study, because calcium and phosphorus intakes were lower than the guideline recommendations [15], the incidence of hypophosphatemia may have been relatively high, and the Ca/P ratio required for its correction may have appeared lower than expected. Therefore, further studies are needed to evaluate the effect of adjusting the Ca/P ratio according to the amounts of calcium and phosphorus supplied on the prevention and correction of hypophosphatemia in preterm infants.

Conclusion

The Ca/P ratio was associated with hypophosphatemia in preterm infants receiving parenteral nutrition. During DOL 0–2, when amino acid intake is relatively low, a higher Ca/P ratio may help maintain mineral balance. However, as amino acid intake increases during DOL 3–6, a lower Ca/P ratio may help reduce the risk of progressive phosphorus depletion and hypophosphatemia. These findings suggest that phase-adapted Ca/P ratios, rather than a fixed ratio throughout the first week of life, may represent a reasonable approach, particularly when overall calcium and phosphorus supply is suboptimal.

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Authors' contribution

Conceptualization: MH. Data curation: MH. Formal analysis: MH. Supervision: JOK, JHL Writing–original draft: MH, YAS. Writing–review & editing: MH, JOK, JHL. 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

Contact the corresponding author for research data availability.

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None.

Supplementary materials

Supplementary materials can be found via https://doi.org/10.15747/ACNM.25.0039
Supplement 1. Flow diagram of participant selection.
Supplement 2. Distribution of the Ca/P mass ratio using a guideline-based cutoff.

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Original Article

Current status and short-term results regarding frailty in patients undergoing gastrointestinal cancer resection in Japan: a retrospective cohort study

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Abstract

Purpose: Frailty is a state of physical and cognitive decline that exists between robust health and the need for nursing care. Frailty is reported to occur at a high rate among patients with cancer and is associated with postoperative complications, such as delirium, infection, reduced survival, and rehospitalization. In this study, we investigated the incidence of frailty and surgical outcomes in patients who underwent surgery for gastrointestinal cancer.

Methods: A total of 201 patients who underwent preoperative physical assessment at Osaka International Cancer Institute between July and September 2021 were included. The Japanese version of the Cardiovascular Health Study (J-CHS) index was used to assess the frequency of frailty and related postoperative outcomes.

Results: Among the 201 patients, 27 (13%) were classified as frail and 126 (63%) as pre-frail. Of the 27 frail patients, 22 (81%) were older adults—a significantly higher proportion compared to the pre-frail/robust group (P=0.004). The median hospital stay for frail patients was 17 days (range, 5–98 days), which was significantly longer than that for robust patients (P<0.001). Postoperative complications occurred in 15 frail patients (56%), which was higher than in pre-frail (n=40, 32%) and robust (n=6, 13%) patients. Furthermore, multivariate analysis showed that frailty was an independent risk factor for postoperative complications.

Conclusion: These findings indicate that frailty is common among older adults with gastrointestinal cancer and has a significant impact on both the length of hospital stay and the risk of postoperative complications.

Keywords: Colorectal neoplasms; Frailty; Gastrointestinal neoplasms; Nutritional support; Sarcopenia

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Introduction

Background

Frailty refers to a state of weakness, vulnerability, and senility and is considered a transitional stage between good health and the need for nursing care. According to the Japan Geriatrics Society, "Frailty is a state in which physiological reserves decline with age, increasing vulnerability to stress and resulting in outcomes such as impaired daily functioning, the need for nursing care, and death. This concept encompasses not only physical issues, such as decreased muscle strength and increased risk of falls due to loss of agility, but also mental and psychological issues, including cognitive impairment and depression, as well as social problems, such as living alone or experiencing economic hardship [1]." It is known that frailty, characterized by physical and mental vulnerability in older adults, can be improved with appropriate and targeted interventions.

It is well established that cancer—particularly when combined with prolonged hospitalization, invasive surgery, or chemotherapy/radiotherapy—can significantly impact prognosis. Frailty is strongly affected by the coexistence of lifestyle-related diseases. According to the "National Cancer Registry: Incidence and Rate Report" published by the Japanese Ministry of Health, Labour and Welfare in 2019, gastrointestinal cancers, especially colorectal cancer, represent a substantial proportion of cases: 43% in men and 29.7% in women [2]. Furthermore, a National Clinical Database survey by Hasegawa et al. (2019) [3] reported an increase in older patients undergoing gastrointestinal cancer surgery, along with a rise in preoperative comorbidities and postoperative complications. Although advanced age is often considered a risk factor, a review of optimal surgical treatment and geriatric assessment in older colorectal cancer patients suggests that surgery should not be withheld solely on the basis of age [4].

However, older patients frequently present with additional risk factors for postoperative complications, such as frailty, malnutrition (including low serum total protein and albumin levels), cognitive decline, comorbidities, polypharmacy, and sarcopenia (loss of skeletal muscle mass). These factors can increase the risks of death, sepsis, postoperative infection, and delirium [5]. Preoperative assessment of such risk factors has been reported to reduce both mortality and postoperative complications, shorten hospital stays, facilitate discharge to home, and help maintain activities of daily living and improve quality of life [6,7]. Nonetheless, a variety of risk factors for postoperative complications exist even among younger adults with cancer, particularly gastrointestinal cancers, yet little is known about frailty risk assessment independent of age.

Objectives

The aim of this study was to investigate the impact of frailty on prognosis according to cancer site and age, and to examine the relationship between the incidence of frailty and surgical outcomes.

Methods

Ethics statement

This study was approved by the Ethics Committee of the Osaka International Cancer Institute (Number: 18033-6). Informed consent was not required in accordance with institutional policy for this retrospective study.

Study design

This retrospective cohort study is described in accordance with the STROBE statement (https://www.strobe-statement.org/).

Setting

From July to September 2021, a retrospective analysis was conducted on 201 cases (131 males, 70 females; mean age, 67 years [range, 28–86 years]) selected from 268 patients who underwent gastrointestinal cancer resection at the Osaka International Cancer Institute. All included patients underwent preoperative physical function assessments, such as the 6-minute walking distance (6MWD), performed by the Department of Rehabilitation.

Participants

Of the 268 patients who underwent gastrointestinal cancer resection, those who did not receive surgical treatment were excluded (Fig. 1).

Variables

Preoperative baseline characteristics included age, five-item physical function, 6MWD, and grip strength. Outcome variables consisted of postoperative complications.

Data source/measurement

The frequency of frailty was assessed using the revised Japanese 2020 version of the Cardiovascular Health Study (J-CHS) criteria [8]. At the time of preoperative physical function assessment, five factors were evaluated: (1) weight loss (≥2 kg in 6 months), (2) fatigue, (3) decreased physical activity (exercise less than once a week), (4) decreased walking speed (<1.0 m/sec), and (5) decreased grip strength (<28 kg for men, <18 kg for women). Patients were categorized into three groups: frail (meeting three or more criteria), pre-frail

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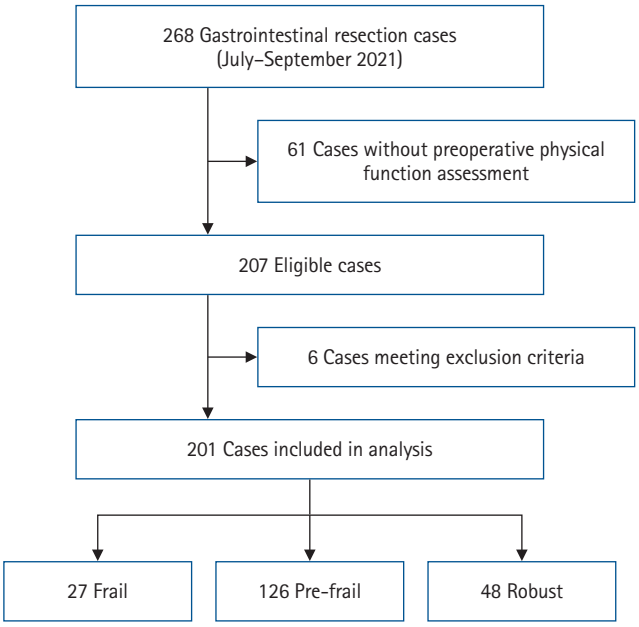

Fig. 1. Flowchart for frailty assessment.

Table 1. Patient background (n=201)

Variable	Value
Sex	
Male	131 (65)
Female	70 (35)
At surgery age (yr)	67 (28–86)
≥65 yr	112 (55)
Preoperative BMI (kg/m^2)	22.2 (14.1–31.6)
Emaciation (BMI <17 kg/m^2)	9 (4)
Upper GI tract	68 (34)
Gastric cancer	32 (47)
Esophageal cancer	30 (44)
Esophagogastric junction cancer	6 (9)
Hepato-biliary-pancreatic	51 (25)
Liver, biliary tract cancer	25 (49)
Pancreatic cancer	26 (51)
Lower GI tract	82 (41)
Colon cancer	38 (46)
Rectal cancer	44 (54)

Values are presented as number (%) or median (range).
BMI, body mass index; GI, gastrointestinal.

(meeting one or two criteria), and robust (meeting none). Weight loss, fatigue, and physical activity were assessed using subjective participant reports. The 6MWD was measured according to American Thoracic Society guidelines. Grip strength was measured twice on each hand using a digital dynamometer (Grip-D, Takei Scientific Instruments Co., Ltd.), with the highest value recorded. Postoperative complications were classified according to the Japan Clinical Oncology Group postoperative complication criteria (Clavien-Dindo classification) [9]; complications not included in this classification were recorded as "other." The severity of complications was graded from I to V according to this system.

Bias

As all eligible patients from a single institution during the study period were included, selection bias was not an issue

Study size

No sample size estimation was performed because the study encompassed the entire target population.

Statistical methods

All numerical data are presented as median (range). Statistical analyses were performed using JMP Pro 14 (SAS Institute Inc.). Differences between groups were analyzed using the Dunnett test, with the robust group as the control. Temporal changes were evaluated using the paired t-test before and after the intervention. The Fisher exact test was used to compare patient backgrounds between groups. Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors for postoperative complications. A P-value less than 0.05 was considered statistically significant in all analyses.

Results

Participants

Among the 201 patients, 68 (34%) had upper gastrointestinal cancers, including gastric and esophageal cancers. Fifty-one patients (25%) had hepatobiliary and pancreatic cancers (such as liver, biliary tract, and pancreatic cancers), and 82 patients (41%) had lower gastrointestinal cancers, such as colon and rectal cancers. The baseline characteristics of the participants are presented in Table 1.

Frail cases

Patient characteristics by perioperative group are shown in Table 2. According to the J-CHS criteria [8], 27 cases (13%) were classified as frail, and 126 (63%) as pre-frail. Among the 27 frail cases, 22 (81%) were aged 65 years or older, a significantly higher proportion compared to 90 cases (52%) in the pre-frail and robust groups (P=0.004). With respect to sex, 20% of female patients were classified as frail, compared to 10% of male patients (P=0.05). The proportion of frailty increased among older adults in all cancer site categories, but there was no significant difference between sites (Fig. 2). The

Table 2. Patient characteristics by group during perioperative period

Factor	Frail (n=27)	Pre-frail (n=126)	Robust (n=48)
Preoperative factors			
Sex			
Male	13 (48)	81 (64)	37 (77)
Female	14 (52)*	45 (36)	11 (33)
Age at surgery (≥65 yr)	22 (81)*	62 (49)	28 (58)
Preoperative BMI (kg/m²)	20.3 (14.1–31.1)	22.35 (14.3–31.6)	22.35 (18.5–31.6)
Emaciation (BMI <17 kg/m²)	1 (4)	8 (6)	0
Malnutrition (albumin <3.5 g/dL)	6 (22)*	11 (9)	2 (4)
Intraoperative factors			
Operation time (min)	379 (167–719)	299 (35–936)	297 (102–687)
Laparoscopic surgery	17 (63)	74 (58)	28 (58)
Robot-assisted surgery	3 (11)	30 (24)	13 (27)
Open surgery	7 (26)	22 (17)	7 (15)
Length of hospital stay	17 (5–98)*	10 (4–74)	9 (5–52)
Postoperative BMI (kg/m²)	20.3 (14.2–27.8)	21.1 (14.5–31.9)	21.8 (17.2–29.2)
Postoperative death (within 30 day)	1 (4)	0	0
Postoperative complications	15 (56)*	40 (32)	6 (13)

Values are presented as number (%) or median (range).
Fisher exact test was used for comparison of numbers of cases; Dunnett's test was used for body mass index (BMI), operation time, and hospital stay, with the robust group as control.
*P<0.05

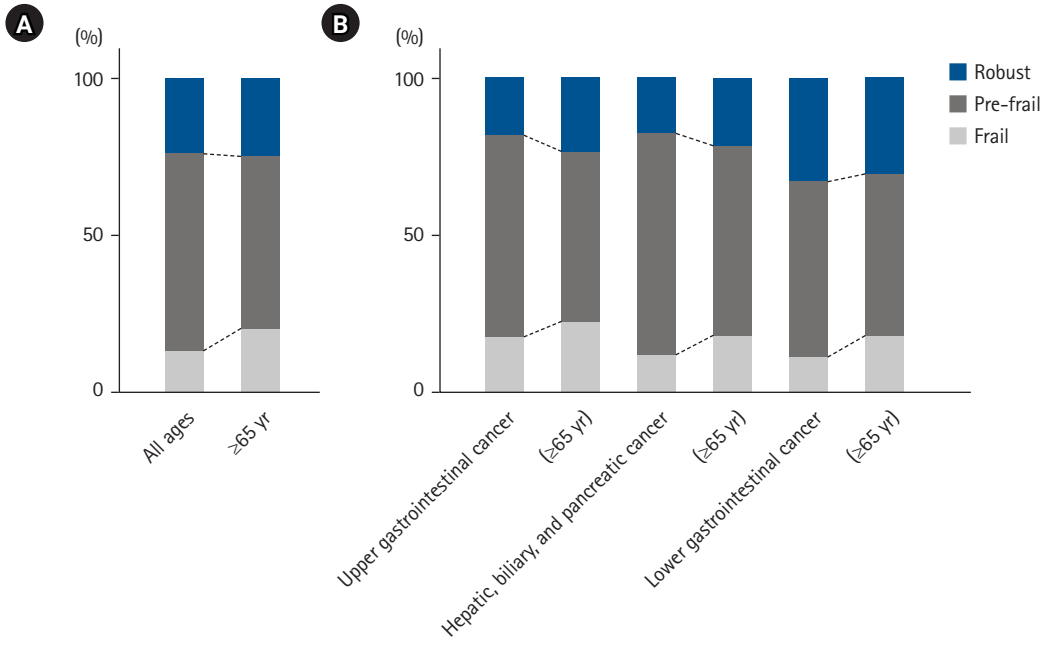

Fig. 2. Prevalence of frailty status. (A) Proportions of each group among all patients and those aged ≥65 years. (B) Proportions of each group according to cancer site, overall and among patients aged ≥65 years.

highest proportion of frailty by cancer site was observed in esophageal cancer at 27% (Fig. 3).

Influence of frailty on preoperative and intraoperative factors

For preoperative factors, there were no differences in body mass index (BMI) or the proportion of patients with emacia-

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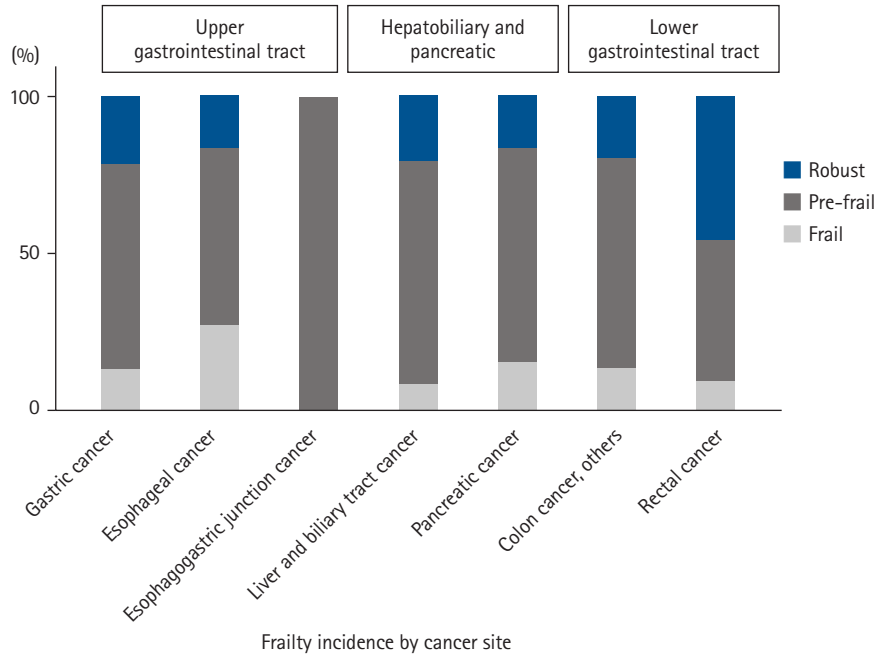

Fig. 3. Proportion of each group by cancer site. Frailty, pre-frailty, and robust proportions in upper gastrointestinal, hepatobiliary-pancreatic, and lower gastrointestinal cancers.

Table 3. Number and proportion of postoperative complications by cancer site and group

Cancer site/subtype	Frail	Pre-frail	Robust
Upper GI tract			
Gastric cancer	4	21	7
Complications (%)	0	2 (10)	0
Esophageal cancer	8	17	5
Complications (%)	5 (63)	9 (53)	1 (20)
Esophagogastric junction cancer	0	6	0
Complications (%)	0	1 (17)	0
Hepato-biliary-pancreatic			
Liver, biliary tract cancer	2	18	5
Complications (%)	1 (50)	8 (44)	1 (20)
Pancreatic cancer	4	18	4
Complications (%)	5 (100)	9 (50)	1 (25)
Lower GI tract			
Colon cancer, others	5	26	7
Complications (%)	1 (20)	7 (27)	1 (14)
Rectal cancer	4	20	2
Complications (%)	3 (75)	4 (20)	2 (10)

Cases with multiple complications are included.

tion (BMI ≤17 kg/m^2) between groups. However, the proportion of frail patients with malnutrition (albumin ≤3.5 g/dL) was significantly higher (6 cases, 22%) compared to 13 cases (7%) in the other groups. No differences were observed in operative time.

Influence of frailty on surgical outcomes

Within 30 days postoperatively, there was one surgical death (due to infection) in the frail group, with none in the pre-frail or robust groups. The postoperative hospital stay was significantly longer in the frail group compared to the robust group (median 17 days [range, 5–98] vs. 9 days [range, 5–52], respectively; P<0.001). Postoperative complications—such as ileus, pneumonia, and surgical site infection—occurred in 15 frail patients (56%), significantly higher than the 46 cases (26%) observed in the other two groups combined (P=0.002) (Table 2). The number of frail, pre-frail, and robust patients by cancer site is shown in Table 3.

A high complication rate in the frail group was observed after esophagectomy (5 cases, 63%), pancreatectomy (5 cases, 100%), and colectomy (3 cases, 75%) (Table 3). Among these, the most common complications after esophagectomy were pneumonia, recurrent laryngeal nerve paralysis, and surgical site infection. Pancreatic fistula was most frequently observed after pancreatectomy (Table 4). In terms of severity, mild complications predominated in lower gastrointestinal cancer cases, and there were no grade III or higher complications in this category (Fig. 4A). When comparing severity by group, there was one grade V case in the frail group. In this group, the highest proportion of complications was grade II, and there were no differences in the rates of grade II or III complications between frail, pre-frail, and robust groups (Fig. 4B).

Risk factors for postoperative complications

Univariate and multivariate analyses revealed that age ≥65 years (P=0.039), frailty (P=0.046), and pancreatic cancer (P=0.011) were significantly associated with an increased risk of postoperative complications (Table 5).

Discussion

Key results

Among the 201 analyzed cases, upper gastrointestinal cancers comprised 34%, hepatobiliary and pancreatic cancers 25%, and lower gastrointestinal cancers 41%. Frailty, as defined by J-CHS criteria, affected 13% of cases, with 81% of frail patients aged 65 years or older. Frailty was more common in females (20%) than in males (10%). Frail patients exhibited higher rates of malnutrition and postoperative complications (56% in frail vs. 26% in non-frail), and experienced longer hospital stays (17 days vs. 9 days). Age, frailty, and pancreatic cancer were all independent risk factors for postoperative complications.

Interpretation/comparison with previous studies

In this study, as in previous reports, frailty was highly prevalent among older adult patients; however, a notable number of frail cases were also observed among patients under 65 years of age. Furthermore, frailty was frequently identified in patients with esophageal cancer and was shown to be an independent risk factor for postoperative complications across all types of gastrointestinal cancer. Previous studies have similarly reported that frailty, as assessed by the Geriatric 8 screening tool, predicts both overall survival and cancer-specific survival following gastrointestinal cancer surgery. It has

Table 4. Breakdown of number of complications by cancer site

	Obstructive ileus	Ureteral injury	Postoperative bleeding	Surgical site infection	Pneumonia	Recurrent laryngeal nerve palsy	Pleural effusion	Cholecystitis	Pancreatic fistula	Delayed gastric emptying	Others
Gastric cancer	0	0	0	0	0	0	0	0	0	0	2
Esophageal cancer	0	0	0	3	4	4	1	0	0	0	4
Esophagogastric junction cancer	0	0	0	0	0	0	0	0	0	0	1
Liver, biliary tract cancer	0	0	1	2	1	0	0	3	2	0	1
Pancreatic cancer	1	0	2	1	0	0	0	2	4	2	3
Colon cancer, others	2	1	1	0	1	0	0	1	0	0	3
Rectal cancer	2	2	0	1	0	0	0	0	0	0	4

Number of postoperative complications according to Japan Clinical Oncology Group Clavien-Dindo classification v.2.0.
Cases with multiple complications are included.

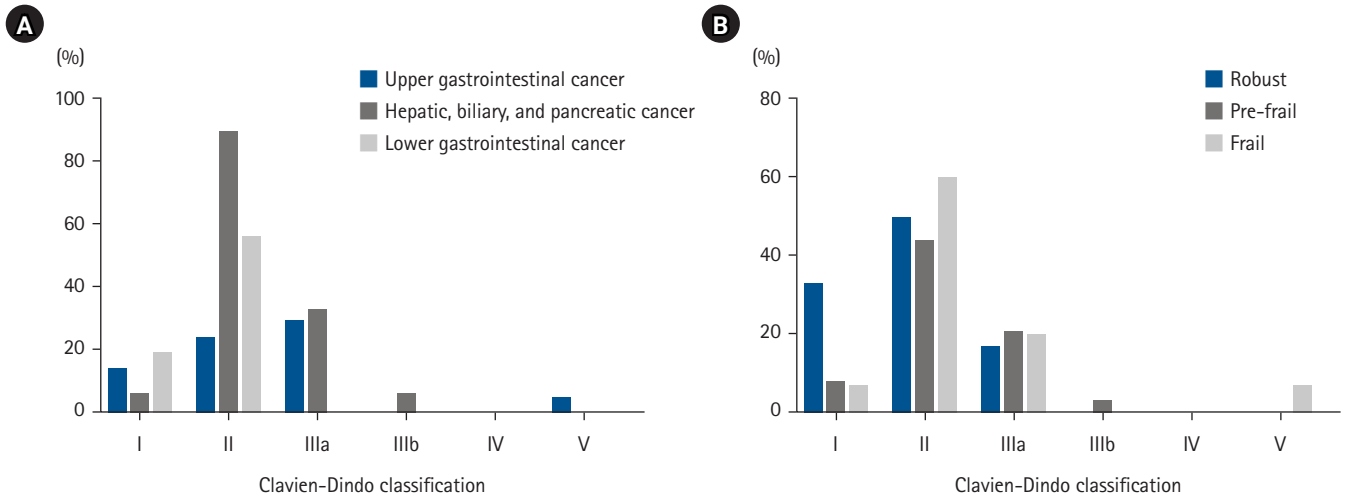

Fig. 4. Clavien-Dindo classification of complications. Proportion of each grade in the Clavien-Dindo classification among the number of complications that occurred, by cancer site (A) and by group (B).

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Table 5. Univariate and multivariate analyses of risk factors for postoperative complications

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	RR	95% CI	P-value
Sex (male/female)	1.27	0.663–2.518	0.471			
Age (≥65 yr/<65 yr)	2.741	1.418–5.523	0.002*	2.252	1.121–4.682	0.039*
Frailty (frail/pre-frail, robust)	2.918	1.261–6.738	0.013*	2.482	1.013–6.042	0.046*
Cancer site						
Gastric cancer	0.078	0.004–0.381	<0.001			
Esophageal cancer	1.925	0.889–4.080	0.096			
Esophagogastric junction cancer	1.300	0.060–13.830	0.834			
Liver, biliary tract cancer	1.037	0.383–2.546	0.939			
Pancreatic cancer	4.602	1.973–11.061	<0.001*	3.173	1.294–7.983	0.011*
Colon cancer, others	1.611	0.743–3.809	0.234			
Rectal cancer	1.267	0.575–3.025	0.568			

OR, odds ratio; CI, confidence interval; RR, relative risk.
Logistic regression was used for the analysis of risk factors for postoperative complications.
*P<0.05.

also been identified as an independent prognostic factor for recurrence and mortality after curative surgery for stage I–III colorectal cancer [10,11].

With the growing adoption of minimally invasive surgery, some studies have demonstrated that, in frail patients, the 30-day mortality rate after laparoscopic colorectal cancer surgery is lower than that after open surgery, likely due to reduced invasiveness [12]. However, studies not limited to cancer surgery have reported that frailty remains a substantial risk factor regardless of the surgical approach, and that even minimally invasive procedures are associated with high mortality rates in frail patients [13]. Notably, while laparoscopic and robot-assisted operations are generally considered to result in fewer postoperative complications than open surgery, some reports indicate that, in frail colorectal cancer patients, robot-assisted surgery is actually associated with a higher incidence of postoperative complications compared to laparoscopic or open surgery [14]. In the present study, we did not observe a significant association between the type of surgical procedure and the incidence of mortality or complications among frail patients. Nevertheless, these findings suggest that surgical procedure selection in frail patients should be approached with greater caution than in robust patients.

In Japan, where the population is rapidly aging, there is increasing interest in the relationship between frailty and cancer treatment. In 2021, as part of a Ministry of Health, Labour and Welfare research project on the development of guidelines for older adult cancer care, the Japanese Society of Coloproctology established clinical guidelines for the evaluation, treatment, and care of pre-frail older adult colorectal cancer patients [15-22]. Frailty and pre-frailty significantly impact postoperative prognosis, complication rates, and mortality in gastrointestinal cancer, underscoring the importance of identifying frail patients and providing appropriate interventions before surgery.

In our study, postoperative hospital stay was significantly longer in frail patients compared to robust patients. Esophageal cancer, known for being the most invasive among gastrointestinal surgeries and for having the highest rate of postoperative complications, had a median hospital stay of 14 days (range, 6–58 days), and accounted for 29% of frail cases. However, even after excluding esophageal cancer cases, postoperative hospital stays remained significantly longer in frail patients (median, 17 days; range, 5–98 days) compared to robust patients (median, 9 days; range, 5–52 days) (P=0.007). Further analysis revealed no correlation between frailty and markers of body constitution or malnutrition, such as albumin or BMI. Although various indices, including subjective evaluations, have been proposed for the assessment of frailty, it is essential that data be collected through objective preoperative physical function assessments. Our institution has initiated efforts to accumulate and share such data following preoperative evaluations, which led to the design of this preliminary study. The benefits of perioperative rehabilitation have been well documented, and for colorectal cancer, preoperative intervention has been shown to reduce postoperative complications compared to rehabilitation initiated only after surgery [23]. Thus, comprehensive interventions, including preventive rehabilitation before surgery and restorative rehabilitation, are required to improve postoperative physical function and assess motor function.

Nutritional intervention also plays a crucial role in the prevention and improvement of frailty. Frailty is closely associated with sarcopenia, cancer cachexia, and subsequent loss

of muscle strength, all of which significantly affect prognosis. In this study, we also examined the provision of nutritional intervention among frail patients. Nutritional support team involvement was documented in 44% of frail cases, 30% of pre-frail cases, and 13% of robust cases, indicating that frail patients were more likely to receive nutritional support team support. Despite growing recognition of the risks associated with frailty in Japan, information essential for the identification and management of frailty is still not sufficiently shared among healthcare professionals. Improving postoperative outcomes for frail patients requires not only efforts by the primary department but also active multidisciplinary collaboration for identification, data sharing, and implementation of appropriate nutritional and rehabilitative interventions to restore muscle strength and facilitate effective information exchange. Notably, because a significant proportion of frail cases were also observed among younger cancer patients in this study, our findings suggest that frailty screening should not be limited to older adults.

Limitations

This study had several limitations. First, its retrospective, single-center design may limit generalizability to other populations. Second, frailty assessment relied in part on subjective, self-reported measures, which could introduce reporting bias. Third, the relatively small sample size of frail patients may have restricted statistical power. Finally, we did not obtain long-term follow-up data, so the impact of frailty on long-term survival and functional outcomes could not be assessed.

Conclusion

In summary, our findings demonstrate that frailty is an independent risk factor for postoperative complications in patients undergoing gastrointestinal cancer resection. To improve surgical outcomes, it is essential to identify frailty through preoperative physical function assessment and to implement targeted interventions through multidisciplinary collaboration.

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Authors' contribution

Conceptualization: AY, JN. Data curation: AY, SI. Formal analysis: JN, AY. Investigation: SI. Methodology: AY, CM, NH. Project administration: HA, HW. Supervision: TO, MY, HT, HT, HM. Validation: JN. Visualization: AY. Writing–original draft: AY. Writing–review: JN, NH, CM, HA, HW, TO, MY, HT, HM, HT. 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

Contact the corresponding author for data availability.

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Supplementary materials

None.

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Guidelines	Structured, 250	5,000	100	15
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[a]The length of each article is negotiable with the editor-in-chief.

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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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