frontiers | Research Topics

Nutritional therapy along the continuum of care

Edited by
Barbara Troesch and Matthias Pirlich

Published in
Frontiers in Nutrition

ISSN 1664-8714
ISBN 978-2-8325-5170-7
DOI 10.3389/978-2-8325-5170-7

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Nutritional therapy along the continuum of care

Topic editors

Barbara Troesch — Barbara Troesch Scientific Writing, Switzerland

Matthias Pirlich — Imperial Oak Outpatient Clinic, Germany

Citation

Troesch, B., Pirlich, M., eds. (2024). *Nutritional therapy along the continuum of care*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5170-7

Table of contents

05 Editorial: Nutritional therapy along the continuum of care
Barbara Troesch and Matthias Pirlich

08 The syndromic triad of COVID-19, type 2 diabetes, and malnutrition
Jeffrey I. Mechanick, Elena A. Christofides, Albert E. Marchetti, Kristin K. Hoddy, Jim Joachim, Refaat Hegazi and Osama Hamdy

21 Impact of obesity on all-cause and cause-specific mortality among critically ill men and women: a cohort study on the eICU database
Shan Li, Wei Zhang, Zhiqing Fu and Hongbin Liu

34 Compliance with a high-protein and energy-dense oral nutritional supplement in patients with disease-related malnutrition: a randomized open-label crossover trial
Miguel Leon-Sanz, Francisca Linares, Montserrat Gonzalo, María José Tapia, María Maiz-Jimenez, Marta Ruiz Aguado, Luis Lizán and Gabriel Olveira

42 Analysis of predictors of malnutrition in adult hospitalized patients: social determinants and food security
Krystel Ouaijan, Nahla Hwalla, Ngianga-Bakwin Kandala, Joelle Abi Kharma and Emmanuel Kabengele Mpinga

50 Exploring the practice of nutritional support during hospitalization across physicians, dietitians, and pharmacists based in Saudi Arabia
Sarah M. Ajabnoor, Sara Zaher, Rania Malatani and Hani Jawa

64 Effectiveness of a starch thickened infant formula with reduced lactose content, probiotics and prebiotics on quality of life and clinical outcome in infants with regurgitation and/or colic
Jean-Pierre Chouraqui, Sandra Brancato, Berenice Delmas and Thierry Hanh

75 The efficacy of fat-free mass index and appendicular skeletal muscle mass index in cancer malnutrition: a propensity score match analysis
Wei Ji, XiangLiang Liu, Pengfei Liu, YuWei He, YiXin Zhao, Kaiwen Zheng, JiuWei Cui and Wei Li

83 The application of a medium-chain fatty diet and enteral nutrition in post-operative chylous leakage: analysis of 63 patients
Ke Wang, Jiaming Xiao, Li Li, Xu Li, Yilun Yang, Zhiyu Liu and Jing Jiang

94 Geriatric nutritional risk index was associated with in-hospital mortality among cardiac intensive care unit patients
Yuefeng Li, Zhengdong Wang, Tienan Sun, Biyang Zhang and Xiangwen Liang

104 Is food insecurity contributing to malnutrition in older adults in Switzerland? – A cross-sectional study
Maurus Rigling, Philipp Schuetz and Nina Kaegi-Braun

113 Routine laboratory parameters to support decision on parenteral nutrition in palliative care
Lea Kum, Elisabeth L. Zeilinger, Dagmar Vohla, Anna Kitta, Nadine Brunevskaya, Feroniki Adamidis, Franziska Ecker, Eva K. Masel, Brigitte Mayr-Pirker, Alexa L. Meyer, Bärbel Sturtzel, Gudrun Kreye and Matthias Unseld

122 Evolution of the diagnosis of malnutrition in adults: a primer for clinicians
Refaat Hegazi, Anthony Miller and Abby Sauer

frontiers | Frontiers in Nutrition

TYPE Editorial
PUBLISHED 02 July 2024
DOI 10.3389/fnut.2024.1398632

OPEN ACCESS

EDITED BY
Michele Barone,
University of Bari Aldo Moro, Italy

REVIEWED BY
Ximena Rosas-Flota,
National Autonomous University of Mexico, Mexico

*CORRESPONDENCE
Barbara Troesch
✉ barbaratroesch@gmail.com
Matthias Pirlich
✉ matthias.pirlich@googlemail.com

RECEIVED 10 March 2024
ACCEPTED 10 June 2024
PUBLISHED 02 July 2024

CITATION
Troesch B and Pirlich M (2024) Editorial: Nutritional therapy along the continuum of care. *Front. Nutr.* 11:1398632. doi: 10.3389/fnut.2024.1398632

Editorial: Nutritional therapy along the continuum of care

Barbara Troesch[1]* and Matthias Pirlich[2]*

[1]Barbara Troesch Scientific Writing, Zurich, Switzerland, [2]Imperial Oak Outpatient Clinic, Berlin, Germany

KEYWORDS

clinical nutrition, nutrition therapy, Human Right to Nutritional Care, GLIM criteria, nutritional screening, nutritional assessment

Editorial on the Research Topic
Nutritional therapy along the continuum of care

At the 2022 ESPEN conference, the International Declaration on the Human Right to Nutritional Care was presented, stating the ethical obligation to ensure optimal nutritional care (1). Increasing evidence supports the beneficial impact that nutritional therapy has on outcomes such as mortality and hospital readmission (2). Given this clear call to action, the objective of this Research Topic on "*Nutritional therapy along the continuum of care*" is to bring together relevant research that contribute to making it a reality. Nutritional therapy can include a range of interventions such as dietary counseling or oral, enteral, or parenteral clinical nutrition as well as a combination of these. In addition, nutritional interventions need to be part of a holistic treatment plan in combination in-depth anamneses, medical interventions, physical activity as well as other forms of therapy.

The International Declaration on the Human Right to Nutritional Care states that "*right to food is often overlooked in the clinical setting, resulting in an unacceptable number of children and adults suffering from disease-related malnutrition in hospitals and in the community, leading to an unacceptable disregard of the right to health*" (1). To address this, it is important to develop a common understanding of the definition and classification of malnutrition. A further narrative review summarized the evolution of the diagnosis of malnutrition during the last two decades (Hegazi et al.). A special emphasis is Global Leadership Initiative on Malnutrition (GLIM) that aimed at creating a consensus on criteria for the diagnosis of malnutrition (3). The authors in the current Research Topic propose an approach that integrates the GLIM criteria into the WHO frameworks and considers different forms of malnutrition in both adult and pediatric populations (Hegazi et al.).

One of the two key pillars of the Human Right to Nutritional Care is the Human Right to Food (1), relevant before a person even enters the healthcare system. In our aging populations, patients often present with a range of chronic conditions that, in combination with poor lifestyle choices and other factors such polypharmacy, affect their nutritional status (4). Often hidden behind adipose tissue, their muscle mass is decreased (5), and intakes of essential nutrients are low (6), while inflammatory levels are chronically increased.

In addition, socio-economic factors affect their ability to maintain an adequate nutritional status as seen in two cohort studies presented here: The analysis of a Swiss sub cohort of the EFFORT trial with 433 elderly patients shows that even in a country with a high level of affluence and a relatively efficient social security system, 6.9% were food

insecure (Rigling et al.). Age, dependence on welfare, and loneliness were significant factors associated with food insecurity, which in turn was linked to a significantly lower quality of life. In the other cohort study presented here, lower levels of food security (defined through educational level and income) were significantly associated with a higher risk of malnutrition (Ouaijan et al.). Among the >340 patients from five hospitals in Lebanon, the malnutrition prevalence was 35.6% based on the Global Leadership Initiative for Malnutrition (GLIM) criteria [(3), Ouaijan et al.]. Addressing nutritional care in the community is the topic of a recent ESPEN publication (7) and goes beyond the scope of this editorial.

Consequently, patients often enter the hospital malnourished, they continue to lose muscle mass during the stay, and they fail to recover it after discharge. Decrease in food intake due to factors such as lack of exercise, stress caused by the hospital stay and metabolic changes because of their medical condition, surgery, or drugs, further aggravates the macro- and micronutrient deficiencies (8). All of this affects their clinical prognosis and the increase in frailty puts them at risk of further health problems, leading to a vicious cycle of malnutrition, ill health, and frailty.

The significant prognostic impact of malnutrition regarding increased in-hospital mortality and longer ICU stay was demonstrated in a large cohort of elderly patients in a cardiac intensive care unit in China (Li Y. et al.). Another study from China showed the prognostic importance of body composition analysis in a large cohort of cancer patients (Ji et al.). About a quarter of all examined cancer patients had reduced muscle mass, which was significantly associated with lower survival. In a cohort study of over 160,000 intensive care patients in China, the obesity paradox concerning cardiovascular mortality was confirmed (Li S. et al.). The lowest mortality rate was observed in mild obesity, but in severely obese and underweight individuals, the mortality was pronounced.

The recent Corona virus 2019 (COVID-19) pandemic taught us that the relationship between different risk and/or prognostic factors can be complex, which also applies to malnutrition: A narrative review in this Research Topic addresses the two major risk factors for an unfavorable course of COVID-19: diabetes mellitus 2, and malnutrition (Mechanick et al.). They postulate a syndromic triad and suggest ways for early preventive care through nutritional and lifestyle interventions.

Following screening and assessment of malnutrition, an individual nutritional care needs to be established to ensure adequate intake of energy and protein as well as other essential nutrients. Oral Nutritional Supplements (ONS) have been shown to be a useful means to improve nutritional status, particularly if they were energy dense (9). This finding is supported by a randomized controlled trial published in this Research Topic: the intervention in an outpatient setting demonstrated that an energy dense ONS (2.4 kcal/ml) was well-tolerated and was non-inferior to high-energy ONS (2.0 kcal/ml) in malnourished patients, allowing for more calories in a lower volume (Leon-Sanz et al.).

Depending on the underlying disease or population group, the nutritional therapy needs to be adjusted in factors other than energy density: A retrospective study on 63 patients found evidence that the application of a medium-chain fatty acid diet might be effective in treating post-operative chylous leakage (Wang et al.). The possible benefits of a starched thickened formula with reduced lactose content and pre- and probiotic ingredient were demonstrated in young infants with regurgitations and colic (Chouraqui et al.).

According to the declaration, clinical nutrition education is another essential factor for the implementation of optimal nutritional care (1). Another study investigated the structures and current practices of nutritional support in Saudi Arabian hospitals (Ajabnoor et al.). Of the 114 participating physicians, pharmacists, and dietitians, only 44.7% reported working with a formal nutritional support team. The unsurprising finding that confidence in using nutritional interventions such as enteral nutrition was associated with nutritional qualification, highlights the key role of dietitians in implementing optimal nutritional care (Ajabnoor et al.). However, it also showed that nutritional care improved if other key stakeholders, such as physicians, were involved (Ajabnoor et al.).

The respect of patient dignity is an important aspect when decisions on optimal nutrition are taken, particularly in a palliative setting at the end of life. It was recommended that nutritional therapy should become less invasive as life expectancy decreases and focus increasingly on relieving eating-related distress and thirst (10). Particularly the use of parenteral nutrition is seen as controversial in these situations, but prognosis of life expectancy is difficult. In this special edition, a Viennese working group examined whether the clinical benefit of parenteral nutrition in a palliative situation can be predicted by an algorithm based on laboratory parameters, which needs further validation (Kum et al.).

In summary, this special edition provides new insights into the effect of malnutrition on patient's clinical prognosis and quality of life as well as potential solutions to improve nutritional interventions along the continuum of care. Moreover, it serves as a call for action to close gaps in our understanding of the problem and for implementation of further initiatives to optimize nutritional therapies.

Author contributions

BT: Conceptualization, Writing – original draft, Writing – review & editing. MP: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

BT also works for Nutricia, a company producing oral and enteral clinical nutrition.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Cardenas D, Correia MI, Hardy G, Gramlich L, Cederholm T, Van Ginkel-Res A, et al. The international declaration on the human right to nutritional care: A global commitment to recognize nutritional care as a human right. *Clin Nutr.* (2023) 42:909–18. doi: 10.1016/j.clnu.2023.04.009

2. Gomes F, Baumgartner A, Bounoure L, Bally M, Deutz NE, Greenwald JL, et al. Association of nutritional support with clinical outcomes among medical inpatients who are malnourished or at nutritional risk: an updated systematic review and meta-analysis. *JAMA Netw Open.* (2019) 2:e1915138. doi: 10.1001/jamanetworkopen.2019.15138

3. Cederholm T, Jensen GL, Correia MI, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr.* (2019) 38:1–9. doi: 10.1016/j.clnu.2019.02.033

4. Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. *Lancet.* (2023) 401:951–966. doi: 10.1016/S0140-6736(22)02612-5

5. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol.* (2013) 10:90–99. doi: 10.1038/nrclinonc.2012.209

6. Troesch B, Eggersdorfer M, Weber P. 100 years of vitamins: adequate intake in the elderly is still a matter of concern. *The J Nutr.* (2012) 142:979–980. doi: 10.3945/jn.112.157826

7. Krznarić Ž, Bender DV, Kovač MB, Cuerda C, van Ginkel-Res A, Hiesmayr M, et al. Clinical nutrition in primary care: ESPEN position paper. *Clin Nutr.* (2024) 43:1678–83. doi: 10.1016/j.clnu.2024.02.017

8. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. *Clin Nutr.* (2022) 41:1357–424. doi: 10.1016/j.clnu.2022.02.015

9. Hubbard GP, Elia M, Holdoway A, Stratton RJ. A systematic review of compliance to oral nutritional supplements. *Clin Nutr.* (2012) 31:293–312. doi: 10.1016/j.clnu.2011.11.020

10. Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines. *ESMO open.* (2021) 6:100092. doi: 10.1016/j.esmoop.2021.100092

frontiers | Frontiers in Nutrition

TYPE Review
PUBLISHED 21 February 2023
DOI 10.3389/fnut.2023.1122203

OPEN ACCESS

EDITED BY
Barbara Troesch,
Self Employed, Zurich, Switzerland

REVIEWED BY
Sousana Konstantinos Papadopoulou,
International Hellenic University, Greece
Xiangdong Jian,
Qilu Hospital, Shandong University, China

*CORRESPONDENCE
Albert E. Marchetti
albertmarchetti@yahoo.com

SPECIALTY SECTION
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

RECEIVED 12 December 2022
ACCEPTED 30 January 2023
PUBLISHED 21 February 2023

CITATION
Mechanick JI, Christofides EA, Marchetti AE, Hoddy KK, Joachim J, Hegazi R and Hamdy O (2023) The syndromic triad of COVID-19, type 2 diabetes, and malnutrition. *Front. Nutr.* 10:1122203. doi: 10.3389/fnut.2023.1122203

The syndromic triad of COVID-19, type 2 diabetes, and malnutrition

Jeffrey I. Mechanick[1,2], Elena A. Christofides[3], Albert E. Marchetti[4,5]*, Kristin K. Hoddy[6], Jim Joachim[7], Refaat Hegazi[8] and Osama Hamdy[9,10]

[1]The Wiener Cardiovascular Institute/Marie-Josée and Henry R. Kravis Center for Cardiovascular Health at Mount Sinai Heart, New York, NY, United States, [2]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [3]Endocrinology Associates, Inc., Columbus, OH, United States, [4]Medical Education and Research Alliance (Med-ERA, Inc.), New York, NY, United States, [5]Rutgers New Jersey Medical School, Newark, NJ, United States, [6]Novo Nordisk Inc., Plainsboro Township, NJ, United States, [7]Internal Medicine and Medical Nutrition, San Diego, CA, United States, [8]Abbott Nutrition, Columbus, OH, United States, [9]Joslin Diabetes Center, Boston, MA, United States, [10]Harvard Medical School, Boston, MA, United States

The coronavirus disease 2019 (COVID-19) pandemic challenges our collective understanding of transmission, prevention, complications, and clinical management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Risk factors for severe infection, morbidity, and mortality are associated with age, environment, socioeconomic status, comorbidities, and interventional timing. Clinical investigations report an intriguing association of COVID-19 with diabetes mellitus and malnutrition but incompletely describe the triphasic relationship, its mechanistic pathways, and potential therapeutic approaches to address each malady and their underlying metabolic disorders. This narrative review highlights common chronic disease states that interact epidemiologically and mechanistically with the COVID-19 to create a syndromic phenotype—the COVID-Related Cardiometabolic Syndrome—linking cardiometabolic-based chronic disease drivers with pre-, acute, and chronic/post-COVID-19 disease stages. Since the association of nutritional disorders with COVID-19 and cardiometabolic risk factors is well established, a syndromic triad of COVID-19, type 2 diabetes, and malnutrition is hypothesized that can direct, inform, and optimize care. In this review, each of the three edges of this network is uniquely summarized, nutritional therapies discussed, and a structure for early preventive care proposed. Concerted efforts to identify malnutrition in patients with COVID-19 and elevated metabolic risks are needed and can be followed by improved dietary management while simultaneously addressing dysglycemia-based chronic disease and malnutrition-based chronic disease.

KEYWORDS

cardiometabolic, cardiometabolic-based chronic disease, coronavirus, COVID-19, COVID-related cardiometabolic syndrome, malnutrition, SARS-CoV-2, type 2 diabetes

Introduction

The coronavirus disease 2019 (COVID-19) pandemic spread rapidly worldwide in less than a year and activated an unprecedented acceleration of medical research, revealing a new understanding of the relationships among viral infections and chronic metabolic diseases. The juxtaposition of threat and swift knowledge acquisition observed during the COVID-19 pandemic contrasts starkly with the slower rise in prevalence of chronic cardiometabolic diseases

and the growing clinical knowledge of residual health risks determined over many decades (1). Of note, cardiometabolic drivers, risk factors, and resulting chronic metabolic states interact with COVID-19 to create a syndromic phenotype of hazards for disease severity, morbidity, and mortality, as well as long-term insults to quality of life, symptom burden, and socioeconomic impact. In a recent narrative review, the COVID-Related Cardiometabolic Syndrome (CIRCS) (2) was introduced based on consistent and compelling evidence linking pre-, acute, and chronic/post-COVID-19 disease stages with cardiometabolic-based chronic disease (CMBCD) (3, 4).

The CMBCD framework is a novel vehicle to expose opportunities for early and sustainable prevention and is comprised of three dimensions: (1) staged progression over time (1- "risk," 2- "predisease," 3- "disease," and 4- "complications"); (2) multiple interacting primary (genetics, environment, and behavior/lifestyle) and secondary/metabolic (abnormal adiposity, dysglycemia, hypertension, dyslipidemia, and nutrition) drivers; and (3) social determinants of health and transcultural factors (SDOH/TF) (**Figure 1**) (3–5). Many of the conventional terms commonly used to describe cardiometabolic risk factors are now subsumed in driver-based chronic disease models. For instance, in adiposity-based chronic disease (ABCD), overweight is stage 2, obesity is stage 3, and obesity-related complications is stage 4 (3). In dysglycemia-based chronic disease (DBCD), insulin resistance is stage 1, prediabetes is stage 2, type 2 diabetes (T2D) is stage 3, and diabetes complications is stage 4 (3, 6). In malnutrition-based chronic disease (MBCD), which is under development, malnutrition is stage 3, and malnutrition complications is 4. The purpose of incorporating the CMBCD model into this discussion is to provide a template for understanding a specific interaction between CIRCS and nutritional status.

In a recent scoping review, various nutritional disorders are linked with pre-, acute, and chronic/post COVID-19 stages (7). A distillation of the complex interactions of CIRCS and nutrition prompts a hypothesized syndromic triad with COVID-19, T2D, and malnutrition as key inter-related disease states (**Figure 2**). The purpose of constructing this new triad model is to expose early opportunities for better lifestyle, glycemic, and nutritional management of patients with COVID-19. The present narrative review will summarize key epidemiological and mechanistic aspects of these networked relationships, discuss relevant nutritional therapies, and propose testable hypotheses and structure for early preventive care.

Abbreviations: ABCD, adiposity-based chronic disease; ARDS, acute respiratory distress syndrome; ASPEN, American Society for Parenteral and Enteral Nutrition; ALM, appendicular lean mass; CDC, centers for disease control; CGM, continuous glucose monitor; CIRCS, COVID-related cardiometabolic syndrome; CMBCD, cardiometabolic-based chronic disease; CONUT, controlling nutritional status; COVID-19, coronavirus disease 2019; DBCD, dysglycemia-base chronic disease; DSNF, diabetes-specific nutrition formula; EN, enteral nutrition; ESPEN, European Society for Parenteral and Enteral Nutrition; GNRI-geriatric nutrition risk index; HbA1c, hemoglobin A1C; HBCD, hypertension-based chronic disease; ICU, intensive care unit; IL-6, interleukin-6; LBCD, lipid-based chronic disease; MBCD, metabolic based chronic disease; PNI, prognostic nutritional index; PPE, personal protective equipment; RAAS, renin-angiotensin-aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCCM, society of critical care medicine; SDOH/TF, social determinants of health/transcultural factors; T1D, type 1 diabetes; T2D, type 2 diabetes; TFN, tumor necrosis factor.

Methodology

To guide this initiative, a virtual meeting of coauthors was held in December 2021 to establish investigative questions, objectives, and methods to support the syndromic triad concept and to plan reporting if findings were thought worthy of publication. Study populations of interest include adults who contracted COVID-19 infections that were complicated by either pre-existing or newly developed T2D and malnutrition to determine if this triad of illnesses exists and has a noticeable impact on clinical outcomes. World literature was searched for relevant articles involving the stated population using several tradition engines (PubMed, Google, Cochrane, Embase, and Science Direct) without language or geographic restrictions. The following terms, alone and in combinations, directed the searches: COVID-19, coronavirus; type 2 diabetes, malnutrition, epidemiology, mechanisms, adiposity-based chronic disease, cardiometabolic-based chronic disease, dysglycemia-base chronic disease, hypertension-based chronic disease, lipid-based chronic disease, metabolic based chronic disease, therapy, treatment, nutrition, and outcomes. Meaningful publications (181 references) among the hundreds that were identified in multiple literature searches report data regarding epidemiologies and disease mechanisms that link triad components as well as clinical information related to outcomes for studied populations. Retrieved information was assessed to confirm or deny the existence of the triad and to propose clinical care to address each component and its drivers, which was the aim of the initiative.

Edge 1: COVID-19 and type 2 diabetes

Epidemiology

Adults with COVID-19 are more likely to develop T2D than those with other acute upper respiratory infections (8). In an analysis of retrospective data from the US Veterans Administration (VA), there are increased risks of incident T2D and additional disease burden among patients with COVID-19 (n = 181,281) vs. both contemporary control patients (n = 4,118,911) and also historical controls (n = 4,286,911) without infection (9). In a study of hospitalized adults, the prevalence of diabetes is higher among those with a positive vs. negative COVID-19 test result 30 days after testing (10). The Centers for Disease Control and Prevention (CDC) reports an observed increased risk for T2D in patients <18 years of age who had COVID-19, compared to those without COVID-19 and those with pre-pandemic acute respiratory infection (11). Moreover, incident cases of pediatric T2D and severity of illness as reflected by the degree of diabetic ketoacidosis at presentation are greater during, compared with before, the pandemic (12); but also worth noting, some increase could have been associated with other issues such as delayed healthcare or supply shortages rather than infection. Pooled data from four observational studies show that SARS-CoV-2-infected patients compared with healthy controls carried a 59% higher risk of developing incident diabetes in the post-acute phase (13). However, in this study, a high degree of heterogeneity and a short follow-up period in the contributing studies (4 months) are limitations of the meta-analysis expressed by investigators.

In a single large retrospective cohort study of VA in- and outpatient men without preexisting diabetes, SARS-CoV-2 infection

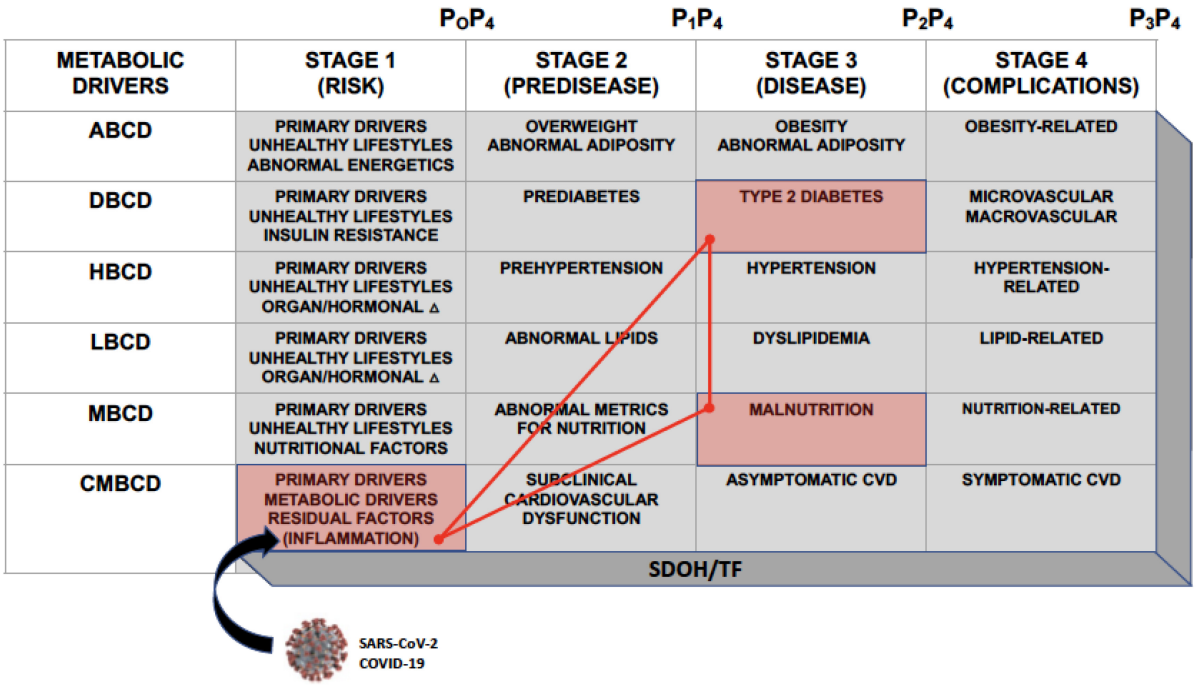


FIGURE 1
The CMBCD template. The CMBCD model comprises 3 dimensions: (1) Staged progression over time along the top row; (2) interactions among metabolic drivers culminating in CVD in the far-left column; and (3) adapting each cell in the stage x driver matrix to SDOH/TF. Prevention modalities are indicated as P_0–P_4. Primary drivers are genetics, environment, and behavior/lifestyle. The SARS-CoV-2 virus responsible for COVID-19 intersects with CMBCD at the level of inflammation in stage 1. This CMBCD template provides context for the novel syndromic triad of COVID-19, T2D, and malnutrition, which is depicted by the red cells and bright red triangle network. ABCD, adiposity-based chronic disease; CMBCD, cardiometabolic-based chronic disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DBCD, dysglycemia-based chronic disease; HBCD, hypertension-based chronic disease; LBCD, lipid-based chronic disease; MBCD, malnutrition-based chronic disease; P_0, primordial prevention; P_1, primary prevention; P_2, secondary prevention; P_3, tertiary prevention; P_4, quaternary prevention; SDOH, social determinants of health; TF, transcultural factors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Adapted from (4).

is associated with a higher risk of incident (120 days, OR 2.56 [95% CI 2.32–2.83]) and all time (237 days, OR 1.95 [1.80–2.12]) diabetes (14). In contrast, among women, who comprised 14% of the total VA study population, an association is not definitively established (120 days, 1.21 [0.88–1.68]; all time, 1.04 [0.82–1.31]; *p*-values were both <0.1) (14).

Many observational studies highlight compelling relationships among cardiometabolic conditions, COVID-19 infection, and severity of illness, with up to 94% of hospitalized patients presenting with at least one significant comorbidity (15–18). In a large cohort (n = 5,700) of hospitalized patients (17), diabetes, hypertension, and obesity are among the top comorbidities associated with COVID-19 infection, with similar patterns replicated globally in other analyses (19). Data also demonstrate a disproportionately high number of COVID-19 deaths in people with diabetes (20, 21). Likewise, obesity, with characteristic insulin resistance (22), also carries a higher risk for COVID-19 death (21).

Hyperglycemia is indicated by elevated fasting plasma glucose, post-challenge plasma glucose, and hemoglobin A1c (A1C) levels, and arises from a pancreatic β-cell defect following chronic exposure to insulin resistance. Hyperglycemia is associated with inflammation, coagulation disorders, low oxygenation, and higher risk of mortality in patients with COVID-19, compared to those without COVID-19 (6, 23). In the intensive care unit (ICU), poorly controlled diabetes with moderate-severe obesity greatly increases the risk of COVID-19-related mortality (24, 25).

Type 2 diabetes and obesity are two principal risk factors for the development of severe COVID-19 symptoms, and individuals with these comorbidities constitute a specific risk group (26). Of related interest, patients with type 1 diabetes (T1D), among other observed factors, require intensive care for COVID-19 twice as often as controls and are more likely to die (HR 2.90, 95% CI 1.66–5.47) of their COVID-19 infection (27).

Abnormal adiposity (i.e., elevated waist circumference and/or body mass index [BMI]), dysglycemia (i.e., insulin resistance or hyperglycemia [prediabetes or T2D]), elevated blood pressure (i.e., hypertension), dyslipidemia (i.e., hypertriglyceridemia and low concentration of high-density lipoprotein cholesterol), and residual risks (e.g., microalbuminuria and other features of insulin resistance) often cluster together as metabolic syndrome, which exhibits a higher odds for intensive care unit (ICU) requirement, invasive ventilation, ARDS (acute respiratory distress syndrome), and mortality compared to individual cardiometabolic risk factors (28, 29). Metabolic syndrome differs from CMBCD by only considering specific features for each metabolic driver at a particular timepoint, not as a staged progression over time based on pathophysiology, and not incorporating SDOH/TF. Aggregate cardiometabolic risk, individual risk factors, and vulnerability to severe COVID-19 each increase with age (30). Thus, cardiometabolic risk factors can be considered discretely as modifiable COVID-19 risk factors, which can be addressed with preventative approaches (i.e., "primordial" to prevent risk; "primary" to prevent disease; "secondary" to prevent disease progression; "tertiary" to prevent suffering and mortality in

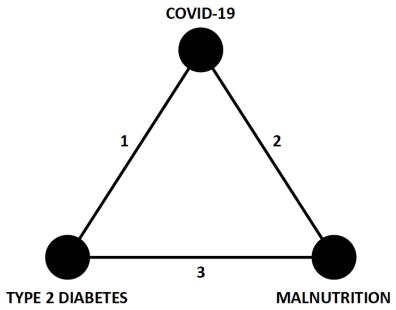


FIGURE 2
Syndromic triad of COVID-19, T2D, and malnutrition. The three edges (1, 2, and 3) of this triangle network represent epidemiological associations and pathophysiological mechanisms that connect each of the nodes (COVID-19, T2D, and malnutrition) and are discussed in the text. Recognition of this triad should prompt earlier consideration of nutritional and glycemic interventions in patients with COVID-19. COVID-19, coronavirus disease 2019; T2D, type 2 diabetes.

advanced disease; and "quaternary" to prevent overmedicalization at each disease stage).

Mechanisms

Infection with SARS-CoV-2 appears to alter pancreatic β-cell function and consequently reduce insulin secretion, while the accompanying hypercytokinemia promotes insulin resistance (30, 31). This combination of decreased insulin secretion and sensitivity induces and then aggravates hyperglycemia. Evidence from animal models have demonstrated markers of diminished immune function in hyperglycemic states (32). In human studies, phagocytosis function is restored in subjects with T2D following an intensive glycemic control intervention combining medication, insulin, and dietary modifications provided in a clinical trial (33). In effect, a vicious cycle is created by the bidirectional relationship wherein T2D worsens COVID-19 severity and COVID-19 worsens dysglycemia.

Relative hyperglycemia for an individual at a certain time, as opposed to absolute hyperglycemia, is defined as a blood glucose concentration at a particular timepoint divided by the estimated average glucose based on a current A1C level (34). This measure, also referred to as "stress hyperglycemia ratio" (SHR) is typically measured at hospital or ICU admission to predict clinical outcomes. The SHR controls for background glycemia in patient evaluations and is also a superior marker of critical illness compared to absolute measurements. The SHR is associated with adverse outcomes for patients with moderate-to-severe COVID-19 (35), including elevated in-hospital morbidity and mortality (34).

An early investigation of patients with COVID-19 (n = 99; 67% men, 33% women) in Wuhan, China reports arterial and/or endocrine comorbidities in 53%, and hyperglycemia in 52% of those studied (36). Subsequently, diabetes, predominantly T2D, emerges as one of the most common and consequential comorbidities to worsen outcomes for those infected with the SARS-CoV-2 virus (37). New-onset hyperglycemia, with and without T2D, is also commonly observed with COVID-19 (38) and may result from inflammation, metabolic stress, and/or steroid therapy.

Regardless of underlying diabetes, stress-induced hyperglycemia is a well-documented occurrence during acute infections and has been observed even in mild cases of COVID-19 (35). The purported mechanisms causing hyperglycemia rely on the imbalance between insulin action and insulin secretion, and are primarily instigated by inflammation, cytokine action, neuroendocrine mechanisms, and counter-regulatory hormones (3). For a patient with T1D, the degree of hyperglycemia can be severe due to the presence of absolute insulin deficiency. The acute rise of blood glucose levels and catabolic processes can lead to diabetic ketoacidosis, a life-threatening event. In a patient with T2D, the severity of the hyperglycemia may not be a medical emergency, but the prolonged nature is associated with increased risk of cardiovascular morbidity and mortality (39). Hyperglycemia can also result in increased morbidity and mortality due to decompensation of the immune system in the face of glucotoxicity (40).

The mechanisms of increased morbidity and mortality associated with acute or chronic hyperglycemia in diabetes are multifocal. The increased cytokines of an acute inflammatory response are known to globally blunt insulin receptor responsiveness (41). Poor insulin receptor function disproportionally allows degradation of the visceral fat compartment releasing a repertoire of proinflammatory adipokines such as leptin and adiponectin (42). The blunting of glucose uptake and insulin action by adipokines further aggravates hyperglycemia. In addition, increased inflammatory cytokines combined with proinflammatory adipokines promote the glycation of proteins, rendering them pro-adherent and prothrombotic (43). The net effect of an overabundance of these reactive glycated proteins promotes endothelial dysfunction, thrombosis, hypertension, compromised cellular function, and organ dysfunction (44).

Of particular interest in patients with SARS-CoV-2 infection is the exploitation of the angiotensin-converting enzyme (ACE)-2 receptor as an entry point into cells and initiation of infection. Patients with T2D have an overactive renin–angiotensin–aldosterone system (RAAS), with ACE-2 as a principal factor (45, 46). Upregulation of ACE-2 expression in cardiomyocytes increases susceptibility to COVID-19 in patients with T2D by facilitating SARS-CoV2 cellular entry (45, 46). Abnormal adiposity is a necessary feature of ABCD and includes unusual quantity (eutopic [including visceral fat] and ectopic [e.g., intrahepatic and peri/epicardial fat]), distribution (primary related to visceral and ectopic fat), and function (i.e., adipocyte secretome; adipokine secretion). Abnormal adiposity not only leads to inflammation, insulin resistance, DBCD, and CMBCD, but also contributes to increased RAAS activation (47). These mechanisms involve cytokine activation of multiple elements of the RAAS cascade, such as angiotensinogen and ACE, resulting in inflammatory adipokine release from fatty tissue (48). This imbalance of RAAS function can increase susceptibility to COVID-19 in patients with T2D (49).

The immunopathogenesis of COVID-19 also involves an excessive inflammatory response that can intensify into a cytokine storm in extreme cases (50, 51). Numerous inflammatory pathways are activated in this process, including facilitation of immune cell (e.g., monocytes, macrophages, neutrophils, natural killer cells, and T cells) as well as stimulation and secretion of proinflammatory cytokines (e.g., interferons, interleukins, tumor necrosis factors, and chemokines [e.g., C-base sequence chemokine ligands]) (51). In turn, a proinflammatory response recruits and activates more innate and adaptive immune cells that overstimulate the immune system, leading to massive inflammation (51). This detrimental inflammatory

process can incite and exacerbate acute respiratory distress syndrome (ARDS), the leading cause of COVID-19 related mortality.

Edge 2: COVID-19 and malnutrition

Epidemiology

Malnutrition is the necessary and central driver of MBCD, which in turn is one of the secondary/metabolic drivers in CMBCD. The American Society for Parenteral and Enteral Nutrition (ASPEN) defines malnutrition as insufficient energy intake leading to loss of weight, muscle, and subcutaneous fat; regional or widespread fluid accumulation; and decreased strength (52). Malnutrition is typically interpreted along these somewhat narrow lines that relate to undernutrition, particularly in COVID-19 discussions, but technically the broader definition includes any abnormal interaction between dietary factors and metabolism. For instance, abnormal adiposity is a form of malnutrition (i.e., imbalance of too much dietary energy for an individual's metabolic needs—overnutrition) and is briefly considered above in the discussions on inflammation, insulin resistance, and T2D with COVID-19. However, for the purposes of presenting the syndromic triad of COVID-19, T2D, and malnutrition, the term "malnutrition" will be based on the ASPEN definition (53). In the MBCD model, stage 1 arises through complex interactions of primary drivers (genetics, environment, and behavior/lifestyle) and defines a state of nutritional risk; MBCD stage 2 arises from progression of nutritional risks to create a phenotype characterized by abnormal metrics of nutritional status, but not yet satisfying current diagnostic criteria for malnutrition (i.e., in terms of undernutrition) (54–57) or other abnormal nutritional states, and defines a state of "pre-malnutrition;" MBCD stage 3 meets established definitions for the disease state referred to as malnutrition (54–57); and stage 4 is malnutrition-related complications (generally in terms of organ dysfunction, behaviors, and other pathophysiological abnormalities).

Population-level malnutrition is associated with increased rates of fatal COVID-19 in areas where undernutrition is commonplace (58). Moreover, nutritional status is adversely affected by acute and chronic infections, which serve as negative prognosticators, especially in institutional settings (59–61). Patients with COVID-19 are especially vulnerable to the metabolic derangements associated with malnutrition, particularly in light of the significant inflammatory response that accompanies both conditions (62–64). A high prevalence of malnutrition in a general cohort of patients with COVID-19 has been reported in prospective studies (65). For example, among elderly patients with COVID-19, the prevalence of malnutrition reaches 52.7% (66). Poor nutritional status is associated with in-hospital death among 295 patients with COVID-19, including 66 with severe illness and 41 with critical illness (67). In this study, the mortality rate is 8.47% for the total study population and 37.88% for the critically ill subgroup (67). Furthermore, despite significantly different nutritional parameters and inflammatory markers across all subgroups, patients with higher Controlling Nutritional Status (CONUT) scores and lower Geriatric Nutrition Risk and Prognostic Nutritional Indices (GNRI and PNI) have a higher risk of in-hospital mortality (67).

Coronavirus disease 2019 symptoms (e.g., anorexia, nausea, vomiting, dysphagia, bloating, abdominal pain, and diarrhea) can disrupt eating and diminish adequate food consumption. In various studies, approximately 50% of patients with COVID-19 report olfactory and gustatory dysfunction, which may contribute to loss of appetite and a subsequent reduction of nutrient intake (65, 68–70). Although malnutrition associated with COVID-19 can be overlooked during the management of critical medical issues, nutrition support for patients with COVID-19 is an essential component of care, though timing and other specifics require further empirical study.

Mechanisms

The intersection of nutritional and cardiometabolic risk in patients with COVID-19 occurs at the level of inflammation and insulin resistance (2, 6, 7). The CMBCD model represents a range of patients who may be more susceptible to infections, including COVID-19, and could benefit from nutritional interventions to mitigate DBCD, MBCD, and CMBCD progression (53, 71–73).

Various micronutrients are known to affect host immunity and the natural history of COVID-19. Some vitamins (e.g., A and D) are direct regulators of immune-cell gene expression, while others (e.g., C and E) promote a pro-oxidant milieu to improve immunity (74). Trace elements, such as zinc, copper, and iron, can modulate susceptibility to respiratory infections (74). Also, phytonutrients (e.g., berberine, curcumin, epigallocatechin gallate, genistein, resveratrol, and sulforaphane) can activate nuclear factor (erythroid-derived 2)–like 2 antioxidant transcription factor, thought to be an important mechanism in COVID-19 pathogenesis (75). Dietary fiber, a critically important component of healthy diets, is fermented into short-chain fatty acids in the intestine and can also mount significant anti-inflammatory effects (76). The net message is that all populations require a healthy eating pattern to control weight and ABCD, prevent DBCD/MBCD/CMBCD progression, and optimize immunity before, during, and after COVID-19 (2, 6, 7, 77).

The co-existence of undernutrition with micronutrient deficiencies is associated with COVID-19 and its sequelae. The effects are compounded by a disrupted sense of smell and taste, food insecurity, and social distancing that disrupts normal lifestyle behavior and leads to unhealthy eating patterns, physical inactivity, and routine change that can affect micronutrient intake (78–81). In some patients, COVID-19 also involves the gastrointestinal tract causing nausea, vomiting, and diarrhea, which further contributes to MBCD staged progression (82). In general, patients with cough, pneumonia, respiratory failure, and immune-neuroendocrine axis activation *via* a stress response to acute or chronic illness have an impaired ability to maintain adequate nourishment (83). Put another way, MBCD and other CMBCD drivers (especially ABCD and DBCD) can sufficiently alter the immune response so that prevention and treatment are compromised, and the progression of COVID-19 results in more severe disease.

Patients hospitalized with COVID-19 are at higher nutrition risk (84). Nutritional status becomes worse in patients with COVID-19 who are admitted to the ICU or require artificial ventilation (84). Immobility in the hospital bed is also associated with sarcopenia, which may affect whole-body functioning in patients with COVID-19 (85). In the short-term, these body composition changes can impact susceptibility and immunological responses to SARS-CoV-2, subsequent inflammatory response, and resulting metabolic and respiratory distress. In the long-term, these body composition

changes can modulate the time required for recovery, risk of ICU-acquired weakness and long-term disabilities, and mortality risk (84). Importantly, malnutrition has been shown to persist 30 days post-COVID-19 discharge (86). As such, patients with COVID-19, especially those with diabetes, may require tailored medical nutrition therapy to improve short- and long-term COVID-19 outcomes (71, 72, 87, 88).

Edge 3: Malnutrition and type 2 diabetes

Epidemiology

Although abnormal adiposity (overnutrition) is one of the most common comorbidities of T2D, undernutrition is also commonplace, with a frequency of one in seven patients with a high BMI, based on an outpatient diabetes cohort (89). A 21.2% malnutrition rate has been observed among elderly patients with diabetes, regardless of BMI (90). Additionally, many other studies have been conducted to determine the frequency of coexisting T2D and malnutrition. Among hospitalized patients in Spain, the risk of malnutrition (52) is higher with T2D (90). The risk of malnutrition and the actual malnutrition rate were 31 and 13%, respectively, among patients with diabetes assessed in a Turkish outpatient clinic; whereas, a similar assessment among hospitalized patients revealed even higher numbers: 39% risk vs. 25% prevalence (91, 92). Taken together, these associations suggest that when T2D is complicated by malnutrition (i.e., when diet is insufficient to meet age-related requirements), clinical challenges worsen and warrant a diligent approach to nutrition support and prudent supplementation with micro- and macronutrients (93, 94).

Patients with T2D can also exhibit sarcopenia (95, 96), a degenerative condition characterized by decreased skeletal muscle mass and weakness, typically observed in elderly populations and commonly associated with neurodegeneration, inflammation, and/or malnutrition (97–102). The association between T2D and sarcopenia had been shown in community-dwelling elderly adults (OR = 1.40, 95% CI: 1.18–1.66) (103). Older adults with either diagnosed or undiagnosed T2D showed excessive loss of skeletal muscle mass compared with those without T2D (103). While those without T2D lose an average of 198 ± 10 g of their total lean mass per year, patients with T2D lose about 222 ± 29 g/year and patients with undiagnosed T2D lose around 340 ± 37 g/year (104). Generalized loss of muscle mass is observed after age 40 and estimated to be 8% per decade up to age 70 years, and 15–25% every decade afterward (105). Additionally, in patients with T2D, plus or minus sarcopenia, omega-3 fatty acid intake is reduced (2.6 vs. 3.0 g/day, respectively) (106). Sarcopenia also compromises glycemic control and contributes to lower energy expenditure and generalized weakness as patients age, amplifying nutritional imperatives (101).

While sarcopenia is commonly conceptualized as weight loss and weakness related to diminished muscle mass, obesity may also accompany the disorder (107, 108). Thus, patients with T2D may present with both a low BMI, characteristic of sarcopenia, and high body fat content, characteristic of adiposity, leading to the descriptive terminology—"sarcopenic obesity." Diagnostic criteria often combine single or multiple assessments of sarcopenia with the quantification of systemic and central adiposity. Depending on definition and population, the prevalence of sarcopenic obesity ranges from 0 to 20% (with average prevalence rates between 5 and 10%) in numerous international studies of older adults (108, 109). Prevalence calculations are lower (3–8%) if the height-adjusted appendicular lean mass (ALM) index is used to define sarcopenia (110) rather than weight- or BMI-adjusted ALM indices (6–10%) (111). Moreover, prevalence rates of sarcopenic obesity are significantly higher (16–25%) among people 80 years of age and older or when lower quintiles of muscle mass or higher quintiles of body fat are factored into the assessments (112).

Among both inpatients and outpatients with diabetes, malnutrition is associated with a dysregulated immune system, higher risk for acute and chronic diseases, and protracted illness (113, 114). Such patients, particularly those with low lean body mass and high adiposity, consistently experience poorer outcomes in many different diseases (115). Manifestations of compromised immunity in patients with COVID-19 include lymphopenia upon admission and thrombocytopenia with leukopenia as infections worsen (116). Likewise, elevated levels of C-reactive protein and proinflammatory cytokines have been associated with increasing severity of illness and attendant nutritional risk (116, 117).

Mechanisms

In general, patients with T2D and sarcopenia exhibit specific underlying pathophysiological mechanisms that have implications for nutritional care and lifestyle modifications. Among them are the consequences of aging, including altered physical activity and dietary patterns, as well as hormonal deficiencies, low-grade systemic inflammation, loss of protein homeostasis in muscle, mitochondrial dysfunction, and reduced quantity and function of small mononuclear satellite cells that abut muscle fibers (118–121). Hormonal deficiencies related to sarcopenia include growth hormone, testosterone, thyroid hormone, and insulin-like growth factor, all of which contribute to loss of muscle mass and subsequent physical weakness starting in midlife (122, 123). As anabolic hormonal signals decrease, catabolic signals increase *via* pro-inflammatory cytokines (tumor necrosis factor alpha [TNF-α] and possibly interleukin-6 [IL-6]), homocysteine and high-sensitive C-reactive protein levels rise, and muscle wasting accelerates (96, 122). Muscle loss, in turn, exacerbates insulin resistance, hyperglycemia and DBCD progression (102).

Changes in muscle metabolism and the diminished capability to synthesize sufficient protein to maintain muscle mass contribute to wasting syndromes (124). Over prolonged time, oxidized proteins accumulate in skeletal muscle, and accrued lipofuscin and cross-linked protein deposits are retained (119). Non-contractile dysfunctional protein replaces normal tissue and leads to the loss of muscle function and the diminished strength that characterize sarcopenia (125). Moreover, motor nerve cells that carry impulses from brain to muscle diminish with age, and movement is compromised by insufficient neurotransmission. Supportive satellite cells, normally responsive to injury or activity, fail to undergo functional differentiation and fusion with myocytes, leading to loss of contractile function (119, 122). These pathophysiological

mechanisms can affect diaphragmatic muscles (126), which has significant implications for patients suffering from the syndromic triad of COVID-19, T2D, and malnutrition.

Nutritional therapy in patients with acute COVID-19, T2D, and malnutrition

Although no unified therapeutic regimen exists for the comprehensive management of patients with the syndromic triad, physical activity and therapeutic nutrition represent two approaches that have proven merit across the triad spectrum. Persistent daily activity and dedicated exercise programs can improve glycemic regulation and decrease muscle degradation, while diets rich in protein or amino acids are helpful for patients with T2D and malnutrition (127). Diets that accentuate protein and antioxidants may combat sarcopenia by increasing muscle mass and strength *via* improved protein homeostasis and autophagy (the orderly degradation and recycling of cellular components) as well as reduced oxidative stress (120). Likewise, branched-chain amino acids, polyunsaturated fatty acids, selenium, vitamin D, and zinc can reduce oxidative stress, support mitochondrial homeostasis, and mitigate low-grade inflammation, thus suggesting their potential roles in the treatment of sarcopenia (128). To the contrary, however, a Mendelian randomization analysis shows little effect from these nutrients with the exception of a genetically high concentration of serum iron, which increased sarcopenia risk (129).

At the onset of the pandemic, limited therapeutic options existed to combat the specific problems eventually seen with COVID-19, especially infection complicated by T2D and malnutrition. Consequently, several expert groups in clinical nutrition adapted standard critical care guidelines centered on nutrition for COVID-19 (130). A comparison of approaches by ASPEN and the European Society for Parenteral and Enteral Nutrition (ESPEN) is given in **Table 1** (131, 132). A brief summary of nutritional recommendations for patients with COVID-19 and critical illness includes: a blood glucose target of 6–8 mmol/L (106–145 mg/dL), nutrition assessments with malnutrition considerations, high-protein enteral and parenteral formulas, and up to a 50:50 ratio of fat-to-carbohydrate in patients receiving ventilatory support (132).

Individualized medical nutrition therapy can include diabetes-specific nutritional formulas (DSNFs) that are commercial products designed to improve glycemic status. The DSNFs are supported by extensive clinical research using oral enteral access routes for better glycemic control in the ICU setting (131–133). Additionally, specific benefits for DSNFs are observed in a randomized clinical trial where 73% of patients are ventilated and 51% of these have diabetes upon admission. Those who receive DSNF vs. a standard enteral formula require significantly less insulin to maintain lower glycemic variability through 48 h of care (134). Likewise, a study of patients with critical illness and hyperglycemia on mechanical ventilation reports lower insulin requirements and diminished glycemic variability using a DSNF compared to a high-protein control formula (135). Patients using a DSNF also experience a lower incidence of ventilator complications (135). Interpretation and application of these findings are important for patients with COVID-19 and T2D, as hyperglycemia and glycemic variability are each associated with worse clinical outcomes (136, 137).

Chronic/post-COVID-19

Recovery from COVID-19 also presents unique nutritional challenges related to both hospital/ICU duration and disease severity. Despite usual recommendations for increased protein intake for patients with critical illness (>1.3–1.5 g/kg/day) (132, 138), muscle loss and potential sarcopenia are still anticipated due, in part, to inactivity coupled with an inflamed hypermetabolic state (139). One Brazilian study reports a 30% decrease in rectus femoris cross-sectional area in patients with COVID-19 after just 10 days in the ICU (140). These patients may also experience post-ICU syndrome and/or dysphagia, which may adversely affect nutritional status (141–143). Special consideration for lingering COVID-19 symptoms is often necessary as 57% of COVID-19 survivors report ongoing problems through 6 months of recovery (144). In such circumstances, individualized rehabilitation efforts and conscientious diets are required to address malnutrition, sarcopenia, and/or dysphagia (145).

For patients with DBCD, particularly stage 3 T2D or stage 4 T2D with complications during prolonged recovery and rehabilitation, DSNF supplementation may be advisable as well. Research pre-dating the COVID-19 pandemic demonstrate that lower A1C values and increased body weight along with improvements in nutritional status and quality of life at 6 and 12 weeks are attainable with 2 servings/day of a high-protein DSNF in compromised older subjects (n = 402) with T2D and malnutrition (146). However, in a small study of enterally fed patients with T2D and unintentional weight loss, subsequent increases in weight are primarily attributed to body fat (147). Therefore, to improve body composition, rehabilitation efforts that include physical therapy or progressive resistance training should be part of multimodality care to increase muscle protein synthesis and enhance functional, metabolic, and psychological status (148, 149).

A significant knowledge gap surrounding specific micronutrient or anti-inflammatory supplementation still exists for patients

TABLE 1 Professional medical society approaches to nutrition in patients with COVID-19*.

Topic	ESPEN	ASPEN/SCCM
Use of PPE	☐	☑
Malnutrition screening	☑	☐
Malnutrition assessment	☑	☑
Nutrition intervention (in patients with malnutrition + COVID-19)	☑	☐
Feeding route	☑	☑
Indications/contraindications for EN	☑	☑
Feeding initiation	☑	☑
Feeding progression	☑	☑
Formula selection	☐	☑
Mention of specialty formulas	☐	☑
Tolerance monitoring	☑	☑
Post-mechanical ventilation considerations	☑	☐
ICU-acquired weakness	☑	☐

*ASPEN, American Society of Parenteral and Enteral Nutrition; COVID-19, coronavirus disease 2019; EN, enteral nutrition; ESPEN, European Society of Parenteral and Enteral Nutrition; ICU, intensive care unit; PPE, personal protective equipment; SCCM, society of critical care medicine.

with COVID-19 (7). Until more specific clinical evidence is available, expert opinions should prevail for implementing standard supplementation practices in patients with critical illness associated with COVID-19 (131). Emerging evidence suggests using vitamins, minerals, or other supportive micronutrients and standard nutrition formulas as tolerated by select patient groups.

For example, clinical practice guidelines propose administration of vitamins A, B complex, D, C, as well as selenium, zinc, and iron (132). Due to their anti-inflammatory qualities, omega-3 fatty acids are also studied in patients with critical illness and included in evidence-based guidelines (132, 150). In one study of critical illness and COVID-19, improved respiratory and renal function, along with higher 1-month survival, is noted in patients who received omega-3 fatty acid (400 mg EPA and 200 mg DHA) supplementation for 2 weeks, compared to patients receiving a standard enteral formula (151). Moreover, vitamin D and zinc gained attention for prophylaxis at the start of the pandemic (152).

In a cohort where over 50% of the sample have T2D, hospitalized patients with mild-to-moderate COVID-19 experience a faster recovery time for cough (∼3 days) and altered taste (∼5 days) when supplemented daily with 5,000 IU compared to 1,000 IU of vitamin D (153). Another study notes attenuated muscle catabolism with post-COVID-19 vitamin D supplementation of 200 IU/day for 6 weeks (154). However, the muscle retention is not reflected by improvements in physical function, which questions the adequacy of vitamin D metabolism to active 1,25-dihydroxyvitamin D in patients with critical illness and COVID-19, which could limit therapeutic potential (154, 155).

Other immunonutrients, including the amino acids glycine, arginine, and glutamine, may mitigate inflammation, protect lung and intestinal integrity during acute illness, and support muscle renewal during recovery (156). Unfortunately, the volatile status of the pandemic continues to limit clinical trials on COVID-19-specific nutrition recommendations, and some reports indicate suboptimal institutional adherence to existing guidelines (157–159). The completion of well-designed clinical trials and then creation and adoption of subsequent evidence-based guidelines is critically important for lowering mortality and shortening hospital stays (158).

Hypotheses and structure for early preventive care: The critical role of lifestyle medicine

Patient surveys conducted during the initial 2020 quarantines and social-distancing mandates disclose disruptive changes in lifestyle and personal routines with the COVID-19 pandemic (81). In particular, routine change negatively affects diabetes self-management, delays required healthcare, and accentuates individual pandemic-associated stress (81, 160–162). The effects of widespread systemic disruptions, such as lulls in screening practices and routine medical oversight, are now more clear and prompting greater attention by healthcare professionals (163–167). Reports and qualitative assessments pointing to patient-perceived practice gaps in usual diabetes support are collectively underscoring the need for countermeasures to reverse these disruptions and restore healthy lifestyles (168). This is particularly true in contemporary multimorbidity care models that seek to manage multiple chronic disease states (e.g., chronic/post-COVID-19 + T2D + malnutrition) concurrently (168, 169). In effect, the COVID-19 pandemic draws much needed attention to comprehensive chronic disease management, creating opportunities to advance diabetes and nutrition care.

Encouragement for lifestyle modification has the potential to minimize infection risk during the COVID-19 era. For example, one prospective cohort study observes higher risk (3.5%) for COVID-19 infection and severe COVID-19 illness in participants in the lowest vs. highest quartile of diet quality (170). Specifically, crude incidence rates are 3.5% higher for COVID-19 infection in the lowest diet quality quartile compared to the highest (170). Using very low-calorie diets, which often utilize meal replacement products, and incorporating DNSFs as part of lifestyle change, support weight loss and adequate glycemic control (171, 172). Awareness of the connection between COVID-19 risk and cardiometabolic impairment presents a unique opportunity to emphasize preventive and complementary initiatives to promote better health, reduce CMBCD risk, and mitigate DBCD progression with comprehensive interventions that incorporate lifestyle modifications.

Although access to health resources is challenged during the pandemic, telehealth offers a solution with a 154% increase in usage at the beginning of the pandemic (173). Telehealth may be especially applicable to diabetes with one study reporting that 95% of diabetes-related visits are virtual during the first year of the pandemic (174), and its use in the diabetes space is associated with improved patient outcomes (175–180). As an example, a recent meta-analysis reports increased time in range by 70.74 min and a slight decrease in A1C (−0.17%) among people using continuous glucose monitors (CGMs) compared to usual care (175). This effect could stem from healthful behavior modification associated with CGM use (technological nudges and motivation) (176). The integration of telehealth stands to diminish pre-pandemic barriers to healthcare, but it is important to consider stakeholder acceptance and inclusion of vulnerable populations (181).

The creation of a new construct—the syndromic triad of COVID-19, T2D, and malnutrition—not only allows the derivation of hypotheses relating early detection and management of malnutrition with mitigation of ABCD, DBCD, MBCD, and even CMBCD progression, but also prompts clinical decision-making now centered on early implementation of healthy lifestyle change. The pragmatic value of this new triad framework is supported by the coalescing of multiple clinical imperatives (i.e., COVID-19, dysglycemia, and nutrition) into a focused comprehensive approach. Core recommendations, which will require clinical validation, include:

1. Conduct aggressive case-finding protocols for malnutrition in all patients with COVID-19 at any DBCD stage;
2. Implement current standards of care to optimize nutrition in all patients with COVID-19 at any DBCD stage who have malnutrition or are at-risk for malnutrition;
3. Clarify and manage specific DBCD stages in all patients with COVID-19 at any MBCD stage; and
4. Assign a higher risk classification to patients newly diagnosed with COVID-19 when any DBCD or MBCD stage is also present.

Conclusion and future directions

There is an inherent association of COVID-19, T2D, and malnutrition supported by theoretical modeling, epidemiological data, and mechanistic relationships. Metabolic changes incurred by COVID-associated systemic inflammation increase the risk of dysglycemia, muscle protein catabolism, and nutritional deficiencies. Moreover, both T2D and malnutrition are risk factors of severe COVID-19. Awareness of these associations should encourage early diagnosis, prevention, and management of dysglycemia and malnutrition especially in vulnerable populations. Nutritional and lifestyle interventions aiming at optimizing glycemic control and improving nutritional status, as well as muscle health, could potentially decrease risk of COVID-19 complications. An individualized T2D-specific lifestyle and nutritional approach, and a close monitoring and management of glycemic status by experienced healthcare professionals, are essential to improve clinical outcomes for people with COVID-19.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Funding

This study received funding from Abbott Nutrition. The funder was not involved in the study design, collection, analysis, interpretation of data, and the writing of this article or the decision to submit it for publication.

Conflict of interest

EA was employed by Endocrinology Associates, Inc. AM was employed by Medical Education and Research Alliance (MedERA, Inc). KH was employed by Abbott Nutrition during the creation of the present manuscript. The manuscript was funded by Abbott Nutrition and completed independently from KH's role at Novo Nordisk, Inc., at the time of submission. Novo Nordisk, Inc., was not involved in the creation, funding, review, or submission of the completed manuscript. RH was employed by Abbott Nutrition.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Liu J, Ren Z, Qiang H, Wu J, Shen M, Zhang L, et al. Trends in the incidence of diabetes mellitus: results from the global burden of disease study 2017 and implications for diabetes mellitus prevention. *BMC Public Health.* (2020) 20:1415. doi: 10.1186/s12889-020-09502-x

2. Mechanick J, Rosenson R, Pinney S, Mancini D, Narula J, Fuster V. Coronavirus and cardiometabolic syndrome: JACC focus seminar. *J Am Coll Cardiol.* (2020) 76:2024–35. doi: 10.1016/j.jacc.2020.07.069

3. Mechanick J, Farkouh M, Newman J, Garvey W. Cardiometabolic-based chronic disease, adiposity and dysglycemia drivers: JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 75:525–38. doi: 10.1016/j.jacc.2019.11.044

4. Mechanick J, Farkouh M, Newman J, Garvey W. Cardiometabolic-based chronic disease, addressing knowledge and clinical practice gaps: JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 75:539–55. doi: 10.1016/j.jacc.2019.11.046

5. de Oliveira Correia E, Mechanick J, Dos Santos Barbetta L, Jorge A, Mesquita E. Cardiometabolic-based chronic disease: adiposity and dysglycemia drivers of heart failure. *Heart Fail Rev.* (2022). doi: 10.1007/s10741-022-10233-x [Epub ahead of print].

6. Mechanick J, Garber A, Grunberger G, Handelsman Y, Garvey W. Dysglycemia-based chronic disease: an American association of clinical endocrinologists position statement. *Endocr Pract.* (2018) 24:995–1011. doi: 10.4158/PS-2018-0139

7. Mechanick J, Carbone S, Dickerson R, Hernandez B, Hurt R, Irving S, et al. Clinical nutrition research and the COVID-19 pandemic: a scoping review of the ASPEN COVID-19 task force on nutrition research. *JPEN J Parenter Enteral Nutr.* (2021) 45:13–31. doi: 10.1002/jpen.2036

8. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. *Diabetologia.* (2022) 65:949–54. doi: 10.1007/s00125-022-05670-0

9. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol.* (2022) 10:311–21. doi: 10.1016/S2213-8587(22)00044-4

10. Hernandez-Romieu A, Carton T, Saydah S, Azziz-Baumgartner E, Boehmer T, Garret N, et al. Prevalence of select new symptoms and conditions among persons aged younger than 20 years and 20 years or older at 31 to 150 days after testing positive or negative for SARS-CoV-2. *JAMA Netw Open.* (2022) 5:e2147053. doi: 10.1001/jamanetworkopen.2021.47053

11. Barrett C, Koyama A, Alvarez P, Chow W, Lundeen E, Perrine C, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 years - united states, march 1, 2020-June 28, 2021. *MMWR Morb Mortal Wkly Rep.* (2022) 71:59–65. doi: 10.15585/mmwr.mm7102e2

12. Modarelli R, Sarah S, Ramaker M, Bolobiongo M, Benjamin R, Gumus Balikcioglu P. Pediatric diabetes on the rise: trends in incident diabetes during the COVID-19 pandemic. *J Endocr Soc.* (2022) 6:bvac024. doi: 10.1210/jendso/bvac024

13. Banerjee M, Pal R, Dutta S. Risk of incident diabetes post-COVID-19: a systematic review and meta-analysis. *Prim Care Diabetes.* (2022) 16:591–3. doi: 10.1016/j.pcd.2022.05.009

14. Wander P, Lowy E, Beste L, Tulloch-Palomino L, Korpak A, Peterson A, et al. The incidence of diabetes among 2,777,768 veterans with and without recent SARS-CoV-2 infection. *Diabetes Care.* (2022) 45:782–8. doi: 10.2337/dc21-1686

15. Docherty A, Harrison E, Green C, Hardwick H, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ.* (2020) 369:m1985. doi: 10.1136/bmj.m1985

16. Garg M, Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai S, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 states, march 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:1081–8. doi: 10.15585/mmwr.mm6932e3

17. Richardson S, Hirsch J, Narasimhan M, Crawford J, McGinn T, Davidson K, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA.* (2020) 323:2052–9. doi: 10.1001/jama.2020.6775

18. Suleyman G, Fadel R, Malette K, Hammond C, Abdulla H, Entz A, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. *JAMA Netw Open.* (2020) 3:e2012270. doi: 10.1001/jamanetworkopen.2020.12270

19. Thakur B, Dubey P, Benitez J, Torres J, Reddy S, Shokar N, et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. *Sci Rep.* (2021) 11:8562. doi: 10.1038/s41598-021-88130-w

20. Wortham J, Lee J, Althomsons S, Latash J, Davidson A, Guerra K, et al. Characteristics of persons who died with COVID-19 - united states, february 12-May 18, 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:923–9. doi: 10.15585/mmwr.mm6928e1

21. Bailly L, Fabre R, Courjon J, Carles M, Dellamonica J, Pradier C. Obesity, diabetes, hypertension and severe outcomes among inpatients with coronavirus disease 2019: a nationwide study. *Clin Microbiol Infect.* (2022) 28:114–23. doi: 10.1016/j.cmi.2021.09.010

22. Hoddy K, Axelrod C, Mey J, Hari A, Beyl R, Blair J, et al. Insulin resistance persists despite a metabolically healthy obesity phenotype. *Obesity.* (2022) 30:39–44.

23. Unluguzel Ustun G, Keskin A, Aci R, Arslanbek Erdem M, Ari M. Association between Hb A1c and severity of COVID-19 patients. *Hemoglobin.* (2021) 45:124–8. doi: 10.1080/03630269.2021.1926278

24. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol.* (2020) 127:104354. doi: 10.1016/j.jcv.2020.104354

25. Corona G, Pizzocaro A, Vena W, Rastrelli G, Semeraro F, Isidori A, et al. Diabetes is most important cause for mortality in COVID-19 hospitalized patients: systematic review and meta-analysis. *Rev Endocr Metab Disord.* (2021) 22:275–96. doi: 10.1007/s11154-021-09630-8

26. Alberti A, Schuelter-Trevisol F, Iser B, Traebert E, Freiberger V, Ventura L, et al. Obesity in people with diabetes in COVID-19 times: important considerations and precautions to be taken. *World J Clin Cases.* (2021) 9:5358–71. doi: 10.12998/wjcc.v9.i20.5358

27. Rawshani A, Kjölhede E, Rawshani A, Sattar N, Eeg-Olofsson K, Adiels M, et al. Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: a nationwide retrospective cohort study. *Lancet Reg Health Eur.* (2021) 4:100105. doi: 10.1016/j.lanepe.2021.100105

28. Xie J, Zu Y, Alkhatib A, Pham T, Gill F, Jang A, et al. Metabolic syndrome and COVID-19 mortality among adult black patients in New Orleans. *Diabetes Care.* (2020) 44:188–93. doi: 10.2337/dc20-1714

29. Sperling L, Mechanick J, Neeland I, Herrick C, Després J, Ndumele C, et al. The cardiometabolic health alliance: working toward a new care model for the metabolic syndrome. *J Am Coll Cardiol.* (2015) 66:1050–67. doi: 10.1016/j.jacc.2015.06.1328

30. Mason K, Maudsley G, McHale P, Pennington A, Day J, Barr B. Age-adjusted associations between comorbidity and outcomes of COVID-19: a review of the evidence from the early stages of the pandemic. *Front Public Health.* (2021) 9:584182. doi: 10.3389/fpubh.2021.584182

31. Pal R, Bhadada S. COVID-19 and diabetes mellitus: an unholy interaction of two pandemics. *Diabetes Metab Syndr.* (2020) 14:513–7. doi: 10.1016/j.dsx.2020.04.049

32. Berbudi A, Rahmadika N, Tjahjadi A, Ruslami R. Type 2 diabetes and its impact on the immune system. *Curr Diabetes Rev.* (2020) 16:442–9. doi: 10.2174/1573399815666191024085838

33. Singh V. Can vitamins, as epigenetic modifiers, enhance immunity in COVID-19 patients with non-communicable disease? *Curr Nutr Rep.* (2020) 9:202–9. doi: 10.1007/s13668-020-00330-4

34. Roberts G, Quinn S, Valentine N, Alhawassi T, O'Dea H, Stranks S, et al. Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. *J Clin Endocrinol Metab.* (2015) 100:4490–7. doi: 10.1210/jc.2015-2660

35. Mondal S, DasGupta R, Lodh M, Garai R, Choudhury B, Hazra A, et al. Stress hyperglycemia ratio, rather than admission blood glucose, predicts in-hospital mortality and adverse outcomes in moderate-to severe COVID-19 patients, irrespective of pre-existing glycemic status. *Diabetes Res Clin Pract.* (2022) 190:109974. doi: 10.1016/j.diabres.2022.109974

36. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7

37. Caballero A, Ceriello A, Misra A, Aschner P, McDonnell M, Hassanein M, et al. COVID-19 in people living with diabetes: an international consensus. *J Diabetes Complications.* (2020) 34:107671. doi: 10.1016/j.jdiacomp.2020.107671

38. Singh A, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. *Diabetes Res Clin Pract.* (2020) 167:108382. doi: 10.1016/j.diabres.2020.108382

39. Hasheminasabgorji E, Jha J. Dyslipidemia, diabetes and atherosclerosis: role of inflammation and ros-redox-sensitive factors. *Biomedicines.* (2021) 9:1602. doi: 10.3390/biomedicines9111602

40. Pezhman L, Tahrani A, Chimen M. Dysregulation of leukocyte trafficking in type 2 diabetes: mechanisms and potential therapeutic avenues. *Front Cell Dev Biol.* (2021) 9:624184. doi: 10.3389/fcell.2021.624184

41. Scheen M, Giraud R, Bendjelid K. Stress hyperglycemia, cardiac glucotoxicity, and critically ill patient outcomes current clinical and pathophysiological evidence. *Physiol Rep.* (2021) 9:e14713. doi: 10.14814/phy2.14713

42. Zatterale F, Longo M, Naderi J, Raciti G, Desiderio A, Miele C, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Front Physiol.* (2020) 10:1607. doi: 10.3389/fphys.2019.01607

43. Rojas A, Lindner C, Gonzàlez I, Morales M. Advanced-glycation end-products axis: a contributor to the risk of severe illness from COVID-19 in diabetes patients. *World J Diabetes.* (2021) 12:590–602. doi: 10.4239/wjd.v12.i5.590

44. Landecho M, Marin-Oto M, Recalde-Zamacona B, Bilbao I, Frühbeck G. Obesity as an adipose tissue dysfunction disease and a risk factor for infections - Covid-19 as a case study. *Eur J Intern Med.* (2021) 91:3–9. doi: 10.1016/j.ejim.2021.03.031

45. D'Onofrio N, Scisciola L, Sardu C, Trotta M, De Feo M, Maiello C, et al. Glycated ACE2 receptor in diabetes: open door for SARS-COV-2 entry in cardiomyocyte. *Cardiovasc Diabetol.* (2021) 20:99. doi: 10.1186/s12933-021-01286-7

46. Norouzi M, Norouzi S, Ruggiero A, Khan M, Myers S, Kavanagh K, et al. Type-2 diabetes as a risk factor for severe COVID-19 infection. *Microorganisms.* (2021) 9:1211. doi: 10.3390/microorganisms9061211

47. Miricescu D, Balan D, Tulin A, Stiru O, Vacaroiu I, Mihai D, et al. Impact of adipose tissue in chronic kidney disease development (review). *Exp Ther Med.* (2021) 21:539. doi: 10.3892/etm.2021.9969

48. Satou R, Penrose H, Navar L. Inflammation as a regulator of the renin-angiotensin system and blood pressure. *Curr Hypertens Rep.* (2018) 20:100. doi: 10.1007/s11906-018-0900-0

49. Steenblock C, Richter S, Berger I, Barovic M, Schmid J, Schubert U, et al. Viral infiltration of pancreatic islets in patients with COVID-19. *Nat Commun.* (2021) 12:3534. doi: 10.1038/s41467-021-23886-3

50. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect.* (2020) 80:607–13. doi: 10.1016/j.jinf.2020.03.037

51. Jiang Y, Zhao T, Zhou X, Xiang Y, Gutierrez-Castrellon P, Ma X. Inflammatory pathways in COVID-19: mechanism and therapeutic interventions. *MedComm (2020).* (2022) 3:e154. doi: 10.1002/mco2.154

52. White J, Guenter P, Jensen G, Malone A, Schofield M, Academy Malnutrition Work Group, et al. Consensus statement: academy of nutrition and dietetics and American society for parenteral and enteral nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr.* (2012) 36:275–83. doi: 10.1177/0148607112440285

53. ASPEN. *ASPEN Definitions.* (2022). Available online at: https://www.nutritioncare.org/ (accessed January 10, 2022).

54. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff S, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr.* (2017) 36:49–64. doi: 10.1016/j.clnu.2016.09.004

55. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition–an ESPEN consensus statement. *Clin Nutr.* (2015) 34:335–40. doi: 10.1016/j.clnu.2015.03.001

56. Mogensen K, Malone A, Becker P, Cutrell S, Frank L, Gonzales K, et al. Academy of nutrition and dietetics/American society for parenteral and enteral nutrition consensus malnutrition characteristics: usability and association with outcomes. *Nutr Clin Pract.* (2019) 34:657–65. doi: 10.1002/ncp.10310

57. Rojer A, Kruizenga H, Trappenburg M, Reijnierse E, Sipilä S, Narici M, et al. The prevalence of malnutrition according to the new ESPEN definition in four diverse populations. *Clin Nutr.* (2016) 35:758–62. doi: 10.1016/j.clnu.2015.06.005

58. Mertens E, Peñalvo J. The burden of malnutrition and fatal COVID-19: a global burden of disease analysis. *Front Nutr.* (2021) 7:619850. doi: 10.3389/fnut.2020.619850

59. Burgos R, García-Almeida J, Matía-Martín P, Palma S, Sanz-Paris A, Zugasti A, et al. Malnutrition management of hospitalized patients with diabetes/hyperglycemia and COVID-19 infection. *Rev Endocr Metab Disord.* (2022) 23:205–13. doi: 10.1007/s11154-022-09714-z

60. Tappenden K, Quatrara B, Parkhurst M, Malone A, Fanjiang G, Ziegler T. Critical role of nutrition in improving quality of care: an interdisciplinary call to action to address adult hospital malnutrition. *JPEN J Parenter Enteral Nutr.* (2013) 37:482–97. doi: 10.1177/0148607113484066

61. Burgos R, Joaquín C, Blay C, Vaqué C. Disease-related malnutrition in hospitalized chronic patients with complex needs. *Clin Nutr.* (2020) 39:1447–53. doi: 10.1016/j.clnu.2019.06.006

62. Bedock D, Bel Lassen P, Mathian A, Moreau P, Couffignal J, Ciangura C, et al. Prevalence and severity of malnutrition in hospitalized COVID-19 patients. *Clin Nutr ESPEN.* (2020) 40:214–9. doi: 10.1016/j.clnesp.2020.09.018

63. Laviano A, Koverech A, Mari A. Cachexia: clinical features when inflammation drives malnutrition. *Proc Nutr Soc.* (2015) 74:348–54. doi: 10.1017/S0029665115000117

64. Wang J, Chen L, Huang Z, Lu J, Yang Y, Zhao X, et al. A synergistic association between inflammation, malnutrition, and mortality in patients with diabetics. *Front Nutr.* (2022) 9:872512. doi: 10.3389/fnut.2022.872512

65. Rouget A, Vardon-Bounes F, Lorber P, Vavasseur A, Marion O, Marcheix B, et al. Prevalence of malnutrition in coronavirus disease 19: the NUTRICOV study. *Br J Nutr.* (2021) 126:1296–303. doi: 10.1017/S0007114520005127

66. Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, et al. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. *Eur J Clin Nutr.* (2020) 74:871–5. doi: 10.1038/s41430-020-0642-3

67. Song F, Ma H, Wang S, Qin T, Xu Q, Yuan H, et al. Nutritional screening based on objective indices at admission predicts in-hospital mortality in patients with COVID-19. *Nutr J.* (2021) 20:46. doi: 10.1186/s12937-021-00702-8

68. Bénézit F, Le Turnier P, Declerck C, Paillé C, Revest M, Dubée V, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *Lancet Infect Dis.* (2020) 20:1014–5. doi: 10.1016/S1473-3099(20)30297-8

69. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis.* (2020) 71:889–90. doi: 10.1093/cid/ciaa330

70. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127

71. Antwi J, Appiah B, Oluwakuse B, Abu B. The nutrition-COVID-19 interplay: a review. *Curr Nutr Rep.* (2021) 10:364–74. doi: 10.1007/s13668-021-00380-2

72. James P, Ali Z, Armitage A, Bonell A, Cerami C, Drakesmith H, et al. The role of nutrition in COVID-19 susceptibility and severity of disease: a systematic review. *J Nutr.* (2021) 151:1854–78. doi: 10.1093/jn/nxab059

73. Lecube A, Pachón G, Petriz J, Hernández C, Simó R. Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement. *PLoS One.* (2011) 6:e23366. doi: 10.1371/journal.pone.0023366

74. Calder P. Nutrition, immunity and COVID-19. *BMJ Nutr Prev Health.* (2020) 3:74–92. doi: 10.1136/bmjnph-2020-000085

75. Bousquet J, Cristol J, Czarlewski W, Anto J, Martineau A, Haahtela T, et al. Nrf2-interacting nutrients and COVID-19: time for research to develop adaptation strategies. *Clin Transl Allergy.* (2020) 10:58. doi: 10.1186/s13601-020-00362-7

76. Iddir M, Brito A, Dingeo G, Fernandez Del Campo S, Samouda H, La Frano M, et al. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis. *Nutrients.* (2020) 12:1562. doi: 10.3390/nu12061562

77. Butler M, Barrientos R. The impact of nutrition on COVID-19 susceptibility and long-term consequences. *Brain Behav Immun.* (2020) 87:53–4. doi: 10.1016/j.bbi.2020.04.040

78. Boscolo-Rizzo P, Borsetto D, Spinato G, Fabbris C, Menegaldo A, Gaudioso P, et al. New onset of loss of smell or taste in household contacts of home-isolated SARS-CoV-2-positive subjects. *Eur Arch Otorhinolaryngol.* (2020) 277:2637–40. doi: 10.1007/s00405-020-06066-9

79. Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of COVID-19 home confinement on eating behaviour and physical activity: results of the ECLB-COVID19 international online survey. *Nutrients.* (2020) 12:1583. doi: 10.3390/nu12061583

80. Bhutani S, vanDellen M, Cooper J. Longitudinal weight gain and related risk behaviors during the covid-19 pandemic in adults in the us. *Nutrients.* (2021) 13:671. doi: 10.3390/nu13020671

81. Ray, JL, Srinath R, Mechanick JI. The negative impact of routine, dietary pattern, and physical activity on obesity and dysglycemia during the COVID-19 pandemic. *Am J Lifestyle Med.* (2022) 21:15598276221084923. doi: 10.1177/15598276221084923

82. Marasco G, Cremon C, Barbaro M, Salvi D, Cacciari G, Kagramanova A, et al. Prevalence of gastrointestinal symptoms in severe acute respiratory syndrome coronavirus 2 infection: results of the prospective controlled multinational GI-COVID-19 Study. *Am J Gastroenterol.* (2022) 117:147–57. doi: 10.14309/ajg.0000000000001541

83. Schulman R, Mechanick J. Metabolic and nutrition support in the chronic critical illness syndrome. *Respir Care.* (2012) 57:958–77; discussion977–8. doi: 10.4187/respcare.01620

84. Bear D, Merriweather J. Nutrition in postacute rehabilitation of COVID-19 survivors. *Curr Opin Clin Nutr Metab Care.* (2022) 25:154–8. doi: 10.1097/MCO.0000000000000819

85. Cava E, Carbone S. Coronavirus disease 2019 pandemic and alterations of body composition. *Curr Opin Clin Nutr Metab Care.* (2021) 24:229–35. doi: 10.1097/MCO.0000000000000740

86. Quilliot D, Gérard M, Bonsack O, Malgras A, Vaillant M, Di Patrizio P, et al. Impact of severe SARS-CoV-2 infection on nutritional status and subjective functional loss in a prospective cohort of COVID-19 survivors. *BMJ Open.* (2021) 11:e048948. doi: 10.1136/bmjopen-2021-048948

87. Galmés S, Serra F, Palou A. Current state of evidence: influence of nutritional and nutrigenetic factors on immunity in the COVID-19 pandemic framework. *Nutrients.* (2020) 12:2738. doi: 10.3390/nu12092738

88. Nieto-Martínez R, González-Rivas J, Mechanick J. Cardiometabolic risk: new chronic care models. *JPEN J Parenter Enteral Nutr.* (2021) 45:85–92. doi: 10.1002/jpen.2264

89. Vural Keskinler M, FeyŸzoglu G, Yildiz K, Oguz A. The frequency of malnutrition in patients with type 2 diabetes. *Medeni Med J.* (2021) 36:117–22. doi: 10.5222/MMJ.2021.44270

90. Sanz París A, García J, Gómez-Candela C, Burgos R, Martín Á, Matía P, et al. Malnutrition prevalence in hospitalized elderly diabetic patients. *Nutr Hosp.* (2013) 28:592–9. doi: 10.3305/nh.2013.28.3.6472

91. Kuyumcu ME, Yeşil Y, Oztürk ZA, Halil M, Ulger Z, Yavuz BB, et al. Challenges in nutritional evaluation of hospitalized elderly; always with mini-nutritional assessment? *Eur Geriatr Med.* (2013) 4:231–6.

92. Saka B, Kaya O, Ozturk G, Erten N, Karan M. Malnutrition in the elderly and its relationship with other geriatric syndromes. *Clin Nutr.* (2010) 29:745–8. doi: 10.1016/j.clnu.2010.04.006

93. Vischer U, Perrenoud L, Genet C, Ardigo S, Registe-Rameau Y, Herrmann F. The high prevalence of malnutrition in elderly diabetic patients: implications for anti-diabetic drug treatments. *Diabet Med.* (2010) 27:918–24. doi: 10.1111/j.1464-5491.2010.03047.x

94. Ahmed N, Choe Y, Mustad V, Chakraborty S, Goates S, Luo M, et al. Impact of malnutrition on survival and healthcare utilization in Medicare beneficiaries with diabetes: a retrospective cohort analysis. *BMJ Open Diabetes Res Care.* (2018) 6:e000471. doi: 10.1136/bmjdrc-2017-000471

95. Stangl M, Böcker W, Chubanov V, Ferrari U, Fischereder M, Gudermann T, et al. Sarcopenia–endocrinological and neurological aspects. *Exp Clin Endocrinol Diabetes.* (2019) 127:8–22. doi: 10.1055/a-0672-1007

96. Mu Z, Fu J, Sun L, Chan P, Xiu S. Associations between homocysteine, inflammatory cytokines and sarcopenia in Chinese older adults with type 2 diabetes. *BMC Geriatr.* (2021) 21:692. doi: 10.1186/s12877-021-02622-y

97. Liccini A, Malmstrom T. Frailty and sarcopenia as predictors of adverse health outcomes in persons with diabetes mellitus. *J Am Med Dir Assoc.* (2016) 17:846–51. doi: 10.1016/j.jamda.2016.07.007

98. Venturelli M, Reggiani C, Schena F. Beyond the current knowledge on sarcopenia: new insight on neuromuscular factors. *Aging Clin Exp Res.* (2022) 34:1183–5. doi: 10.1007/s40520-022-02082-3

99. Mesinovic J, Zengin A, De Courten B, Ebeling P, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. *Diabetes Metab Syndr Obes.* (2019) 12:1057–72. doi: 10.2147/DMSO.S186600

100. Qiao Y, Chai Y, Gong H, Zhuldyz Z, Stehouwer C, Zhou J, et al. The association between diabetes mellitus and risk of sarcopenia: accumulated evidences from observational studies. *Front Endocrinol (Lausanne).* (2021) 12:782391. doi: 10.3389/fendo.2021.782391

101. Izzo A, Massimino E, Riccardi G, Della Pepa G. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. *Nutrients.* (2021) 13:183. doi: 10.3390/nu13010183

102. Sousa-Victor P, Muñoz-Cánoves P. Regenerative decline of stem cells in sarcopenia. *Mol Aspects Med.* (2016) 50:109–17. doi: 10.1016/j.mam.2016.02.002

103. Gao Q, Hu K, Yan C, Zhao B, Mei F, Chen F, et al. Sarcopenia in community-dwelling older adults: a systematic review and meta-analysis. *Nutrients.* (2021) 13:4291. doi: 10.3390/nu13124291

104. Park S, Goodpaster B, Lee J, Kuller L, Boudreau R, de Rekeneire N, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care.* (2009) 32:1993–7. doi: 10.2337/dc09-0264

105. Filippin L, Teixeira V, da Silva M, Miraglia F, da Silva F. Sarcopenia: a predictor of mortality and the need for early diagnosis and intervention. *Aging Clin Exp Res.* (2015) 27:249–54. doi: 10.1007/s40520-014-0281-4

106. Okamura T, Hashimoto Y, Miki A, Kaji A, Sakai R, Iwai K, et al. Reduced dietary omega-3 fatty acids intake is associated with sarcopenia in elderly patients with type 2 diabetes: a cross-sectional study of KAMOGAWA-DM cohort study. *J Clin Biochem Nutr.* (2020) 66:233–7. doi: 10.3164/jcbn.19-85

107. Xie W, Xiao G, Fan Y, He M, Lv S, Li Y. Sarcopenic obesity: research advances in pathogenesis and diagnostic criteria. *Aging Clin Exp Res.* (2021) 33:247–52. doi: 10.1007/s40520-019-01435-9

108. Lee D, Shook R, Drenowatz C, Blair S. Physical activity and sarcopenic obesity: definition, assessment, prevalence and mechanism. *Future Sci OA.* (2016) 2:FSO127. doi: 10.4155/fsoa-2016-0028

109. Meng P, Hu Y, Fan L, Zhang Y, Zhang M, Sun J, et al. Sarcopenia and sarcopenic obesity among men aged 80 years and older in Beijing: prevalence and its association with functional performance. *Geriatr Gerontol Int.* (2014) 14(Suppl. 1):29–35. doi: 10.1111/ggi.12211

110. Hwang B, Lim J, Lee J, Choi N, Ahn Y, Park B. Prevalence rate and associated factors of sarcopenic obesity in Korean elderly population. *J Korean Med Sci.* (2012) 27:748–55. doi: 10.3346/jkms.2012.27.7.748

111. Kim Y, Lee Y, Chung Y, Lee D, Joo N, Hong D, et al. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the fourth Korean national health and nutritional examination surveys. *J Gerontol A Biol Sci Med Sci.* (2012) 67:1107–13. doi: 10.1093/gerona/gls071

112. Muñoz-Arribas A, Mata E, Pedrero-Chamizo R, Espino L, Gusi N, Villa G, et al. Obesidad sarcopénica y condición física en octogenarios; proyecto multi-céntrico EXERNET [Sarcopenic obesity and physical fitness in octogenarians: the multi-center EXERNET Project]. *Nutr Hosp.* (2013) 28:1877–83.

113. Norman K, Haß U, Pirlich M. Malnutrition in older adults – recent advances and remaining challenges. *Nutrients.* (2021) 13:2764. doi: 10.3390/nu13082764

114. Omura T, Araki A. Skeletal muscle as a treatment target for older adults with diabetes mellitus: the importance of a multimodal intervention based on functional category. *Geriatr Gerontol Int.* (2022) 22:110–20. doi: 10.1111/ggi.14339

115. Silverio R, Gonçalves D, Andrade M, Seelaender M. Coronavirus disease 2019 (COVID-19) and nutritional status: the missing link? *Adv Nutr.* (2021) 12:682–92. doi: 10.1093/advances/nmaa125

116. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. China medical treatment expert group for covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032

117. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3

118. Hasegawa Y, Takahashi F, Hashimoto Y, Munekawa C, Hosomi Y, Okamura T, et al. Effect of COVID-19 pandemic on the change in skeletal muscle mass in older patients with type 2 diabetes: a retrospective cohort study. *Int J Environ Res Public Health.* (2021) 18:4188. doi: 10.3390/ijerph18084188

119. Dhillon R, Hasni S. Pathogenesis and management of sarcopenia. *Clin Geriatr Med.* (2017) 33:17–26. doi: 10.1016/j.cger.2016.08.002

120. Barbiera A, Pelosi L, Sica G, Scicchitano B. Nutrition and microRNAs: novel insights to fight sarcopenia. *Antioxidants (Basel).* (2020) 9:951. doi: 10.3390/antiox9100951

121. Sebastián D, Sorianello E, Segalés J, Irazoki A, Ruiz-Bonilla V, Sala D, et al. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. *EMBO J.* (2016) 35:1677–93. doi: 10.15252/embj.201593084

122. Ryall J, Schertzer J, Lynch G. Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness. *Biogerontology.* (2008) 9:213–28. doi: 10.1007/s10522-008-9131-0

123. Faulkner J, Larkin L, Claflin D, Brooks S. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol.* (2007) 34:1091–6. doi: 10.1111/j.1440-1681.2007.04752.x

124. Yang Q, Chan P. Skeletal muscle metabolic alternation develops sarcopenia. *Aging Dis.* (2022) 13:801–14. doi: 10.14336/AD.2021.1107

125. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. he mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? *J Cachexia Sarcopenia Muscle.* (2020) 11:348–65. doi: 10.1002/jcsm.12536

126. Elliott J, Greising S, Mantilla C, Sieck G. Functional impact of sarcopenia in respiratory muscles. *Respir Physiol Neurobiol.* (2016) 226:137–46. doi: 10.1016/j.resp.2015.10.001

127. Argyropoulou D, Geladas N, Nomikos T, Paschalis V. Exercise and nutrition strategies for combating sarcopenia and type 2 diabetes mellitus in older adults. *J Funct Morphol Kinesiol.* (2022) 7:48. doi: 10.3390/jfmk7020048

128. Romani M, Berger M, D'Amelio P. From the bench to the bedside: branched amino acid and micronutrient strategies to improve mitochondrial dysfunction leading to sarcopenia. *Nutrients.* (2022) 14:483. doi: 10.3390/nu14030483

129. Sha T, Li W, He H, Wu J, Wang Y, Li H. Causal relationship of genetically predicted serum micronutrients levels with sarcopenia: a Mendelian randomization study. *Front Nutr.* (2022) 9:913155. doi: 10.3389/fnut.2022.913155

130. Cawood A, Walters E, Smith T, Sipaul R, Stratton RJ. A review of nutrition support guidelines for individuals with or recovering from COVID-19 in the community. *Nutrients.* (2020) 12:3230. doi: 10.3390/nu12113230

131. Martindale R, Patel J, Taylor B, Arabi Y, Warren M, McClave S. Nutrition therapy in critically ill patients with coronavirus disease 2019. *JPEN J Parenter Enteral Nutr.* (2020) 44:1174–84. doi: 10.1002/jpen.1930

132. Barazzoni R, Bischoff S, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr.* (2020) 39:1631–8. doi: 10.1016/j.clnu.2020.03.022

133. Noronha J, Mechanick J. Is there a role for diabetes-specific nutrition formulas as meal replacements in type 2 diabetes? *Front Endocrinol (Lausanne).* (2022) 13:874968. doi: 10.3389/fendo.2022.874968

134. Doola R, Deane A, Tolcher D, Presneill J, Barrett H, Forbes J, et al. The effect of a low carbohydrate formula on glycaemia in critically ill enterally-fed adult patients with hyperglycaemia: a blinded randomised feasibility trial. *Clin Nutr ESPEN.* (2019) 31:80–7. doi: 10.1016/j.clnesp.2019.02.013

135. Mesejo A, Montejo-González J, Vaquerizo-Alonso C, Lobo-Tamer G, Zabarte-Martinez M, Herrero-Meseguer J, et al. Diabetes-specific enteral nutrition formula in hyperglycemic, mechanically ventilated, critically ill patients: a prospective, open-label, blind-randomized, multicenter study. *Crit Care.* (2015) 19:390. doi: 10.1186/s13054-015-1108-1

136. Zhu B, Jin S, Wu L, Hu C, Wang Z, Bu L, et al. J-shaped association between fasting blood glucose levels and COVID-19 severity in patients without diabetes. *Diab Res Clin Pract.* (2020) 168:108381.

137. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab.* (2020) 31: 1068–1077.e3.

138. Deer R, Volpi E. Protein requirements in critically ill older adults. *Nutrients.* (2018) 10:378. doi: 10.3390/nu10030378

139. Soares M, Eggelbusch M, Naddaf E, Gerrits K, van der Schaaf M, van den Borst B, et al. Skeletal muscle alterations in patients with acute COVID-19 and post-acute sequelae of Covid-19. *J Cachexia Sarcopenia Muscle.* (2022) 13:11–22. doi: 10.1002/jcsm.12896

140. de Andrade-Junior M, de Salles I, de Brito C, Pastore-Junior L, Righetti R, Yamaguti W. Skeletal muscle wasting and function impairment in intensive care patients with severe COVID-19. *Front Physiol.* (2021) 12:640973. doi: 10.3389/fphys.2021.640973

141. Rousseau A, Minguet P, Colson C, Kellens I, Chaabane S, Delanaye P, et al. Post-intensive care syndrome after a critical COVID-19: cohort study from a Belgian follow-up clinic. *Ann Intensive Care.* (2021) 11:118. doi: 10.1186/s13613-021-00910-9

142. Grilli G, Giancaspro R, Del Colle A, Quarato C, Lacedonia D, Foschino Barbaro M, et al. Dysphagia in non-intubated patients affected by COVID-19 infection. *Eur Arch Otorhinolaryngol.* (2022) 279:507–13. doi: 10.1007/s00405-021-07062-3

143. Marchese M, Ausili Cefaro C, Mari G, Proietti I, Carfì A, Tosato M, et al. Oropharyngeal dysphagia after hospitalization for COVID-19 disease: our screening results. *Dysphagia.* (2022) 37:447–53. doi: 10.1007/s00455-021-10325-0

144. Taquet M, Dercon Q, Luciano S, Gettes J, Husain M, Harrison P. Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med.* (2021) 18:e1003773. doi: 10.1371/journal.pmed.1003773

145. Cereda E, Clavé P, Collins P, Holdoway A, Wischmeyer P. Recovery-focused nutritional therapy across the continuum of care: learning from COVID-19. *Nutrients.* (2021) 13:3293. doi: 10.3390/nu13093293

146. Matia Martin P, Robles Agudo F, Lopez Medina J, Sanz Paris A, Tarazona Santabalbina F, Domenech Pascual J, et al. Effectiveness of an oral diabetes-specific supplement on nutritional status, metabolic control, quality or life, and functional status in elderly patients. A multicentre study. *Clin Nutr.* (2019) 38:1253–61. doi: 10.1016/j.clnu.2018.05.007

147. de Luis D, Izaola O, Aller R, Cuellar L, Terroba M, Martin T, et al. A randomized clinical trial with two enteral diabetes-specific supplements in patients with diabetes mellitus type 2: metabolic effects. *Eur Rev Med Pharmacol Sci.* (2008) 12:261–6.

148. Gentil P, de Lira C, Coswig V, Barroso W, Vitorino P, Ramirez-Campillo R, et al. Practical recommendations relevant to the use of resistance training for COVID-19 survivors. *Front Physiol.* (2021) 12:637590. doi: 10.3389/fphys.2021.637590

149. Ahmadi Hekmatikar A, Ferreira Júnior J, Shahrbanian S, Suzuki K. Functional and psychological changes after exercise training in post-COVID-19 patients discharged from the hospital: a PRISMA-compliant systematic review. *Int J Environ Res Public Health.* (2022) 19:2290. doi: 10.3390/ijerph19042290

150. Singer P, Blaser A, Berger M, Alhazzani W, Calder P, Casaer M, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr.* (2019) 38:48–79. doi: 10.1016/j.clnu.2018.08.037

151. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri S, et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *J Transl Med.* (2021) 19:128. doi: 10.1186/s12967-021-02795-5

152. Grant W, Lahore H, McDonnell S, Baggerly C, French C, Aliano J, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients.* (2020) 12:988. doi: 10.3390/nu12040988

153. Sabico S, Enani M, Sheshah E, Aljohani N, Aldisi D, Alotaibi N, et al. Effects of a 2-week 5000 IU versus 1000 IU vitamin D3 supplementation on recovery of symptoms in patients with mild to moderate COVID-19: a randomized clinical trial. *Nutrients.* (2021) 13:2170. doi: 10.3390/nu13072170

154. Caballero-García A, Pérez-Valdecantos D, Guallar P, Caballero-Castillo A, Roche E, Noriega D, et al. Effect of vitamin D supplementation on muscle status in old patients recovering from COVID-19 infection. *Medicina (Kaunas).* (2021) 57:1079. doi: 10.3390/medicina57101079

155. Notz Q, Herrmann J, Schlesinger T, Kranke P, Sitter M, Helmer P, et al. Vitamin D deficiency in critically ill COVID-19 ARDS patients. *Clin Nutr.* (2021). doi: 10.1016/j.clnu.2021.03.001 [Epub ahead of print].

156. Ferrara F, De Rosa F, Vitiello A. The central role of clinical nutrition in COVID-19 patients during and after hospitalization in intensive care unit. *SN Compr Clin Med.* (2020) 2:1064–8. doi: 10.1007/s42399-020-00410-0

157. Suliman S, McClave S, Taylor B, Patel J, Omer E, Martindale R. Barriers to nutrition therapy in the critically ill patient with COVID-19. *JPEN J Parenter Enteral Nutr.* (2022) 46:805–16. doi: 10.1002/jpen.2263

158. Ho D, Nguyen H, Irnandi D, Faradina A, Dang T, Wiratama B, et al. Adherence to COVID-19 nutritional guidelines and their impact on the clinical outcomes of hospitalized COVID-19 patients. *Clin Nutr ESPEN.* (2021) 46:491–8. doi: 10.1016/j.clnesp.2021.09.003

159. Faradina A, Tseng S, Ho D, Nurwanti E, Hadi H, Purnamasari S, et al. Adherence to COVID-19 nutrition guidelines is associated with better nutritional management behaviors of hospitalized COVID-19 patients. *Nutrients.* (2021) 13:1918. doi: 10.3390/nu13061918

160. Singhai K, Swami M, Nebhinani N, Rastogi A, Jude E. Psychological adaptive difficulties and their management during COVID-19 pandemic in people with diabetes mellitus. *Diabetes Metab Syndr.* (2020) 14:1603–5. doi: 10.1016/j.dsx.2020.08.025

161. Grabowski D, Overgaard M, Meldgaard J, Johanson L, Willaing I. Disrupted self-management and adaption to new diabetes routines: a qualitative study of how people with diabetes managed their illness during the COVID-19 lockdown. *Diabetol.* (2021) 2:1–15.

162. Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: a systematic review. *Diabetol Metab Syndr.* (2021) 13:95. doi: 10.1186/s13098-021-00705-9

163. Czeisler M, Marynak K, Clarke K, Salah Z, Shakya I, Thierry J, et al. Delay or avoidance of medical care because of COVID-19-related concerns - united states, june 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:1250–7. doi: 10.15585/mmwr.mm6936a4

164. Zhu S, Meehan T, Veerasingham M, Sivanesan K. COVID-19 pandemic gestational diabetes screening guidelines: a retrospective study in Australian women. *Diabetes Metab Syndr.* (2021) 15:391–5. doi: 10.1016/j.dsx.2021.01.021

165. Holland D, Heald A, Stedman M, Hanna F, Wu P, Duff C, et al. Assessment of the effect of the COVID-19 pandemic on UK HbA1c testing: implications for diabetes management and diagnosis. *J Clin Pathol.* (2021):jclinpath-2021-207776. doi: 10.1136/jclinpath-2021-207776 [Epub ahead of print].

166. Carr M, Wright A, Leelarathna L, Thabit H, Milne N, Kanumilli N, et al. Impact of COVID-19 restrictions on diabetes health checks and prescribing for people with type 2 diabetes: a UK-wide cohort study involving 618 161 people in primary care. *BMJ Qual Saf.* (2022) 31:503–14. doi: 10.1136/bmjqs-2021-013613

167. Caruso P, Longo M, Signoriello S, Gicchino M, Maiorino M, Bellastella G, et al. Diabetic foot problems during the COVID-19 pandemic in a tertiary care center: the emergency among the emergencies. *Diabetes Care.* (2020) 43:e123–4. doi: 10.2337/dc20-1347

168. Evert A, Dennison M, Gardner C, Garvey W, Lau K, MacLeod J, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care.* (2019) 42:731–54. doi: 10.2337/dci19-0014

169. Rodriguez-Blazquez, C, João Forjaz M, Gimeno-Miguel A, Bliek-Bueno K, Poblador-Plou B, Pilar Luengo-Broto S, et al. Assessing the pilot implementation of the Integrated multimorbidity care model in five European settings: results from the joint action CHRODIS-PLUS. *Int J Environ Res Public Health.* (2020) 17:5268. doi: 10.3390/ijerph17155268

170. Merino J, Joshi A, Nguyen L, Leeming E, Mazidi M, Drew D, et al. Diet quality and risk and severity of COVID-19: a prospective cohort study. *Gut.* (2021) 70:2096–104. doi: 10.1136/gutjnl-2021-325353

171. Churuangsuk C, Hall J, Reynolds A, Griffin S, Combet E, Lean M. Diets for weight management in adults with type 2 diabetes: an umbrella review of published meta-analyses and systematic review of trials of diets for diabetes remission. *Diabetologia.* (2022) 65:14–36. doi: 10.1007/s00125-021-05577-2

172. Mechanick J, Marchetti A, Hegazi R, Hamdy O. Diabetes-specific nutrition formulas in the management of patients with diabetes and cardiometabolic risk. *Nutrients.* (2020) 12:3616. doi: 10.3390/nu12123616

173. Koonin L, Hoots B, Tsang C, Leroy Z, Farris K, Jolly T, et al. Trends in the use of telehealth during the emergence of the COVID-19 pandemic - united states, january-march 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:1595–9. doi: 10.15585/mmwr.mm6943a3

174. Pendrith C, Nayyar D, Chu C, O'Brien T, Lyons O, Agarwal P, et al. Outpatient visit trends for internal medicine ambulatory care sensitive conditions after the COVID-19 pandemic: a time-series analysis. *BMC Health Serv Res.* (2022) 22:198. doi: 10.1186/s12913-022-07566-6

175. Maiorino M, Signoriello S, Maio A, Chiodini P, Bellastella G, Scappaticcio L, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: a systematic review with meta-analysis of randomized controlled trials. *Diabetes Care.* (2020) 43:1146–56. doi: 10.2337/dc19-1459

176. Taylor P, Thompson C, Brinkworth G. Effectiveness and acceptability of continuous glucose monitoring for type 2 diabetes management: a narrative review. *J Diabetes Investig.* (2018) 9:713–25. doi: 10.1111/jdi.12807

177. Huang L, Yan Z, Huang H. The effect of short message service intervention on glycemic control in diabetes: a systematic review and meta-analysis. *Postgrad Med.* (2019) 131:566–71. doi: 10.1080/00325481.2019.1668723

178. Sahin C, Courtney K, Naylor P, E Rhodes R. Tailored mobile text messaging interventions targeting type 2 diabetes self-management: a systematic review and a meta-analysis. *Digit Health.* (2019) 5:2055207619845279. doi: 10.1177/2055207619845279

179. Yammine K, Estephan M. Telemedicine and diabetic foot ulcer outcomes. a meta-analysis of controlled trials. *Foot (Edinb).* (2022) 50:101872. doi: 10.1016/j.foot.2021.101872

180. Knox E, Quirk H, Glazebrook C, Randell T, Blake H. Impact of technology-based interventions for children and young people with type 1 diabetes on key diabetes self-management behaviours and prerequisites: a systematic review. *BMC Endocr Disord.* (2019) 19:7. doi: 10.1186/s12902-018-0331-6

181. Randall M, Winchester D. The new role of telehealth in contemporary medicine. *Curr Cardiol Rep.* (2022) 24:271–5. doi: 10.1007/s11886-022-01640-5

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 21 April 2023
DOI 10.3389/fnut.2023.1143404

OPEN ACCESS

EDITED BY
Barbara Troesch,
Self-Employed, Zurich,
Switzerland

REVIEWED BY
Emmanouella Magriplis,
Agricultural University of Athens,
Greece
Prateek Lohia,
Wayne State University,
United States

*CORRESPONDENCE
Shan Li
lishan301301@163.com

†These authors share first authorship

RECEIVED 13 January 2023
ACCEPTED 03 April 2023
PUBLISHED 21 April 2023

CITATION
Li S, Zhang W, Fu Z and Liu H (2023) Impact of obesity on all-cause and cause-specific mortality among critically ill men and women: a cohort study on the eICU database.
Front. Nutr. 10:1143404.
doi: 10.3389/fnut.2023.1143404

Impact of obesity on all-cause and cause-specific mortality among critically ill men and women: a cohort study on the eICU database

Shan Li[1,2*†], Wei Zhang[2,3†], Zhiqing Fu[1,2] and Hongbin Liu[1,2]

[1]Department of Cardiology, The Second Medical Center, Chinese People's Liberation Army General Hospital, Beijing, China, [2]National Clinical Research Center for Geriatric Disease, Beijing, China, [3]Department of Outpatient, The Second Medical Center, Chinese People's Liberation Army General Hospital, Beijing, China

Background: The effect of obesity on intensive care unit outcomes among critically ill patients and whether there are sex differences have not been well investigated. We sought to determine the association between obesity and 30-day all-cause and cause-specific mortality among critically ill men and women.

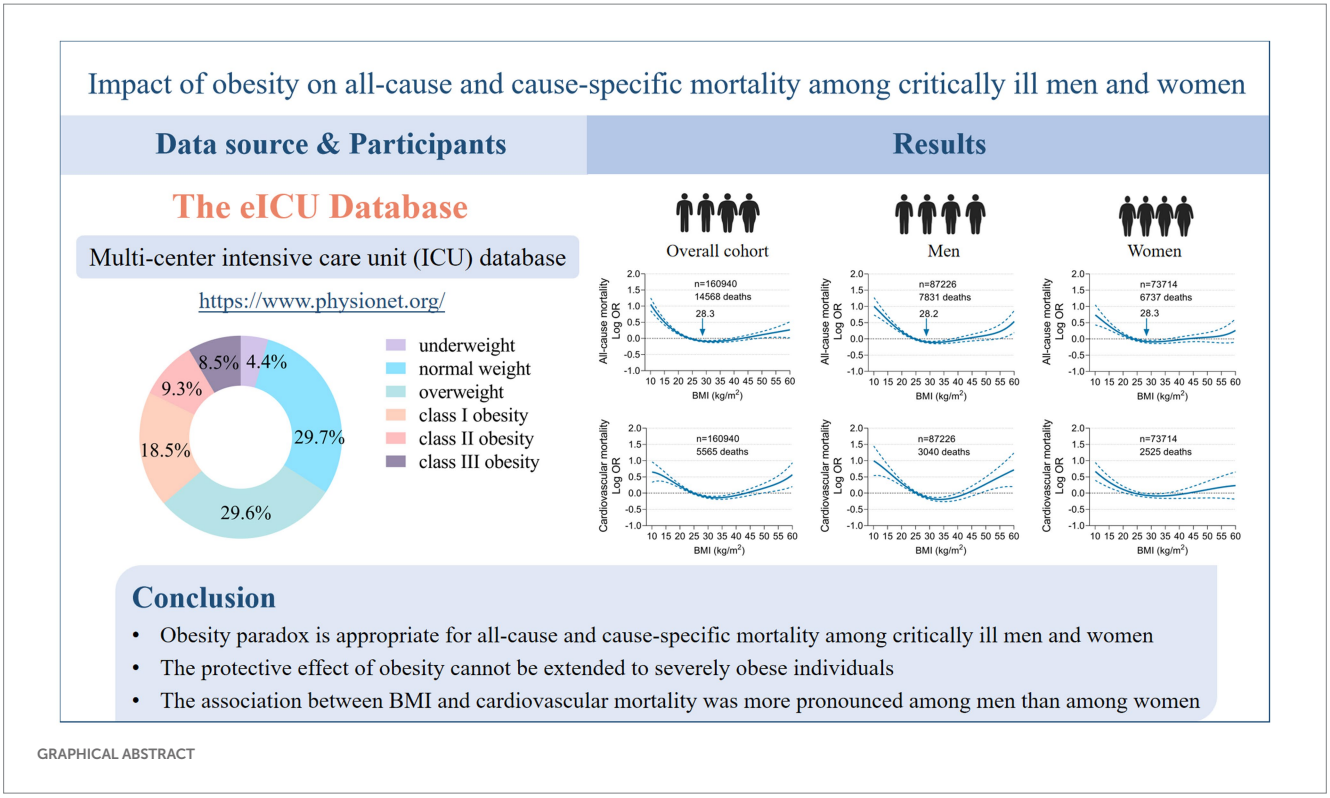
Methods: Adult participants who had body mass index (BMI) measurements were included from the eICU database. Participants were divided into six groups according to BMI (kg/m^2) categories (underweight, <18.5; normal weight, 18.5–24.9; overweight, 25–29.9; class I obesity, 30–34.9; class II obesity, 35–39.9; class III obesity, ≥40). A multivariable adjusted logistic model was conducted with odds ratios (ORs) and 95% confidence intervals (CIs). A cubic spline curve based on the generalized additive model was used to represent the nonlinear association. Stratified analysis and sensitivity analysis were also performed.

Results: A total of 160,940 individuals were included in the analysis. Compared with the class I obesity category, the underweight and normal weight categories had higher all-cause mortality, and the multivariable adjusted ORs were 1.62 (95% CI: 1.48–1.77) and 1.20 (95% CI: 1.13–1.27) for the general population, 1.76 (95% CI: 1.54–2.01) and 1.22 (95% CI: 1.13–1.32) for men, and 1.51 (95% CI: 1.33–1.71) and 1.16 (95% CI: 1.06–1.27) for women, respectively. Accordingly, multivariable adjusted ORs for the class III obesity category were 1.14 (95% CI: 1.05–1.24) for the general population, 1.18 (95% CI: 1.05–1.33) for men, and 1.10 (95% CI: 0.98–1.23) for women. With cubic spline curves, the association between BMI and all-cause mortality was U-shaped or reverse J-shaped. Similar findings were observed for cause-specific mortality, with the underweight category associated with a higher risk of mortality. Class III obesity increased the risk of cardiovascular death among men (OR 1.51; 95% CI: 1.23–1.84) and increased the risk of other-cause death among women (OR 1.33; 95% CI: 1.10–1.61).

Conclusion: The obesity paradox appears to be suitable for all-cause and cause-specific mortality among critically ill men and women. However, the protective effect of obesity cannot be extended to severely obese individuals. The association between BMI and cardiovascular mortality was sex-specific and was more pronounced among men than among women.

KEYWORDS

obesity, sex difference, all-cause mortality, cause-specific mortality, critically ill patients



GRAPHICAL ABSTRACT

Introduction

The prevalence and disease burden of obesity is increasing worldwide, posing a substantial public health challenge and clinical concern. By 2025, the global prevalence of obesity is expected to reach 18% for men and 21% for women, and severe obesity will surpass 9% in women and 6% in men (1). Epidemiological studies have revealed that obesity is strongly correlated with a series of pathophysiological disturbances, including atherosclerosis, diabetes, hypertension, chronic obstructive pulmonary disease, renal insufficiency and cancer (2–4). In recent years, the evidence that obesity promotes valvular heart disease, cardiomyopathy and multimorbidity has been further consolidated (5–7). These problems are direct consequences of excessive fat mass or indirect consequences of obesity-related metabolic dysfunction. Due to the high metabolic activity of adipose tissue, abnormal and detrimental adipocyte secretion patterns promote chronic proinflammatory, prothrombotic and procoagulant states. Although obesity carries a range of disease risks, elevated BMI is paradoxically associated with better survival in various clinical settings, including heart failure, atrial fibrillation, nephropathy, sepsis, acute respiratory distress syndrome and critical illness (8–13). This so-called 'obesity paradox' phenomenon appears to be more pronounced among men according to several studies (14, 15). However, recent studies on coronavirus disease 2019 (COVID-19) have consistently shown that obesity is independently correlated with severe outcomes and mortality from COVID-19 infection (16, 17). Its pathophysiological mechanisms involve obesity-induced weakened immune response, hypercoagulation and metabolic disorder (18). Therefore, the existence of the obesity paradox in different populations remains controversial.

Critically ill patients admitted to the intensive care unit (ICU) have a variety of systemic diseases, which are more dangerous and have a higher risk of death. Obesity brings greater diagnostic challenges (CT or ultrasound image quality reduction), increased operation difficulty (such as tracheal intubation), and pharmacokinetic and pharmacodynamic changes, which may complicate acute diseases and weaken the effectiveness of evidence-based interventions. Therefore, it is imperative to understand the impact of obesity on the clinical prognosis of these patients. However, reliable data on the relationship between obesity and mortality in critical settings are scarce and discrepant, showing positive, zero, or negative correlations (19, 20). Some studies reported positive results but involved only all-cause mortality and no cause-specific mortality. Moreover, it is now believed that fat mass and distribution vary by sex, and whether there is a sex difference in the association between obesity and mortality is also a matter of concern that has not been well assessed. To address this evidence gap, we analysed data from a large contemporary multicentre ICU cohort to explore whether there is an obesity paradox in all-cause and cause-specific mortality among critically ill patients, and if the obesity paradox exists, the existence of a sex-related difference therein.

Methods

Study participants

Data were extracted from the publicly available eICU Collaborative Research Database (eICU-CRD). The eICU-CRD is a telemedicine system developed by Philips Healthcare in cooperation with the Laboratory for Computational Physiology (LCP) of the

Massachusetts Institute of Technology to optimize the management of critically ill patients (21). The LCP has previously successfully shared the Medical Information Mart for Intensive Care (MIMIC) database to support academic research and ICU quality improvement (22). The eICU-CRD is a complete and expanded dataset independent of MIMIC, which collects comprehensive clinical data of more than 200,000 ICU encounters from 208 U.S. hospitals. This high-quality data integration system contains a large amount of information on demographic profiles, vital signs, disease severity scores, laboratory parameters, fluid balance, medications, diagnostic codes, treatments, survival status, and hospital-level data, including regional location, teaching status, bed capacity, etc. All data were deidentified, and the requirement for informed consent from patients was waived. Data are free to access after completing the required training course and signing a usage agreement. This study was conducted in accordance with the Declaration of Helsinki. The study is exempt from institutional review board approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by an independent privacy expert (Privacert, Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2). One author (Shan Li) obtained database access and was responsible for data extraction (certification number: 46622370). We included individuals admitted to the ICU from 2014 to 2015. The exclusion criteria were (1) age under 18 years, (2) no weight or height data available, and (3) BMI < 10 kg/m^2 or > 60 kg/m^2. Finally, 160,940 individuals were included in the analysis.

Exposure

The primary exposure of interest was BMI, calculated by the formula BMI (kg/m^2) = weight/height^2. For this calculation, the weight and height documented at ICU admission were used. According to the international classification criteria, individuals were divided into six categories: underweight, <18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; class I or mild obesity, 30–34.9 kg/m^2; class II or moderate obesity, 35–39.9 kg/m^2; and class III or severe obesity, ≥40 kg/m^2.

Outcomes

The primary outcome was all-cause mortality within 30 days of ICU admission. The secondary outcomes were cardiovascular mortality, infectious mortality, and other-cause mortality. ICU death statistics were determined according to the International Classification of Diseases codes (9th revision). All-cause death was defined as death caused by any cause from the date of admission until the time of death. Cardiovascular death was defined as death from diseases with ICD-9 codes 390–459. Infectious disease death was defined as death from diseases with ICD-9 codes 320–326, 460–488, 566–567, 590, 595, 597, 614–616, 680–686, and 995. Noncardiovascular and noninfectious causes death were defined as other-cause death. Death from acute myocardial infarction was defined as death from disease with ICD-9 code 410, death from heart failure was defined as death from disease with ICD-9 code 428, death from sepsis was defined as death from a condition with ICD-9 code 995, death from ischaemic stroke was defined as death from conditions with ICD-9 codes 430–432, and death from intracranial haemorrhage was defined as death from conditions with ICD-9 codes 433–434.

Covariates

The following factors were considered for covariate selection: (1) individual-level factors, including age, sex, ethnicity, heart rate, mean blood pressure, disease severity score (Acute Physiology, Age and Chronic Health Evaluation [APACHE] score and Glasgow Coma Scale [GCS] score); (2) clinical risk factors, including primary disease at admission (cardiovascular disease, respiratory disease, digestive disease, genitourinary disease, neurological disease, endocrine disease, trauma, other infectious disease [nonrespiratory, nonurinary, nondigestive tract infections disease]) and prehospital comorbidities (coronary artery disease, stroke/transient ischaemic attack, diabetes mellitus, hypertension, congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, renal dysfunction); (3) important treatments, including mechanical ventilation, dialysis and vasoactive drugs; and (4) hospital-level factors, including admission source, geographic location and discharge year.

Statistical analysis

Statistical analyses were performed using R software (version 3.6.1)[1] and EmpowerStats (X&Y Solutions, Inc., Boston, MA).[2] Statistical significance was defined as a 2-sided p value <0.05. Continuous variables are presented as the means with standard deviations (SDs) or medians with interquartile ranges (IQRs) and analysed using unpaired t tests or Mann–Whitney U tests depending on their distribution. Categorical variables are presented as numbers with percentages and were compared using the chi-square or Fisher's exact test. The R package multiple imputation by chained equation ($N_{imputation} = 5$) was used to account for missing data (13.3% for APACHE score, 2.5% for GCS score).

A multivariable logistic regression model was used to examine adjusted ORs for the association between BMI on a categorical scale and all-cause and cause-specific mortality, with the BMI category related to the lowest mortality as a reference. Three models were constructed: Model I unadjusted, Model II adjusted by age, sex and ethnicity, and Model III adjusted by all covariates without selection. The cubic spline curves based on the generalized additive model that adjusted for all covariates were used to visually display the nonlinear relationship between BMI on a continuous scale and all-cause and cause-specific mortality. Stratified analysis was conducted to examine the interaction between BMI and stratified covariates on all-cause mortality by including two or multiple interaction terms with adjustment for predefined covariates. Several sensitivity analyses were conducted to evaluate the robustness of the primary analysis. First, we excluded deaths that occurred within the first 48 h of ICU entry to determine whether the association between BMI and mortality could be explained by a reverse

1 http://www.r-project.org

2 http://www.empowerstats.com

causality of severe disease. Second, we performed a complete case analysis using only the complete data of all covariates to test whether the missing data distorted the current findings. Third, we plotted Kaplan–Meier survival curves by taking the length of ICU stay time as an underlying time scale and censoring at discharge or death to assess whether different statistical methods might change the results.

Results

Baseline characteristics

A total of 160,940 individuals were included in this study (mean [SD] age, 63.2 [17.1] years; 87,226 men [54.2%] and 123,959 Caucasians [77.0%]), 14,568 (9.1%) all-cause deaths, 5,565 (3.5%) cardiovascular deaths, 4,308 (2.7%) infectious disease deaths and 4,695 (2.9%) other-cause deaths were recorded within 30 days of ICU admission. The average BMI was 28.7 (SD 7.6) kg/m^2, and 58,518 (36.4%) individuals had class I to class III obesity. Figure 1 shows the distribution of BMI categories in the overall population and among men and women. Individuals with a higher BMI were younger and had a higher prevalence of diabetes mellitus, hypertension, chronic heart failure and renal dysfunction. Individuals with a lower BMI were older, had higher APACHE scores, and had a higher prevalence of respiratory disease and digestive disease. More dependence on mechanical ventilation was observed among individuals with class III obesity. Both underweight and class III obese patients had longer ICU stays. Underweight individuals accounted for 4.4% of the total population, resulting in 14.4% of all-cause deaths, which was approximately twice that of class I obese individuals. Baseline characteristics classified by BMI category are shown in Table 1.

Obesity and all-cause mortality

With a multivariable logistic regression model, the association between BMI on a categorical scale and all-cause mortality was U-shaped in the general population and in men, with both a low and high BMI correlated with a greater risk of mortality. However, a reverse J-shaped association was noted in women, with only a low BMI increasing the risk of mortality. Underweight individuals had the highest mortality in the overall population (OR 1.62; 95% CI: 1.48–1.77), followed by those with normal weight (OR 1.20; 1.13–1.27), and the lowest mortality was observed among class I obese individuals. Underweight and normal weight men had corresponding odds ratios of 1.76 (95% CI: 1.54–2.01) and 1.22 (95% CI: 1.13–1.32) compared with class I obese men, respectively Similarly, underweight and normal weight among women were also independently associated with all-cause mortality, with odds ratios of 1.51 (95% CI: 1.33–1.71) and 1.16 (95% CI: 1.06–1.27), respectively, after adjustment for potential confounders. In the class III obese category, the multivariable adjusted odds ratios for all-cause mortality were 1.14 (95% CI: 1.05–1.24) for the overall population, 1.18 (95% CI: 1.05–1.33) for men and 1.10 (95% CI: 0.98–1.23) for women (Figure 2; Supplementary Table 1).

Based on the cubic spline curve, the association between BMI on a continuous scale and all-cause mortality was also U-shaped in the general population and in men, whereas it was reverse J-shaped in women. The risk inflection point correlated with the lowest all-cause mortality was 28.3 kg/m^2 in the general population, 28.2 kg/m^2 in men and 28.3 kg/m^2 in women (Figure 3). Among the overall population, men and women with a BMI below the risk inflection point accounted for 54.6% (87906), 54.9% (47922) and 53.5% (39401), respectively. Before the corresponding risk inflection points, for every 5 kg/m^2 decrease in BMI, the risk of all-cause mortality increased by 18% in the whole population, 21% in men and 15% in women. After the inflection points, the risk of death plateaued. For every 5 kg/m^2 increase in BMI, the risk of all-cause mortality in the whole population, men and women increased by only 1% (Supplementary Table 2).

In stratified analysis, no clear evidence of a statistical interaction between BMI category and stratified variables on all-cause mortality was found. Compared with the class I obesity category, both the underweight category and normal weight category were independently associated with higher all-cause mortality, although the CI risk estimates were slightly wider in certain groups due to the relatively small number of individuals and events (Supplementary Table 3).

Obesity and cause-specific mortality

A U-shaped association between BMI and cardiovascular mortality was observed in the general population and in men, while a reverse J-shaped association was noted in women. Low BMI was consistently associated with increased cardiovascular mortality in the overall population and both sexes. However, the association between class III obesity and cardiovascular mortality was more pronounced among men (OR 1.51; 95% CI: 1.23–1.84) than among women (OR 1.03; 95% CI: 0.85–1.24) (P for interaction 0.0046) (Supplementary Figure 1). Regarding infectious disease mortality, there was a consistent monotonic decreased risk with increasing BMI in the general population and both sexes. Low BMI was strongly associated with an increased risk of infectious disease mortality, while high BMI was not related to it. The association between BMI and other-cause mortality exhibited U-shaped in the general population and in women but reverse J-shaped in men. Contrary to cardiovascular death, the relationship between class III obesity and other-cause mortality was significant among women (OR 1.33; 95% CI: 1.10–1.61) but not significant among men (OR 1.16; 95% CI: 0.95–1.42). Moreover, class II obese women also had an increased risk of other-cause mortality (OR 1.25; 95% CI:

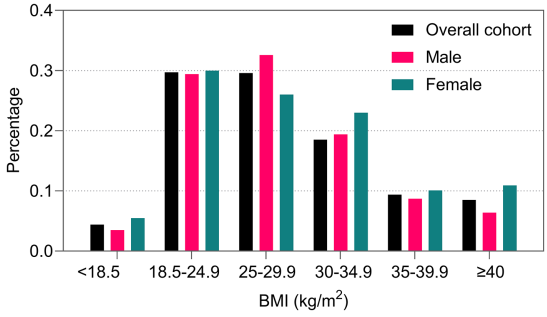


FIGURE 1
Distribution of BMI categories among men and women.

TABLE 1 Baseline characteristics of individuals by BMI categories.

BMI, kg/m^2	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40	*p* value
N (%)	7,067 (4.4)	47,768 (29.7)	47,587 (29.6)	29,818 (18.5)	15,042 (9.3)	13,658 (8.5)	
Age, years	64.2 ± 19.1	64.1 ± 19.0	64.3 ± 16.7	62.8 ± 15.5	61.1 ± 14.9	58.6 ± 14.2	<0.001
Male, *n* (%)	4,056 (57.4)	22,112 (46.3)	19,170 (40.3)	12,874 (43.2)	7,440 (49.5)	8,062 (59.0)	<0.001
Ethnicity							<0.001
Caucasian, *n* (%)	5,327 (75.4)	36,638 (76.7)	36,710 (77.1)	23,243 (77.9)	11,622 (77.3)	10,419 (76.3)	
African American, *n* (%)	952 (13.5)	4,962 (10.4)	4,724 (9.9)	3,207 (10.8)	1,876 (12.5)	2,058 (15.1)	
Hispanic, *n* (%)	206 (2.9)	1,846 (3.9)	2,001 (4.2)	1,065 (3.6)	492 (3.3)	393 (2.9)	
Asian, *n* (%)	212 (3.0)	1,219 (2.6)	802 (1.7)	299 (1.0)	101 (0.7)	53 (0.4)	
Other/unknown, *n* (%)	370 (5.2)	3,103 (6.5)	3,350 (7.0)	2,004 (6.7)	951 (6.3)	735 (5.4)	
BMI, kg/m^2	16.7 ± 1.5	22.2 ± 1.8	27.3 ± 1.4	32.2 ± 1.4	37.1 ± 1.4	45.9 ± 5.0	<0.001
Heart rate, bpm	106 ± 32	101 ± 33	98 ± 33	98 ± 32	99 ± 32	100 ± 32	<0.001
Mean blood pressure, mmHg	81 ± 41	83 ± 41	86 ± 42	88 ± 43	89 ± 44	89 ± 45	<0.001
Severity score							
APACHE score	52 (34–71)	49 (31–67)	47(30–64)	45(30–64)	45(29–64)	46(29–64)	<0.001
GCS	14 (11–15)	15 (12–15)	15 (12–15)	15 (12–15)	15 (12–15)	15 (12–15)	<0.001
Primary reason of ICU admission							
Cardiovascular disease, *n* (%)	1,744 (24.7)	15,694 (32.9)	19,504 (41.0)	12,877 (43.2)	6,173 (41.0)	4,850 (35.5)	<0.001
Respiratory disease, *n* (%)	2,053 (29.1)	8,772 (18.4)	7,125 (15.0)	4,524 (15.2)	2,581 (17.2)	2,942 (21.5)	<0.001
Digestive disease, *n* (%)	834 (11.8)	5,553 (11.6)	5,096 (10.7)	2,841 (9.5)	1,435 (9.5)	1,157 (8.5)	<0.001
Genitourinary disease, *n* (%)	365 (5.2)	2,438 (5.1)	2,239 (4.7)	1,547 (5.2)	868 (5.8)	965 (7.1)	<0.001
Neurological disease, *n* (%)	474 (6.7)	3,181 (6.7)	2,964 (6.2)	1,784 (6.0)	878 (5.8)	764 (5.6)	<0.001
Endocrine disease, *n* (%)	363 (5.1)	2,266 (4.7)	1,519 (3.2)	768 (2.6)	365 (2.4)	341 (2.5)	<0.001
Trauma, *n* (%)	221 (3.1)	2,323 (4.9)	1,984 (4.2)	1,085 (3.6)	379 (2.5)	277 (2.0)	<0.001
Other infectious disease, *n* (%)	296 (4.2)	1,793 (3.8)	1,667 (3.5)	1,155 (3.9)	662 (4.4)	778 (5.7)	<0.001
Other disease, *n* (%)	717 (11.1)	5,748 (12.0)	5,489 (11.5)	3,237 (10.8)	1,701 (11.3)	1,584 (11.6)	<0.001
Pre-admission comorbidities							
Coronary artery disease, *n* (%)	966 (13.7)	8,272 (17.3)	9,524 (20.0)	6,078 (20.4)	3,009 (20.0)	2,316 (17.0)	<0.001
Stroke/TIA, *n* (%)	687 (9.7)	4,709 (9.9)	4,710 (9.9)	2,704 (9.1)	1,235 (8.2)	1,031 (7.5)	<0.001
Diabetes mellitus, *n* (%)	572 (8.1)	4,674 (9.8)	5,291 (11.1)	4,221 (14.2)	2,711 (18.0)	3,007 (22.0)	<0.001
Hypertension, *n* (%)	2,522 (35.7)	19,372 (40.6)	21,825 (45.9)	14,641 (49.1)	7,685 (51.1)	7,117 (52.1)	<0.001
Congestive heart failure, *n* (%)	724 (10.2)	5,769 (12.1)	6,058 (12.7)	4,267 (14.3)	2,468 (16.4)	2,806 (20.5)	<0.001

(Continued)

10.3389/fnut.2023.1143404

TABLE 1 (Continued)

BMI, kg/m^2	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40	*p* value
Peripheral arterial disease, *n* (%)	306 (4.3)	2087 (4.4)	2,150 (4.5)	1,266 (4.2)	632 (4.2)	526 (3.9)	0.024
Chronic obstructive pulmonary disease, *n* (%)	1,527 (21.6)	6,474 (13.6)	5,533 (11.6)	3,646 (12.2)	2,132 (14.2)	2,399 (17.6)	<0.001
Renal dysfunction, *n* (%)	662 (9.4)	5,177 (10.8)	5,308 (11.2)	3,467 (11.6)	1866 (12.4)	1860 (13.6)	<0.001
Therapeutics							
Mechanical ventilation, *n* (%)	1,800 (25.5)	10,748 (22.5)	10,844 (22.8)	7,301 (24.5)	4,050 (26.9)	4,395 (32.2)	<0.001
Dialysis, *n* (%)	280 (4.0)	1927 (4.0)	1715 (3.6)	1,056 (3.5)	541 (3.6)	467 (3.4)	<0.001
Vasoactive drugs, *n* (%)	259 (3.7)	1,686 (3.5)	1760 (3.7)	1,042 (3.5)	526 (3.5)	481 (3.5)	0.624
Admission source							<0.001
Emergency department, *n* (%)	3,926 (55.6)	25,341 (53.1)	23,582 (49.6)	13,979 (46.9)	7,028 (46.7)	6,592 (48.3)	
Acute care/floor, *n* (%)	1,381 (19.5)	8,013 (16.8)	7,598 (16.0)	4,838 (16.2)	2,609 (17.3)	2,584 (18.9)	
Other, *n* (%)	1760 (24.9)	14,414 (30.2)	16,407 (34.5)	11,001 (36.9)	5,405 (35.9)	4,482 (32.8)	
Geographic location							<0.001
Midwest, *n* (%)	2,110 (29.9)	15,092 (31.6)	15,825 (33.3)	10,475 (35.1)	5,551 (36.9)	5,237 (38.3)	
South, *n* (%)	2,280 (32.3)	14,262 (29.9)	14,127 (29.7)	8,822 (29.6)	4,345 (28.9)	4,076 (29.8)	
West, *n* (%)	1,400 (19.8)	9,802 (20.5)	9,694 (20.4)	5,700 (19.1)	2,706 (18.0)	2,250 (16.5)	
Northeast, *n* (%)	451 (6.4)	3,122 (6.5)	3,156 (6.6)	2,130 (7.1)	1,132 (7.5)	1,025 (7.5)	
Other, *n* (%)	826 (11.7)	5,490 (11.5)	4,785 (10.1)	2,691 (9.0)	1,308 (8.7)	1,070 (7.8)	
Hospital discharge year							0.703
2014, *n* (%)	3,348 (47.4)	22,416 (46.9)	22,364 (47.0)	14,136 (47.4)	7,023 (46.7)	6,417 (47.0)	
2015, *n* (%)	3,719 (52.6)	25,352 (53.1)	25,223 (53.0)	15,682 (52.6)	8,019 (53.3)	7,241 (53.0)	
Length of stay, days	5.1 (2.8–8.9)	4.8 (2.5–8.3)	4.7 (2.5–8.1)	4.8 (2.6–8.2)	4.9 (2.6–8.7)	5.1 (2.8–9.2)	<0.001
All-cause death, *n* (%)	1,016 (14.4)	4,830 (10.1)	4,007 (8.4)	2,329 (7.8)	1,248 (8.3)	1,138 (8.3)	<0.001
Cardiovascular death, *n* (%)	289 (4.1)	1,641 (3.4)	1,654 (3.5)	1,008 (3.4)	523 (3.5)	450 (3.3)	0.040
Infectious-cause death, n (%)	385 (5.4)	1,560 (3.3)	1,112 (2.3)	627 (2.1)	311 (2.1)	313 (2.3)	<0.001
Other-cause death, *n* (%)	342 (4.8)	1,629 (3.4)	1,241 (2.6)	694 (2.3)	414 (2.8)	375 (2.7)	<0.001

Values are mean (standard deviation), median (inter-quartile range) or number (percentage). APACHE, acute physiology, age and chronic health evaluation. GCS, glasgow coma score.

10.3389/fnut.2023.1143404

1.03–1.52) (Figure 2; Supplementary Table 4). These findings were reconfirmed by a cubic spline model with BMI as a continuous variable (Figure 4).

Obesity and specific disease-related mortality

Regarding fatal myocardial infarction and fatal ischaemic stroke, no significant association was found between BMI and disease-related death. A J-shaped association between BMI and fatal heart failure-related death was observed, with a plateau at approximately a BMI of 25 to 30 kg/m^2. When BMI exceeded this plateau, the risk of heart failure-related death increased significantly. There was a reverse J-shaped relationship for sepsis-related death, with a low BMI associated with high mortality, whereas a high BMI was not. A strongly monotonic decreased risk for intracranial haemorrhage-related death with increasing BMI was detected, and this significant negative correlation dominated the association between BMI and all stroke deaths, including ischaemic and haemorrhagic stroke (Figure 5).

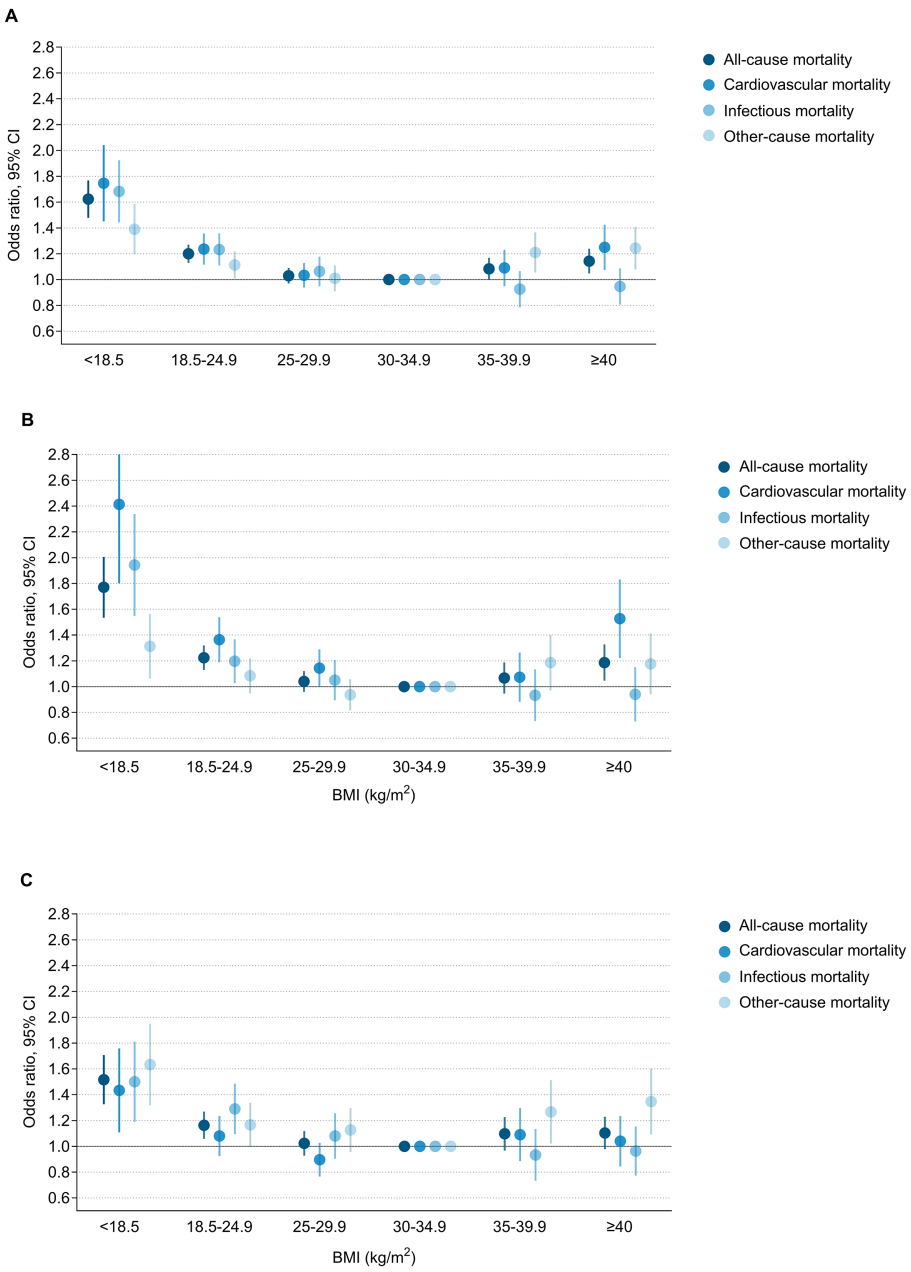


FIGURE 2
Multivariable adjusted odds ratios for all-cause and cause-specific mortality according to BMI on a categorical scale among **(A)** Overall population, **(B)** Men and **(C)** Women. Odds ratios and 95% confidence intervals were from multivariable adjusted logistic regression model.

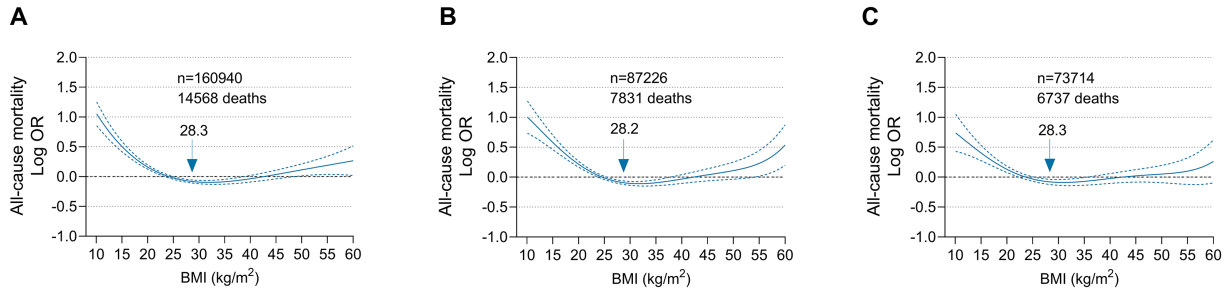


FIGURE 3
Multivariable adjusted odds ratios for all-cause mortality according to BMI on a continuous scale among **(A)** Overall population, **(B)** Men and **(C)** Women. Odds ratios (solid line) and 95% confidence intervals (dashed lines) were from cubic spline curves based on the generalized additive model. Arrows indicate BMI associated with the lowest mortality.

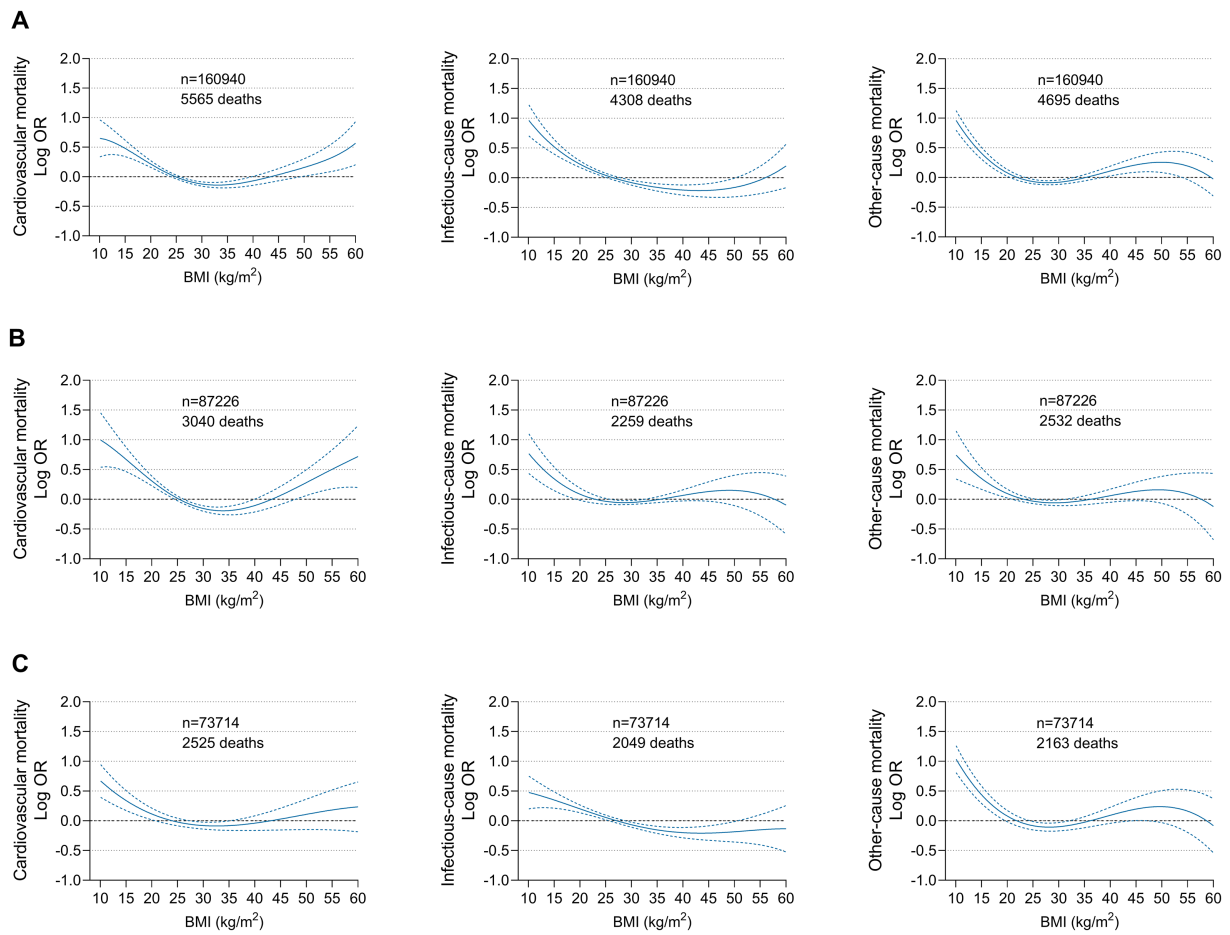


FIGURE 4
Multivariable adjusted odds ratios for cause-specific mortality according to BMI on a continuous scale among **(A)** Overall population, **(B)** Men and **(C)** Women. Odds ratios (solid line) and 95% confidence intervals (dashed lines) were from cubic spline curves based on the generalized additive model.

Sensitivity analysis

To evaluate the possible impact of reverse causality from severe illness, we examined the association between BMI and risk of mortality by excluding deaths that occurred within the first 48 h of ICU entry. The overall odds ratio was similar, only slightly attenuated (Supplementary Figure 2; Supplementary Table 5). The results from complete case analyses that included only individuals with complete data on all covariates were consistent with those of the main analysis, and the findings were greatly similar for men and women separately (Supplementary Figure 3; Supplementary Table 6). Finally, the result from Kaplan–Meier survival analysis considering

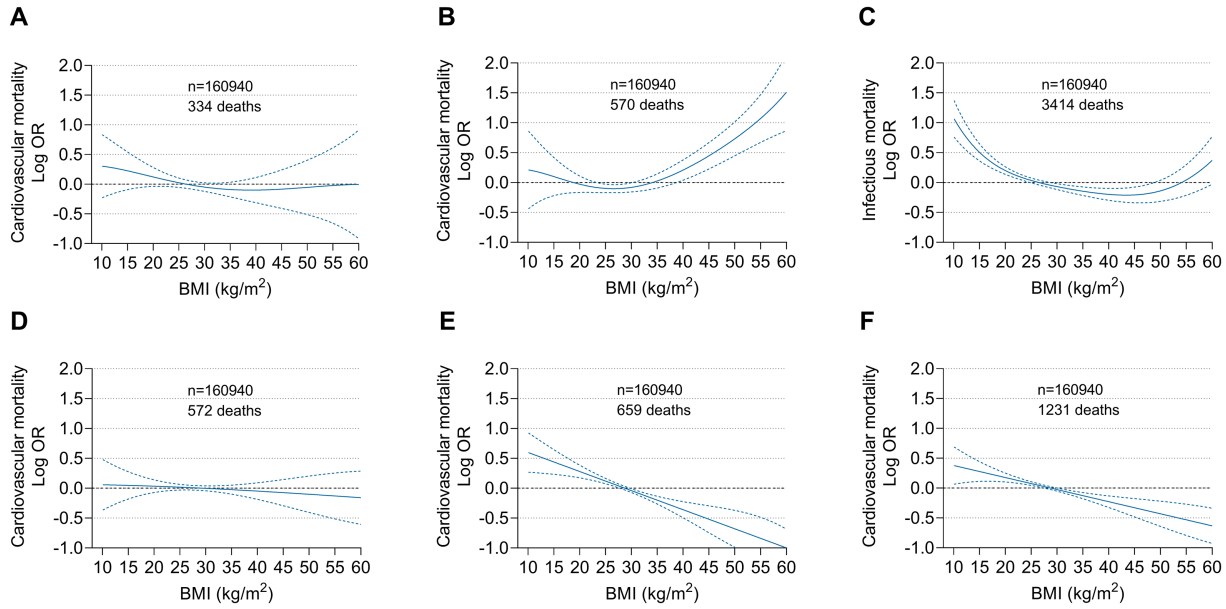


FIGURE 5
Multivariable adjusted odds ratios for specific disease related mortality according to BMI on a continuous scale. **(A)** Myocardial infarction, **(B)** Heart failure, **(C)** Sepsis, **(D)** Ischaemic stroke, **(E)** Intracranial hemorrhage and **(F)** Ischaemic and hemorrhagic stroke related mortality among the overall population. Odds ratios (solid line) and 95% confidence intervals (dashed lines) were from cubic spline curves based on the generalized additive model.

mortality as a time-to-event variable with length of ICU stay as the timescale was also consistent with that of the primary analysis (Supplementary Figure 4).

Discussion

In a large multicentre ICU cohort, we found a striking U-shaped or reverse J-shaped association between BMI and all-cause and cause-specific mortality among critically ill men and women, independent of obesity-related comorbidities and other potential confounding factors. Both underweight and normal weight individuals had a greater risk of death than their obese counterparts. These findings suggest that obesity exerts a protective effect on all-cause and cause-specific mortality among men and women, consistent with the obesity paradox. However, this protective effect appears not to extend to individuals with severe obesity (class III obesity). The relationship between severe obesity and cardiovascular mortality diverged between men and women. The current results confirm that the obesity paradox remains apparent among critically ill patients, but it is not applicable to severely obese patients. There is a sex difference in the impact of severe obesity on cause-specific mortality. These findings provide more information for predicting disease prognosis and improving the quality of ICU management.

In the past 30 years, the prevalence of obesity and the burdens of obesity-related diseases have gradually increased globally. It is predicted that as the prevalence of obesity in the general population increases, the incidence of obesity among critically ill patients will also increase. A meta-analysis reported that approximately one-third of ICU patients were obese, and nearly 7% were morbidly obese (20). The high incidence of obesity in this study was consistent with previous results, with 36.3% of obese patients and 8.5% of severely obese patients. The association pattern of obesity and adverse outcomes has been investigated in some relatively small studies in the critical care field, with the obesity paradox existing in short-term and long-term all-cause mortality (23, 24). Akinnusi et al. reported a U-shaped correlation between BMI and mortality, with worse survival among underweight (BMI <18.5 kg/m^2) and morbidly obese (>40 kg/m^2) patients (20). Oliveros et al. found a lower mortality among obese patients (BMI 30.0–39.9 kg/m^2) but not among morbidly obese patients (BMI > 40 kg/m^2) when using normal weight patients as a reference (25). In alignment with previous studies, this analysis showed that obese individuals had a better 30-day survival rate, although they had a higher incidence of clinical comorbidities, including hypertension, diabetes mellitus, heart failure and renal insufficiency, and the differences in these comorbidity patterns may be the major confounding factors affecting the clinical prognosis. Underweight individuals had an approximately 1.7-fold increased risk, and normal weight individuals had a 1.2-fold increased risk of all-cause mortality compared to their class I obese counterparts, which was noted among the overall population, among men and women. Among class III obese individuals, increased all-cause mortality was observed among men but not among women, resulting in a U-shaped association among the overall population and among men and a reverse J-shaped association among women. These findings support the existence of the obesity paradox, but the survival benefit does not extend to class III obese individuals, especially men. Furthermore, extremely close BMI inflection points for all-cause mortality were generated by the cubic spline curves, with 28.3 kg/m^2 for the whole population, 28.2 kg/m^2 for males and 28.3 kg/m^2 for females. There are several potential explanations for the obesity paradox. First, adipocytes positively regulate worsening inflammatory processes by secreting immunomodulatory substances such as leptin and interleukin-10, thereby improving survival during severe illness

(26). Second, high cholesterol and lipoprotein levels in obese individuals may provide the precursors for adrenal steroid hormone synthesis to combat lethal stress (27). Third, adipose tissue also affords important nutritional reserves for critically ill patients with highly catabolic status and negative energy balance (28). Fourth, underweight individuals are usually more vulnerable and have less positive responses to supportive therapy (29). Finally, disparities in medical care may also lead to survival differences. Due to subconsciously entrenched concerns about obesity, obese patients often receive earlier and more aggressive management and are assigned closer monitoring, higher care standards and a lower threshold for transfer to the ICU. Indeed, this analysis showed that obese patients had higher rates of mechanical ventilation usage, partly reflecting more aggressive interventions.

The association pattern between BMI and cardiovascular death was largely consistent with that of all-cause death, supporting the obesity paradox. Notably, an obviously increased cardiovascular mortality was found among class III obese men but not women. Sex hormones may play an important role in determining fat mass and distribution. Oestrogen increases fat deposition, while testosterone inhibits fat deposition, so men tend to have less fat mass than women (30). In addition, because oestrogen blocks the androgen effect by downregulating the androgen receptor, women tend to accumulate more subcutaneous fat but less visceral fat than men (31). Visceral fat appears to be the major pathogenic fat depot associated with cardiovascular and metabolic alterations. Its proinflammatory, prothrombotic and low-fibrinogen milieus have a negative impact on cardiovascular protection and metabolic regulation, while subcutaneous fat acts more as a metabolic reserve, helping other tissues defend against lipotoxicity (32). These mechanisms could partly explain our findings that extremely obese men still face an increased risk of cardiovascular death, while women may be exempt due to the heterogeneity in adipose distribution. A recent study of a large cohort of women with coronary artery disease treated with drug-eluting stents also showed that the adjusted risk estimates for cardiovascular mortality among severely obese women were not statistically significant (33), which was in line with our findings. In addition, a cardiovascular magnetic resonance study explained this issue from an imaging perspective, that is, there was a sex-specific difference in left ventricular remodelling among obese subjects (34). Men predominantly exhibited concentric hypertrophy, while women presented a combination of eccentric and concentric hypertrophy. Concentric hypertrophy is proven to be more closely associated with cardiovascular mortality than eccentric hypertrophy.

The obesity paradox among patients with pneumonia and sepsis has been observed, despite evidence supporting that obesity impairs the immune response and increases susceptibility to infection (35). In this study, there was a consistent reverse J-shaped association between BMI and infectious disease mortality across the whole population, men and women. Only underweight and normal weight individuals had an increased risk, and when BMI exceeded 25 kg/m^2, the risk of infectious disease death no longer increased but tended to decrease. The potential link between obesity and lower infectious disease mortality may be related to adipocytes positively regulating worsening inflammatory processes, high lipid levels neutralizing circulating endotoxin, and adipocytes providing adrenal steroid synthesis precursors and energy storage (26–28).

Other-cause deaths in this study included trauma, cancer, and uncommon disease-related deaths. Due to the relatively small number of events, separate analysis of a single disease could not be performed. Obesity had a protective effect on risk-adjusted mortality among individuals who died of noncardiovascular and noninfectious causes. However, this protective effect did not extend to severely obese individuals. Severely obese women remained at significantly increased risk of death compared with their mildly obese counterparts.

Previous studies have shown that obesity has a contradictory protective effect on heart failure (14, 15). However, it has also been suggested that the obesity paradox disappears after adjusting for B-type natriuretic peptide levels (36). We found that obesity was positively correlated with 30-day mortality among patients with acute heart failure. One possible explanation is that high BMI in the acute phase may be due to fluid retention rather than fat accumulation, affecting short-term prognosis, while cardiac cachexia and tissue hypoperfusion may contribute to worse long-term prognosis. These findings indicate that obesity may have different impacts on short-term and long-term prognoses among patients with heart failure. A prior heart failure study also showed that high BMI had a protective effect on 1-year mortality but not on 30-day mortality (37). The monotonous negative correlation between BMI and intracranial haemorrhage-related death was in line with expectations. A prospective study among 1.3 million British women revealed a robust relationship between low BMI and haemorrhagic stroke-related death (38). The trend in sepsis-related death was consistent with that of infectious disease death, with sepsis-related deaths accounting for 79.3% (3,414 of 4,308) of infectious disease deaths.

The unequal presentation of the obesity paradox between sexes has been reported. Studies among patients with heart failure and cardiogenic shock showed that the obesity paradox occurred only among men and not among women (14, 39). Clark et al. found that both women and men with systolic heart failure were affected by the obesity paradox (15). Our study showed that the obesity paradox apparently existed among both men and women, which was identified by BMI as a categorical variable and a continuous variable. However, the impact of the obesity paradox did not extend to severely obese individuals, and there was a sex difference between extremely high BMI and cause-specific mortality. Severe obesity increased cardiovascular deaths among men and increased other-cause deaths among women, leading to increased cardiovascular deaths and other-cause deaths among severely obese individuals in the overall population. According to these findings, we have several considerations. First, BMI may not be a perfect anthropometric indicator for characterizing obesity due to its inherent limitations in assessing body composition and fat distribution. Obese individuals may have increased lean mass or more favourable subcutaneous fat distribution than visceral fat distribution, and these clinical phenotypes may confuse the findings of the obesity paradox. However, there is no corresponding suspicion when BMI is considered a risk predictor for pathophysiological disorders. Therefore, the defects of evaluation indicators cannot completely deny the obesity paradox. The obesity paradox may indicate a lack of comprehension of the complex pathophysiological link between

obesity and clinical outcomes, requiring further study. Second, reports on the obesity paradox have brought a confusing message to clinicians and policy-makers, leading to misguided healthy lifestyle management. However, given that obesity is a significant contributor to various pathophysiological dysfunctions and causes a substantial multimorbidity burden, the debate of the obesity paradox should not reduce efforts to control obesity while awaiting further evidence. Moreover, our study also showed that severe obesity led to worse survival. Third, the current results are generally consistent with and further extend previous reports on the obesity paradox in various clinical milieus. Although this paradox exists among both men and women, it cannot be extended to severely obese individuals. The increased cardiovascular death among severely obese men drove the increased all-cause mortality risk, while the increased other-cause death among severely obese women led to an upward trend of all-cause mortality risk. However, infectious deaths did not appear to be involved. Therefore, in addition to focusing on the greater risk among underweight and normal weight patients, clinicians should pay special attention to the risk of cardiovascular death among severely obese men and other-cause death among severely obese women and manage potential complications and risk factors that may compromise survival. Finally, the association between BMI and disease-specific mortality underscores that the impact of obesity on mortality may be subdivided and cannot be simply summarized in terms of the obesity paradox. Developing more accurate and targeted predictors to provide precise and personalized assessments is needed for future research.

Strengths and limitations

This study included more than 160,000 ICU patients from a contemporary multicentre database. It was heterogeneous in terms of disease composition, ICU type and admission source, yielding a certain extrapolation validity for the study results. The model was extensively adjusted for confounding factors and had significant statistical power. Moreover, we extended the existing view of the obesity paradox and posited that it cannot be extended to severely obese individuals and that there was a sex difference in the impact of obesity on cause-specific mortality. Several limitations need to be considered. First, given that the retrospective design is inherently limited, we could not prove a causal relationship between obesity and mortality. Second, we broadly adjusted for confounding factors in multivariate analysis, including not only disease type and clinical comorbidities but also mechanical ventilation, dialysis, and vasoactive drug usage. Obesity leads to increased use and duration of mechanical ventilation, requires more frequent dialysis to achieve sufficient clearance, and affects the titration of vasoactive drugs, which may have an impact on mortality. However, obesity may be a net result of complex interactions between genetic, behavioural and environmental factors. Residual confounding factors, including dietary habits, smoking history, alcohol consumption, physical activity, income and socioeconomic status, may be involved, which were not extracted from the database. Third, we did not have any information about abdominal obesity or adipose distribution, such as waist circumference and waist-hip ratio, which may have an additional impact on the outcomes. Fourth, the subset of severely obese individuals was relatively small in number, which may have limited the statistical power of this group. Fifth, this study has a large heterogeneity in ethnic composition, and the majority of the cohort is Caucasians, accounting for 77% of the total population, which limits the extrapolation of the current results to other ethnic populations. Finally, given the regional differences in the definition of obesity based on BMI, a large proportion of individuals from the United States and European countries may restrict the extrapolation of these findings.

Conclusion

With the rapid development of the global economy and the general improvement of living standards, obesity is likely to become an increasingly prominent concern in the ICU. Our study provides new evidence on the obesity paradox, which is a well-known phenomenon in a variety of disease entities and is still evident among critically ill patients. Although the protective effect of obesity on all-cause and cause-specific mortality is largely consistent among men and women, this effect cannot be extended to severely obese individuals. Special attention needs to be paid to cardiovascular death risk among severely obese men and other-cause death risk among severely obese women.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.physionet.org/content/eicu-crd-demo/2.0.1/.

Ethics statement

The studies involving human participants were reviewed and approved by the institutional review board of the Massachusetts Institute of Technology. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

SL has fully obtained all the data and takes responsibility for the integrity of the data and the accuracy of the analysis. SL and HL contributed to the concept and study design. SL and WZ contributed to the acquisition, statistical analysis, and interpretation of the data. SL and ZF contributed to the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank the Massachusetts Institute of Technology and Philips Healthcare for providing a freely available multicenter eICU database for clinical research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1143404/full#supplementary-material

References

1. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet*. (2016) 387:1377–96. doi: 10.1016/S0140-6736(16)30054-X

2. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. (2017) 377:13–27. doi: 10.1056/NEJMoa1614362

3. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. (2011) 377:1085–95. doi: 10.1016/S0140-6736(11)60105-0

4. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer–viewpoint of the IARC working group. *N Engl J Med*. (2016) 375:794–8. doi: 10.1056/NEJMsr1606602

5. Kaltoft M, Langsted A, Nordestgaard BG. Obesity as a causal risk factor for aortic valve stenosis. *J Am Coll Cardiol*. (2020) 75:163–76. doi: 10.1016/j.jacc.2019.10.050

6. Robertson J, Lindgren M, Schaufelberger M, Adiels M, Björck L, Lundberg CE, et al. Body mass index in young women and risk of cardiomyopathy: a long-term follow-up study in Sweden. *Circulation*. (2020) 141:520–9. doi: 10.1161/CIRCULATIONAHA.119.044056

7. Kivimäki M, Strandberg T, Pentti J, Nyberg ST, Frank P, Jokela M, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. *Lancet Diabet Endocrinol*. (2022) 10:253–63. doi: 10.1016/S2213-8587(22)00033-X

8. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, et al. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. *Am J Cardiol*. (2015) 115:1428–34. doi: 10.1016/j.amjcard.2015.02.024

9. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol*. (2017) 70:2022–35. doi: 10.1016/j.jacc.2017.09.002

10. Lu JL, Molnar MZ, Naseer A, Mikkelsen MK, Kalantar-Zadeh K, Kovesdy CP. Association of age and BMI with kidney function and mortality: a cohort study. *Lancet Diabet Endocrinol*. (2015) 3:704–14. doi: 10.1016/S2213-8587(15)00128-X

11. Pepper DJ, Sun J, Welsh J, Cui X, Suffredini AF, Eichacker PQ. Increased body mass index and adjusted mortality in ICU patients with sepsis or septic shock: a systematic review and meta-analysis. *Crit Care*. (2016) 20:181. doi: 10.1186/s13054-016-1360-z

12. Ni YN, Luo J, Yu H, Wang YW, Hu YH, Liu D, et al. Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. *Crit Care*. (2017) 21:36. doi: 10.1186/s13054-017-1615-3

13. Sakr Y, Alhussami I, Nanchal R, Wunderink RG, Pellis T, Wittebole X, et al. Being overweight is associated with greater survival in ICU patients: results from the intensive care over nations audit. *Crit Care Med*. (2015) 43:2623–32. doi: 10.1097/CCM.0000000000001310

14. Hong S, Lee JH, Kim KM, Lee JW, Youn YJ, Ahn MS, et al. Is there a sex-related difference in the obesity paradox in systolic heart failure? Sex-related difference in the obesity paradox. *Yonsei Med J*. (2018) 59:57–62. doi: 10.3349/ymj.2018.59.1.57

15. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. *Am J Cardiol*. (2012) 110:77–82. doi: 10.1016/j.amjcard.2012.02.050

16. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. *Ann Intern Med*. (2020) 173:773–81. doi: 10.7326/M20-3742

17. Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. *JAMA Netw Open*. (2020) 3:e2012270. doi: 10.1001/jamanetworkopen.2020.12270

18. Steenblock C, Schwarz PEH, Ludwig B, Linkermann A, Zimmet P, Kulebyakin K, et al. COVID-19 and metabolic disease: mechanisms and clinical management. *Lancet Diab Endocrinol*. (2021) 9:786–98. doi: 10.1016/S2213-8587(21)00244-8

19. Hogue CW Jr, Stearns JD, Colantuoni E, Robinson KA, Stierer T, Mitter N, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. *Intensive Care Med*. (2009) 35:1152–70. doi: 10.1007/s00134-009-1424-5

20. Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. *Crit Care Med*. (2008) 36:151–8. doi: 10.1097/01.CCM.0000297885.60037.6E

21. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU collaborative research database, a freely available multi-center database for critical care research. *Sci Data*. (2018) 5:180178. doi: 10.1038/sdata.2018.178

22. Johnson AE, Pollard TJ, Shen L, Lehman LWH, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. *Sci Data*. (2016) 3:160035. doi: 10.1038/sdata.2016.35

23. Hutagalung R, Marques J, Kobylka K, Zeidan M, Kabisch B, Brunkhorst F, et al. The obesity paradox in surgical intensive care unit patients. *Intensive Care Med*. (2011) 37:1793–9. doi: 10.1007/s00134-011-2321-2

24. Zhou D, Wang C, Lin Q, Li T. The obesity paradox for survivors of critically ill patients. *Crit Care*. (2022) 26:198. doi: 10.1186/s13054-022-04074-1

25. Oliveros H, Villamor E. Obesity and mortality in critically ill adults: a systematic review and meta-analysis. *Obesity*. (2008) 16:515–21. doi: 10.1038/oby.2007.102

26. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol*. (2006) 6:772–83. doi: 10.1038/nri1937

27. Murch O, Collin M, Hinds CJ, Thiemermann C. Lipoproteins in inflammation and sepsis. I. Basic science. *Intensive Care Med*. (2007) 33:13–24. doi: 10.1007/s00134-006-0432-y

28. Marques MB, Langouche L. Endocrine, metabolic, and morphologic alterations of adipose tissue during critical illness. *Crit Care Med*. (2013) 41:317–25. doi: 10.1097/CCM.0b013e318265f21c

29. Reeves GK, Balkwill A, Cairns BJ, Green J, Beral V. Hospital admissions in relation to body mass index in UK women: a prospective cohort study. *BMC Med*. (2014) 12:45. doi: 10.1186/1741-7015-12-45

30. Mayes JS, Watson GH. Direct effects of sex steroid hormones on adipose tissues and obesity. *Obes Rev*. (2004) 5:197–216. doi: 10.1111/j.1467-789X.2004.00152.x

31. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev*. (2000) 21:697–738. doi: 10.1210/edrv.21.6.0415

32. Lee SJ, Shin SW. Mechanisms, pathophysiology, and Management of Obesity. *N Engl J Med*. (2017) 376:1491–2. doi: 10.1056/NEJMc1701944

33. Faggioni M, Baber U, Afshar AE, Giustino G, Sartori S, Sorrentino S, et al. Effects of body mass index on clinical outcomes in female patients undergoing percutaneous coronary intervention with drug-eluting stents: results from a patient-level pooled analysis of randomized controlled trials. *JACC Cardiovasc Interv*. (2018) 11:68–76. doi: 10.1016/j.jcin.2017.06.060

34. Rider OJ, Lewandowski A, Nethononda R, Petersen SE, Francis JM, Pitcher A, et al. Gender-specific differences in left ventricular remodelling in obesity: insights from cardiovascular magnetic resonance imaging. *Eur Heart J*. (2013) 34:292–9. doi: 10.1093/eurheartj/ehs341

35. Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. *BMC Med*. (2014) 12:61. doi: 10.1186/1741-7015-12-61

36. Pozzo J, Fournier P, Lairez O, Vervueren PL, Delmas C, Elbaz M, et al. Obesity paradox: origin and best way to assess severity in patients with systolic HF. *Obesity*. (2015) 23:2002–8. doi: 10.1002/oby.21216

37. Shah R, Gayat E, Januzzi JL Jr, Sato N, Cohen-Solal A, DiSomma S, et al. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. *J Am Coll Cardiol*. (2014) 63:778–85. doi: 10.1016/j.jacc.2013.09.072

38. Kroll ME, Green J, Beral V, Sudlow CLM, Brown A, Kirichek O, et al. Adiposity and ischemic and hemorrhagic stroke: prospective study in women and meta-analysis. *Neurology*. (2016) 87:1473–81. doi: 10.1212/WNL.0000000000003171

39. Kwon W, Lee SH, Yang JH, Choi KH, Park TK, Lee JM, et al. Impact of the obesity paradox between sexes on in-hospital mortality in cardiogenic shock: a retrospective cohort study. *J Am Heart Assoc*. (2022) 11:e024143. doi: 10.1161/JAHA.121.024143

frontiers | Frontiers in Nutrition

TYPE Clinical Trial
PUBLISHED 02 May 2023
DOI 10.3389/fnut.2023.1182445

OPEN ACCESS

EDITED BY
Matthias Pirlich,
Imperial Oak Outpatient Clinic, Germany

REVIEWED BY
Serena Della Valle,
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Italy
Alessandro Laviano,
Sapienza University of Rome, Italy

*CORRESPONDENCE
Miguel Leon-Sanz
✉ mleon@h12o.es
Gabriel Olveira
✉ gabrielm.olveira.sspa@juntadeandalucia.es

RECEIVED 08 March 2023
ACCEPTED 03 April 2023
PUBLISHED 02 May 2023

CITATION
Leon-Sanz M, Linares F, Gonzalo M, Tapia MJ, Maiz-Jimenez M, Ruiz Aguado M, Lizán L and Olveira G (2023) Compliance with a high-protein and energy-dense oral nutritional supplement in patients with disease-related malnutrition: a randomized open-label crossover trial.
Front. Nutr. 10:1182445.
doi: 10.3389/fnut.2023.1182445

Compliance with a high-protein and energy-dense oral nutritional supplement in patients with disease-related malnutrition: a randomized open-label crossover trial

Miguel Leon-Sanz[1,2,3]*, Francisca Linares[4,5,6], Montserrat Gonzalo[4,5], María José Tapia[4,5], María Maiz-Jimenez[1,2], Marta Ruiz Aguado[1,2], Luis Lizán[7,8] and Gabriel Olveira[4,5,6,9]*

[1]Department of Endocrinology and Nutrition, Hospital Universitario Doce de Octubre, Madrid, Spain, [2]Instituto de Investigación 1+12, Madrid, Spain, [3]Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain, [4]Department of Endocrinology and Nutrition, Hospital Regional Universitario de Málaga, Málaga, Spain, [5]IBIMA, Instituto de Investigación Biomédica de Málaga y Plataforma BIONAND, Málaga, Spain, [6]CIBERDEM, Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Málaga, Spain, [7]Outcomes'10, Castellón de la Plana, Spain, [8]Facultad de Medicina, Universidad Jaume I, Castellón de la Plana, Spain, [9]Facultad de Medicina de Málaga, Universidad de Málaga, Málaga, Spain

Introduction: Patient compliance with oral nutritional supplements (ONS) is not optimal for meeting energy and nutritional requirements in a high proportion of patients with disease-related malnutrition (DRM). Energy density or prescribed volume of ONS may impact compliance.

Methods: A randomized, open-label crossover trial was conducted in outpatients with DRM to compare compliance with a high energy-dense ONS (edONS, 2.4kcal/mL) and a reference ONS (heONS, 2.0kcal/mL; NCT05609006). Patients were randomly assigned to two 8-week treatment sequences of four-weeks periods: edONS + heONS (sequence A) or heONS + edONS (sequence B). Patients daily reported the amount of product left over gastrointestinal tolerance and satisfaction with ONS. A non-inferiority analysis was performed to compare the compliance rate (percentage of consumed energy over the prescribed) for each period and sequence.

Results: Fifty-three patients were assigned to sequence A and 50 to sequence B (55.7±13.9years, 37.0% female, 67.1% oncology patients). In sequence A, the compliance rates were 88.6%±14.3% vs. 84.1±21.8% (p=0.183), while in sequence B, they were 78.9% ±23.8% vs. 84.4%±21.4% (p<0.01). In both sequences, the lower range of the confidence interval for compliance with edONS was greater than the non-inferiority threshold (for sequence A Δ_{Comp}^{A} was 4.5% [95% CI, −2.0% to 10.0%], and for sequence, B Δ_{Comp}^{B} was 5.6% [95% CI, −3.0% to 14.0%]). The total discarded cost for each ONS was higher for heONS than edONS, being the difference statistically significant in sequence B. BMI increased slightly and not significantly in both sequences, and the percentage of patients with severe malnutrition was reduced. The frequency of gastrointestinal symptoms was low for both sequences, and satisfaction with ONS was slightly higher for edONS.

Conclusion: Our findings highlight that edONS was non-inferior to heONS in terms of consumed energy over the prescribed, with a lower amount of edONS discarded, which suggests a higher efficiency of edONS.

KEYWORDS

oral nutritional supplement, energy density, compliance, cost, nutritional status, gastrointestinal tolerance

1. Introduction

The primary cause of malnutrition in developed countries is disease (1). Disease-related malnutrition (DRM) is a prevalent condition, ranging between 20 and 50% in the hospital setting (2–4), and a major health public problem with high costs associated (4, 5). DRM can be triggered by a disease-specific inflammatory response as in cancer or major surgical procedures or linked to non-inflammatory etiologic mechanisms such as intestinal disorders (6, 7).

Increased daily nutritional needs (8), decreased intake and inadequate absorption of nutrients can result in a loss of weight and muscle mass. Malnutrition leads to a poor prognosis and treatment outcome (longer hospital stay, readmissions, infections, increased risk of chemotherapy-induced toxicity, postoperative complications and mortality), reduced functional status and health-related quality of life (2, 3, 9).

Clinical guidelines recommend performing nutritional assessment in all patients identified as at risk of malnutrition. For them, a personalized nutritional care plan should be established (6, 10). In order to meet the energy and protein requirements, this plan can include dietary advice, the treatment of symptoms impairing food intake, and offering oral nutritional supplements (ONS) (10). ONS have been shown to be effective in the treatment of DRM. However, compliance with intake is an important aspect to consider in order to achieve nutritional treatment goals and reduce the amount of product waste (11).

Although evidence has shown that, in general, adherence to ONS is adequate, there is a high proportion of patients in whom compliance is not optimal for meeting energy and nutritional requirements (11). Product-related factors such as energy density or prescribed volume should be taken into account in nutritional management as they may have an impact on compliance. Although a previous study suggests that consumption of energy-dense ONS (2.4 kcal/mL) results in a higher total energy and protein intake than the use of standard hypercaloric ONS (1.5–2.0 kcal/mL) (12), this study included a small sample of patients with a short follow-up of compliance, therefore more evidence is needed.

Currently, different hypercaloric ONS are available in Spain as nutritional support in DRM; however, only those with an energy density of no more than 2.1 kcal/ml are funded by the Spanish Health System (13). Evidence on the use of supplements with a higher energy density than currently funded is needed, so this pragmatic trial was carried out to compare compliance with two ONS, one with a high energy density (2.4 kcal/mL) and another hypercaloric one used as a reference (2.0 kcal/mL), in patients with DRM in different clinical situations. We hypothesized that compliance with high energy density ONS would be at least non-inferior to compliance with lower energy density ONS, with less product waste in the former.

2. Materials and methods

2.1. Study design and participants

This is a randomized, open-label crossover trial conducted in two Spanish tertiary hospitals in outpatients with DRM who required ONS. The protocol was approved by the Provincial Ethics Committee of Málaga (protocol code: NUT-ADHR-2.4; date of approval: 03/05/2019), and written informed consent was obtained from the patients. The protocol for this study was registered in ClinicalTrials.gov (NCT05609006).

The study included two 8-week sequences during which compliance with an energy-dense ONS (edONS; Fortimel Compact Protein®; Nutricia, Danone, Madrid, Spain; 2.4 kcal/mL) was compared with a high-energy ONS as a control/reference (heONS, Fortimel Extra®; Nutricia, Danone, Madrid, Spain; 2.0 kcal/mL), each for a period of 4 weeks in random order. The nutritional composition of both products is shown in Supplementary Table 1. Patients were randomly assigned to study sequences: edONS + heONS (sequence A) or heONS + edONS (sequence B). Since the nutritional status of the patient could be affected in case of temporary interruption, and because the carryover effect was not considered to have an impact on the measure of compliance, a washout period was not programmed between study periods.

Patients were eligible for inclusion in the trial if they were 18 years of age or older, presented with malnutrition or suspected malnutrition according to the Subjective Global Assessment (SGA categories B and C), had a high energy requirement and therefore needed the intake of two bottles/day of an ONS (≥2 kcal/mL) for a minimum period of 8 weeks. They were included if they were in any of the following situations: oncological patients who did not undergo surgery during the month prior to inclusion, including head and neck, esophagus, stomach, pancreas, or colon cancer; surgical patients who underwent surgery less than 1 month, including all types of surgical processes; and other non-surgical patients diagnosed with benign esophageal stricture, chronic radiation enteritis, and non-oncological maxillofacial lesions, cystic fibrosis, human immunodeficiency virus (HIV), malabsorption syndrome, ulcerative colitis, Crohn's disease, fistula, intestinal pseudo-obstruction, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), or who were scheduled to major surgery or transplantation within a period of no less than 2 months until inclusion. Except for surgical patients, and according to the site's standard procedures, patients with other

conditions should not have received a supplement during the month prior to inclusion. All included patients voluntarily agreed to participate in the study and give their signed consent for participation.

Patients were excluded if they suffered from chronic kidney disease or diabetes mellitus, required enteral tube feeding or parenteral nutrition, had any allergy or intolerance to the components of the study products, or had a scheduled surgery during the study period. Based on the physician's opinion, patients were also excluded if they were unable to adhere to the protocol instructions, including lack of ability of the patient/caregiver to make use of the patient-directed study electronic case report form, and unable to complete the 8 weeks of study follow-up.

2.2. Procedures

Eligible patients were allocated in a 1:1 ratio to sequence A or B. Randomization was performed by a centralized computer-generated randomization service (sealed envelope™). To balance factors that could affect study outcomes, patients were stratified with a permuted block randomization method of blocks of size four according to their age (≤65 or >65 years) and their clinical condition (oncological, surgical or others).

After the allocation, patients were instructed to consume 2 bottles/day (morning and afternoon) of edONS (sequence A) or heONS (sequence B) for 4 weeks at home. In order to reduce taste fatigue, patients received ONS with two different flavors (strawberry and vanilla). In week 4, patients came to the hospital for nutritional assessment and were prescribed 2 bottles/day of the other product for a further 4 weeks. After 8 weeks, they came to the hospital for nutritional assessment. They could continue medical nutrition therapy as per standard practice if needed. Whenever possible the visits were face-to-face for the collection of the patient's weight. However, due to pandemic restrictions, some patients were unable to come to the center and reported the weight obtained on home or community pharmacy scales.

2.3. Data collection

Sociodemographic (age and gender) and clinical data (main diagnosis, body mass index [BMI], nutritional status according to Subjective Global Assessment [SGA], and functional status according to Barthel Index for Activities of Daily Living) were collected by the investigators at the time of the inclusion (baseline visit) using an electronic case report form (eCRF). Two follow-up visits were established in weeks 4 (visit 1) and 8 (visit 2) to collect nutritional and functional status.

Patients daily collected the amount of product left over from the two intakes (morning and afternoon), through a patient's electronic form sent to their smartphones (Supplementary Figure 1). To indicate the correct amount, patients were provided with a measuring cup to pour the leftover product to facilitate the completion of the form. In addition, to verify the amount indicated, patients were asked to photograph the measuring cup whenever possible and to record the picture together with the form.

Moreover, patients weekly collected information regarding gastrointestinal tolerance using the patient's electronic form. To minimize a possible carryover effect between periods, gastrointestinal tolerance was registered by the patient on weeks 2, 3, and 4 of each period.

Lastly, patients' satisfaction with the ONS was collected by the same method at the end of each period.

2.4. Outcomes

The primary outcome was the compliance rate (%) for each period defined as the percentage of consumed energy over the prescribed. From the daily amount left over and the amount consumed, the number of kcal consumed vs. prescribed kcals were estimated to obtain the compliance rate.

Secondary outcomes included changes in nutritional and functional status according SGA categories and Barthel Index, respectively. Other outcomes were gastrointestinal tolerance and satisfaction with ONS. Tolerance was measured using a numeric rate scale (NRS) of the frequency of symptoms (0, not at all; 10, very frequently) for the last 7 days such as nausea, vomiting, diarrhea, constipation, acid reflux, abdominal pain, bloated belly, stomach pain, flatulence, and satiety.

Satisfaction with the ONS taste, satiety, ease of completing the intake, and overall satisfaction were measured using an NRS of the level of satisfaction (0, very dissatisfied; 10, very satisfied). The mean score given by patients in both sequences to each ONS was estimated, regardless of the period.

2.5. Sample size predetermination

The primary analysis was designed to test whether compliance with edONS was non-inferior to heONS. Non-inferiority would be shown if the lower limit of the 95% confidence interval (CI) for the between-periods difference in the primary outcome was more than −5% (i.e., the difference between compliance with edONS and heONS for each sequence). This estimation is equivalent to one-sided noninferiority testing with an alpha of 0.05. Our original intention was to enroll 40 patients per sequence, which given a standard deviation of 15, would have provided 80% of power at an alpha level of 0.05, assuming 20% for possible dropouts.

However, enrollment proved much slower than expected due to the pandemic, and although the estimated sample was reached, drop-outs from the study were more frequent than expected. Thus, recruiting was stopped after at least 31 patients had been included into each sequence to be analyzed. This smaller sample reduced the power to test non-inferiority to 78%.

2.6. Statistical analysis

Using an intention-to-treat approach, we performed the primary analysis including all the patients who had undergone randomization and received ONS for at least 1 week in each period. For each sequence, the mean compliance with ONS was determined in both periods and the difference was calculated (Figure 1).

First, continuous variables were tested for normality using the Shapiro–Wilk test evidencing non-normality. As they are paired

FIGURE 1
Study outcomes.

samples, compliance between periods was compared using Wilcoxon signed-rank test. Compliance between arms for first and second period was compared using Kruskal-Wallis test. Non-inferiority of edONS was calculated based on the mean difference of compliance and its CI for each sequence ($\Delta_{Comp}{}^{A}$ and $\Delta_{Comp}{}^{B}$), to test the lower limit of the 95% CI was greater than the non-inferiority limit established ($-\delta = -5\%$).

Additionally, a cost analysis was performed to estimate the cost of product discarded in each period per sequence by multiplying the average energy (kcal) of ONS not consumed by the cost per kcal (€, Spain; see Table 1). Wilcoxon signed-rank test was used to determine whether there were significant differences between periods in each arm.

All statistical analyses were performed using the software STATA v.14 (Stata Corp, College Station, TX, United States).

3. Results

3.1. Study participants and baseline characteristics

From July 2019 to December 2021, a total 234 patients were screened across the two hospitals, and 103 were randomized (Figure 2) being 53 patients assigned to sequence A and 50 to sequence B.

The baseline characteristics of the patients are summarized in Table 2. The mean age was 55.7 ± 13.9 years, 37.0% were female, most of them being oncology patients (67.1%).

3.2. Compliance with ONS

Patients in sequence A recorded compliance with edONS and heONS a mean of 27.5 ± 1.6 and 25.1 ± 5.5 days, respectively. In this sequence, no significant differences in the compliance rate between periods were found (88.6% ± 14.3% vs. 84.1% ± 21.8%; $p = 0.183$; Figure 3).

Mean energy intake with edONS and heONS in sequence A was 532 and 634 kcal/day, respectively.

On the other hand, in sequence B, patients recorded compliance with heONS and edONS a mean of 27.3 ± 2.1 and 27.4 ± 2.5 days, respectively, showing significant differences in the compliance rate between periods (78.9% ± 23.8% vs. 84.4% ± 21.4%; $p < 0.01$; Figure 3). Mean energy intake with heONS and edONS in sequence B was 676 and 507 kcal/day, respectively.

TABLE 1 Cost of each product per bottle, volume, and kcal.

	edONS	heONS
Volume per bottle (mL)	125 mL	200 mL
Energy per bottle (kcal)	300 kcal	402 kcal
Cost per bottle	1.75 €	1.99 €
Cost per ml	0.014 €	0.010 €
Cost per Kcal	0.0058 €	0.0050 €

Unit costs as provided by Nutricia, Danone, Madrid, Spain.

Comparing the compliance with the first ONS received in each sequence, i.e., up to week 4 of treatment (period 1), the mean compliance with edONS was significantly higher than with heONS (88.6% ± 14.3% vs. 78.9% ± 23.8%; $p = 0.0687$).

According with the non-inferiority analysis, in both sequences A and B, the lower range of the CI for compliance with the edONS was greater than the non-inferiority threshold, so it can be established that the edONS was non-inferior to the heONS (Figure 4). For sequence A, the $\Delta_{Comp}{}^{A}$ was 4.5% (95% CI, −2.0% to 10.0%), and for sequence B, the $\Delta_{Comp}{}^{B}$ was 5.6% (95% CI, −3.0% to 14.0%).

3.3. Nutritional and functional evolution

BMI remained stable throughout follow-up within each sequence, increasing slightly from baseline to the final visit (Figure 5), although not significantly.

At 4 and 8 weeks, the percentage of patients with severe malnutrition according to SGA was reduced (Figure 6). However, there was little change in functional dependency status, with a slight increase in the moderate-highly dependent patients in sequence A at 8 weeks, from 6 patients (14.3%) at the baseline to 8 patients (19.2%) at visit 2.

3.4. Gastrointestinal tolerance and satisfaction

Overall, patients in both sequences perceived the frequency of occurrence of gastrointestinal symptoms to be low, being slightly higher in sequence B, mainly in symptoms such as abdominal pain and flatulence, but similar between the two periods within each sequence (Supplementary Table 2). Patients were more satiated with heONS in both sequences, with a greater numerical difference in the

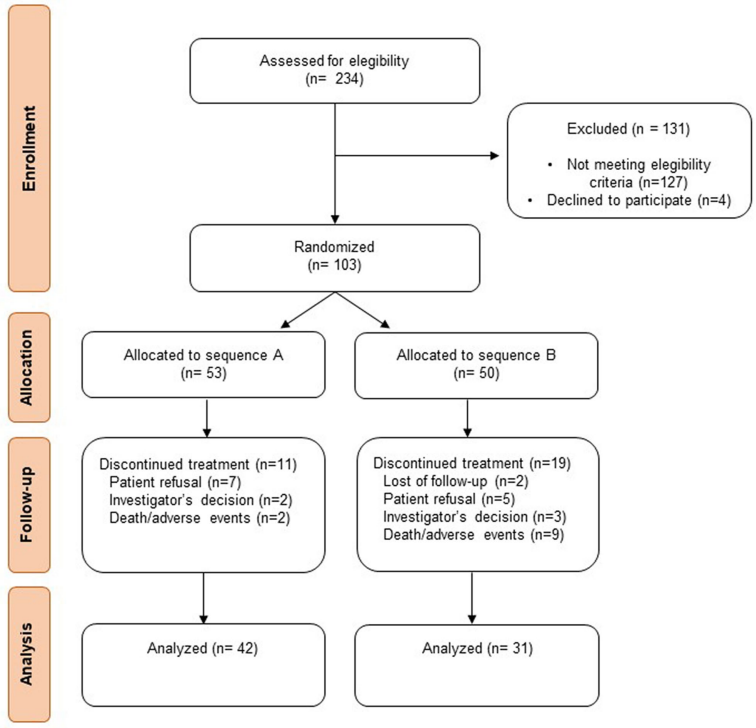


FIGURE 2
Flow diagram of the participants' allocation.

first period between sequences (Supplementary Figure 2). The mean scores on the satisfaction questions show a no statistically significant but slightly higher satisfaction obtained for the edONS in terms of taste, satiety, ease of finishing the supplement and overall satisfaction (Supplementary Figure 3).

3.5. Cost analysis

The mean ± SD total discarded cost for each sequence was: for sequence A, €10.78 ± 13.49 in the first period (edONS) and €15.20 ± 22.72 in the second period (heONS), with no statistically significant difference in discarded cost between periods of -€4.43 ± 19.20 ($p = 0.1768$); for sequence B, the discarded cost was €23.28 ± 26.48 in the first period (heONS) and €14.60 ± 20.56 in the second period (edONS), with a statistically significant difference in discarded cost between periods of -€8.68 ± 24.05 ($p = 0.0431$).

4. Discussion

This is the first randomized trial comparing the compliance with a low-volume energy-dense ONS of 2.4 kcal/mL and other standard-volume high-energy ONS of 2.0 kcal/mL conducted in malnourished or at risk of malnutrition patients in Spain.

Unlike in other countries, there is no funding by the Spanish Health System for ONS with a higher density of 2.1 kcal/mL, so the results of our study could be of particular interest both to the scientific community in general and to our health system in particular.

This study shows a high compliance with both ONS in the community setting, although slightly lower than that observed with energy-dense ONS as reported in previous studies (11).

Our findings highlighted that compliance with edONS was non-inferior to heONS, which confirms our research hypothesis. As this was a crossover trial, the patient was his or her own control, and although there were no statistically significant differences in compliance between ONS in sequence A, they were found in sequence B. These differences could be a consequence of intake fatigue. Even though intake fatigue may be associated with taste fatigue (14), our population received ONS with two different flavors to combine as preferred by the patient. Therefore, in our study it could be due to the prolonged consumption of the highest volume ONS during the first period of sequence B. It suggests that starting nutritional treatment with a low-volume ONS could reduce intake fatigue throughout the treatment period. Future studies should be carried out to test this hypothesis.

A previous study comparing low-volume high-energy ONS (2.4 kcal/mL) and a standard ONS (between 1.5–2.0 kcal/mL) in older people at risk of malnutrition showed a significantly higher compliance with the first one (12). Firstly, patients received the standard ONS in addition to their diet for 3 days, achieving an overall mean percentage of compliance of 77%, and then they received the low-volume high-energy ONS for 4 days, with a compliance of 91%. Although this study involved a short period of time, the results are in line with those found in the sequence B of our research (79% vs. 84%). Another study investigating the effects of energy-dense ONS vs. standard ONS of 1.5 kcal/mL in pediatric population, showed similar results with a greater proportion of patients with high compliance in the group receiving the energy-dense ONS (15). The authors attribute

TABLE 2 Key demographic and clinical characteristics of the study population.

Patient characteristics	Sequence A (*N* = 42)	Sequence B (*N* = 31)	*p*
Age—year, mean ± SD	56.2 ± 13.1	55.1 ± 15.1	0.7208
Sex, *n* (%)			
Male	25 (59.5)	21 (67.7)	0.472
Female	17 (40.5)	10 (32.3)	
Clinical condition, *n* (%)			
Oncological patient	27 (64.3)	22 (71.0)	0.569
	6 (14.3)	2 (6.5)	
Surgical patient	9 (21.4)	7 (22.6)	
Other patients			
Main diagnoses, *n* (%)			
Head and neck cancer	9 (21.4)	6 (19.4)	--
Colorectal cancer	8 (19.0)	1 (3.2)	
Crohn Disease	5 (11.9)	2 (6.5)	
Stomach cancer	3 (7.1)	3 (9.7)	
Pancreatic cancer	3 (7.1)	1 (3.2)	
Lung cancer	1 (2.4)	3 (9.7)	
Breast cancer	2 (4.8)	1 (3.2)	
Skin cancer	1 (2.4)	2 (6.5)	
COPD	1 (2.4)	2 (6.5)	
Cervical cancer	1 (2.4)	1 (3.2)	
Malabsorption syndrome	1 (2.4)	1 (3.2)	
Cystic fibrosis	1 (2.4)	1 (3.2)	
Germ cancer	1 (2.4)	1 (3.2)	
HIV	1 (2.4)	1 (3.2)	
Liver cancer	2 (4.8)	-	
Brain tumor	-	2 (6.5)	
Esophageal cancer	1 (2.4)	-	
Chronic lymphocytic leukemia	1 (2.4)	-	
Pancreatic insufficiency	-	1 (3.2)	
Bile duct cancer	-	1 (3.2)	
Rectal cancer	-	1 (3.2)	
BMI, mean ± SD	22.1 (3.5)	21.9 (4.1)	0.444
Classification according to BMI, *n* (%)			
Low weight (BMI < 18,5)	8 (19.0)	7 (22.6)	--
Normal weight (18.5 < BMI < 25)	27 (64.3)	18 (58.1)	
Overweight (25 < BMI < 30)	6 (14.3)	4 (12.9)	
Obesity (BMI ≥ 30)	1 (2.4)	2 (6.5)	
Nutritional status according to SGA, *n* (%)			
Suspected malnutrition/ moderate malnutrition (cat. B)	20 (47.6)	16 (51.6)	0.78
Severe malnutrition (Cat. C)	22 (52.4)	15 (48.4)	
Functional status according Barthel index, *n* (%)			
Independency (score 100)	35 (83.3)	26 (83.9)	0.809
Low dependency (score 91–99)	1 (2.4)	2 (6.5)	
Moderate dependency (score 61–90)	6 (14.3)	3 (9.7)	
Severe dependency (score 21–60)	-	-	
Total dependency (score ≤ 20)	-	-	

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SGA, subjective global assessment.

this to the good acceptability, and higher energy and nutrient density of the formula in a smaller volume.

Other studies have shown that volume and energy density could affect to nutritional intake, suggesting that small volume and energy-dense ONS may be an effective treatment for optimizing nutritional outcomes (11, 16). Our findings indicate that both ONS provide an acceptable daily caloric intake of more than 500 kcal/day. In fact, the nutritional outcomes in both sequences were similar, with a reduction in the proportion of patients with severe malnutrition at the end of the two follow-up periods. Although no significant differences in weight were found between baseline and final visit, it is important to note that many of the patients included in the study were oncology patients, and in this population, weight maintenance could be already a goal of nutritional treatment. Nevertheless, in the periods when patients took the more energy-dense ONS (2.4 kcal/mL), there was a tendency for BMI to increase, which was not the case with the ONS 2.0 kcal/mL.

As the amount of product discarded vs. prescribed was higher with heONS, this had a direct impact on cost, with the cost of discarded product being higher in this case, suggesting that edONS is more efficient, providing adequate caloric intake with a lower amount of product discarded because of higher compliance. This becomes even more important considering that many of the nutritional treatments are chronic, and therefore the funding and reimbursement of these ONS would represent a considerable saving for the national health system.

Additionally, both ONS showed adequate gastrointestinal tolerance in our study population. Within each sequence, the frequency of symptoms was similar between periods being low in all of them. It may indicate that in those patients with a higher frequency of symptoms, it may be associated with the main diagnosis. Moreover, satisfaction with

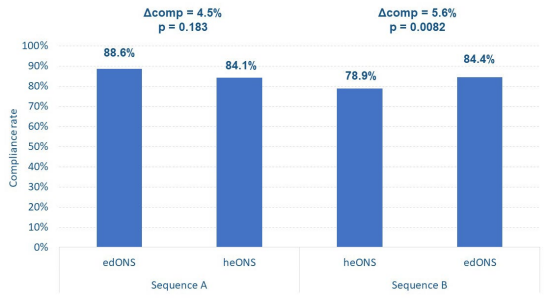


FIGURE 3
Compliance with the ONS in each study sequence.

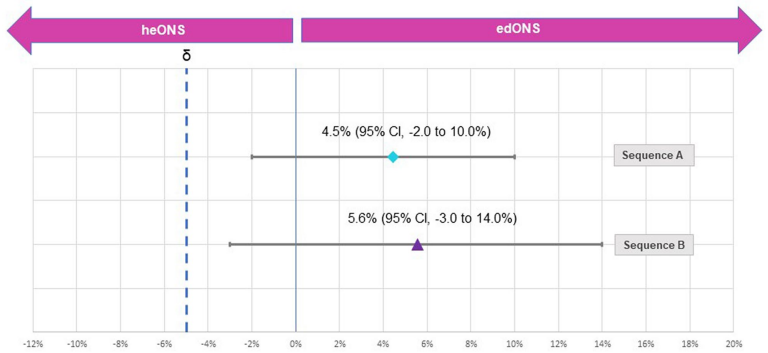


FIGURE 4
Difference in the compliance rate between periods for study sequences.

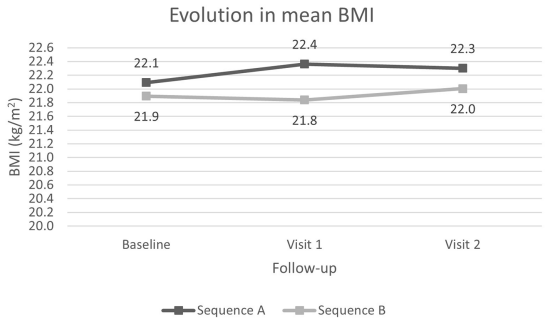


FIGURE 5
Evolution of the mean BMI from baseline visit over the course of the study.

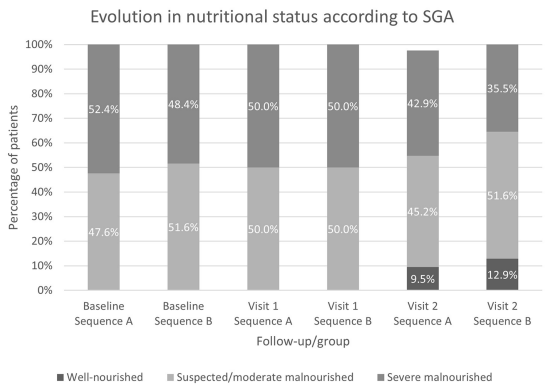


FIGURE 6
Evolution of the nutritional status according to SGA from baseline visit over the course of the study.

both ONS was similar. Satiety with edONS was slightly lower than heONS, and the former was more ease to finish than the latter.

The study has several strengths. One of the main strengths is the multicentre and pragmatic character of the study, including patients from two centers belonging to different geographical areas in Spain, who required ONS as established in the usual clinical practice. On the other hand, the study was not restricted to patients with a single clinical situation (oncological, surgical and other non-surgical patients), which allows for the extension of the results to different pathologies.

Some study limitations need to be acknowledged. Firstly, the study was conducted throughout 2020, when the COVID-19 pandemic occurred, which influenced patient enrollment and resulted in not reaching the preliminary expected sample, but fortunately the results could be confirmed with significant statistical power. Secondly, both products not only differed on energy density but in volume too, which could make an influence on the comparison of them. On the one hand, due to the difference in volume of the two study ONS bottles, blinding to the interventions was not possible. On the other hand, each provided a different caloric intake, so it would be expected that their nutritional effects would be different, with a greater contribution from heONS. However, an intake of at least 500 kcal per day from each was considered adequate. Lastly, for the analysis of nutritional status, only BMI and nutritional assessment by SGA were taken into account. BMI may not reflect early changes in body composition with sufficient sensitivity, whereas results of SGA could be difficult to interpret in case of normal weight and obese patients (17). In addition, due to pandemic restrictions, at some visits several patients were weighed on different weighing scales which could lead to variations, albeit minimal, inpatient weight unrelated to nutritional intake. Future studies should include other nutritional measures or parameters to detect both changes in body composition and functionality.

5. Conclusion

Our findings highlight that the edONS was non-inferior to the heONS in terms of compliance defined as consumed energy over the prescribed, but with a lower amount of edONS discarded, which suggests a higher efficiency with the use of energy-dense ONS. EdONS may be a good alternative to other higher volume hyperprotein and hypercaloric formulas, which can help improve patient compliance while maintaining the nutritional status of patients malnourished or at risk of malnutrition.

Data availability statement

The data presented in this study are available on reasonable request from the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Provincial Ethics Committe of Málaga. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ML-S and GO supervised and coordinated the study. ML-S, GO, and LL conceptualized the study and developed and coordinated the methodology. FL, MT, MG, MM-J, and MR performed the investigation. LL validated the data and conducted the formal analysis. All authors contributed to the article and approved the submitted version.

Funding

The authors declare that this study received funding from Danone Specialized Nutrition. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

Acknowledgments

The authors would like to thank the collaborators and medical staff who supported the research. In addition, the authors want to thank Francisco Javier Pérez-Sádaba at Outcomes'10 (Castellón, Spain) for their assistance with medical writing. Danone Specialized Nutrition funded Outcomes'10 to support medical writing.

Conflict of interest

LL works for an independent research entity, Outcomes'10, that received funding from Danone Specialized Nutrition to conduct the project and for medical writing.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1182445/full#supplementary-material

References

1. Stratton R, Green C, Elia M. *Disease-related malnutrition: An evidence-based approach to treatment*. Wallingford: CABI (2003).

2. Contreras-Bolívar V, Sánchez-Torralvo F, Ruiz-Vico M, González-Almendros I, Barrios M, Padín S, et al. GLIM criteria using hand grip strength adequately predict six-month mortality in cancer inpatients. *Nutrients*. (2019) 11:2043. doi: 10.3390/nu11092043

3. Sánchez-Torralvo FJ, Ruiz-García I, Contreras-Bolívar V, González-Almendros I, Ruiz-Vico M, Abuín-Fernández J, et al. CT-determined sarcopenia in GLIM-defined malnutrition and prediction of 6-month mortality in cancer inpatients. *Nutrients*. (2021) 13:2647. doi: 10.3390/nu13082647

4. Burgos R, Joaquin C, Blay C, Vaque C. Disease-related malnutrition in hospitalized chronic patients with complex needs. *Clin Nutr*. (2020) 39:1447–53. doi: 10.1016/j.clnu.2019.06.006

5. Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nutr*. (2008) 27:5–15. doi: 10.1016/j.clnu.2007.10.007

6. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. (2017) 36:49–64. doi: 10.1016/j.clnu.2016.09.004

7. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the international consensus guideline committee. *JPEN J Parenter Enteral Nutr*. (2010) 34:156–9. doi: 10.1177/0148607110361910

8. Freijer K, Tan SS, Koopmanschap MA, Meijers JM, Halfens RJ, Nuijten MJ. The economic costs of disease related malnutrition. *Clin Nutr*. (2013) 32:136–41. doi: 10.1016/j.clnu.2012.06.009

9. Lee JLC, Leong LP, Lim SL. Nutrition intervention approaches to reduce malnutrition in oncology patients: a systematic review. *Support Care Cancer*. (2016) 24:469–80. doi: 10.1007/s00520-015-2958-4

10. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst*. (2012) 104:371–85. doi: 10.1093/jnci/djr556

11. Hubbard GP, Elia M, Holdoway A, Stratton RJ. A systematic review of compliance to oral nutritional supplements. *Clin Nutr*. (2012) 31:293–312. doi: 10.1016/j.clnu.2011.11.020

12. Hubbard GP, Buchan B, Sanders K, Brothers S, Stratton RJ. Improved compliance and increased intake of energy and protein with a high energy density, low volume multi-nutrient supplement. *Proc Nutr Soc*. (2010) 69:E164. doi: 10.1017/S0029665109993600

13. León Sanz M, Martínez-Prado Casanova M, Moreno Villares J, Pedrón Giner C, Virgili CM. *Guía descriptiva de la prestación con productos dietéticos del Sistema Nacional de Salud*. Servicios Sociales e Igualdad: Ministerio de Sanidad (2015).

14. de Luis DA, Izaola O, Lopez JJ, Torres B, Gomez HE. Oral nutritional supplements and taste adherence in malnourished adults inpatients, effect on adhesion during hospital stance. *Ann Nutr Metab*. (2015) 67:205–9. doi: 10.1159/000440684

15. Hubbard GP, Fry C, Sorensen K, Casewell C, Collins L, Cunjamalay A, et al. Energy-dense, low-volume paediatric oral nutritional supplements improve total nutrient intake and increase growth in paediatric patients requiring nutritional support: results of a randomised controlled pilot trial. *Eur J Pediatr*. (2020) 179:1421–30. doi: 10.1007/s00431-020-03620-9

16. Nieuwenhuizen WF, Weenen H, Rigby P, Hetherington MM. Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. *Clin Nutr*. (2010) 29:160–9. doi: 10.1016/j.clnu.2009.09.003

17. García Almeida JM, García García C, Bellido Castañeda V, Bellido GDNuevo enfoque de la nutrición. Valoración del estado nutricional del paciente: función y composición corporal. *Nutr Hosp*. (2018) 35:1–14. doi: 10.20960/nh.2027

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 09 May 2023
DOI 10.3389/fnut.2023.1149579

OPEN ACCESS

EDITED BY
Barbara Troesch,
Self-employed, Zurich, Switzerland

REVIEWED BY
Carlo Pedrolli,
Azienda Provinciale per i Servizi Sanitari (APSS), Italy
Alison Steiber,
Academy of Nutrition and Dietetics Foundation, United States

*CORRESPONDENCE
Emmanuel Kabengele Mpinga
✉ emmanuel.kabengele@unige.ch

RECEIVED 22 January 2023
ACCEPTED 07 April 2023
PUBLISHED 09 May 2023

CITATION
Ouaijan K, Hwalla N, Kandala N-B, Abi Kharma J and Kabengele Mpinga E (2023) Analysis of predictors of malnutrition in adult hospitalized patients: social determinants and food security. *Front. Nutr.* 10:1149579. doi: 10.3389/fnut.2023.1149579

Analysis of predictors of malnutrition in adult hospitalized patients: social determinants and food security

Krystel Ouaijan[1,2], Nahla Hwalla[3], Ngianga-Bakwin Kandala[4,5], Joelle Abi Kharma[6] and Emmanuel Kabengele Mpinga[2]*

[1]Department of Clinical Nutrition, Saint George Hospital University Medical Center, Beirut, Lebanon, [2]Institute of Global Health, University of Geneva, Geneva, Switzerland, [3]Department of Nutrition and Food Sciences, American University of Beirut, Beirut, Lebanon, [4]Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, [5]Division of Epidemiology and Biostatistics, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa, [6]Faculty of Arts and Sciences, Lebanese American University, Beirut, Lebanon

Background: Malnutrition in hospitalized patients is becoming a priority during the patient care process due to its implications for worsening health outcomes. It can be the result of numerous social factors beyond clinical ones. This study aimed to evaluate the link between these various risk factors considered social determinants of health, food security levels, and malnutrition and to identify potential predictors.

Methods: A cross-sectional observational study was conducted on a random sample of adult patients in five different hospitals in Lebanon. Malnutrition was assessed using the Global Leadership Initiative on Malnutrition (GLIM) criteria. Patients were interviewed to collect social and economic characteristics and were categorized into four criteria: (1) area of residence (urbanization level), (2) level of education, (3) employment status, and (4) source of health coverage. The food security level was screened by a validated two-question tool, adapted from the US Department of Agriculture Household Food Security Survey, targeting both quantity and quality.

Results: In a random sample of 343 patients, the prevalence of malnutrition according to the GLIM criteria was 35.6%. Patients with low levels of food security, mainly low quality of food, had higher odds of being malnourished (OR = 2.93). Unemployed or retired patients and those who have only completed only elementary school had higher odds of being diagnosed with malnutrition as compared to those who were employed or had university degrees, respectively (OR = 4.11 and OR = 2.33, respectively). Employment status, education level, and type of health coverage were identified as predictors of malnutrition in the multiple regression model. Household location (urban vs. rural) was not associated with malnutrition.

Conclusion: The social determinants of health identified in our study, mainly the level of education and income level, in addition to food security, were identified as predictors of malnutrition in hospitalized patients. These findings should guide healthcare professionals and national policies to adopt a broader perspective in targeting malnutrition by including social determinants in their nutrition care.

KEYWORDS

social determinants, food security, hospital malnutrition, Global Leadership Initiative on Malnutrition GLIM, prevalence, health coverage, Right to Health

1. Introduction

Malnutrition in hospitalized patients has been associated with an increasing rate of complications and worsening outcomes (1). Malnutrition impairs many physiologic functions of the body, impairing the immune system, delaying wound healing, and leading to loss of muscle mass and strength (2). Major consequences resulting from these implications include increased morbidity, increased length of stay, nosocomial infections, and hospital readmission (1, 3). Patients diagnosed with malnutrition have in addition 5-fold higher mortality rate than patients with normal nutrition status (4). Malnutrition among hospitalized patients is typically categorized as disease-related malnutrition, as it is assumed to be mainly caused by the patient's clinical condition and the inflammatory process associated with their current illness (5–7).

However, malnutrition in hospitals may also arise from a combination of factors that extend beyond clinical factors, as observed in community settings (8, 9). An analysis of data from the Healthcare Cost and Utilization Project (HCUP) in the United States revealed a correlation between patients' income levels and their nutritional status upon admission to the hospital, with a higher incidence of malnutrition diagnosed in patients below the 50th percentile of income (10). These results highlight that a person's socioeconomic status can significantly affect their health, including their nutritional wellbeing (11). The World Health Organization (WHO) has long established that various factors, such as education level, employment, and urbanization, in addition to income, play a role in shaping population health via different mechanisms and have been categorized as social determinants of health (12, 13). However, studies on the impact of these determinants on nutritional status have been scarce and focused only on the growth of children (14, 15). More specifically, the influence of these determinants on the nutritional status of adult hospitalized patients has not been accounted for in previous studies.

Food security, another significant social determinant, has also an impact on both the quantity and quality of food intake affecting, as a result, the nutritional status of the hospitalized patient (16). Decreased food intake caused by insufficient food quantity is a primary contributor to weight loss, while inadequate food quality leads to reduced intake of essential nutrients and impacts nutritional status in patients (2). Although studies on food security have mainly examined the association between poor nutrient-dense foods and obesity, there is still limited evidence linking food security with malnutrition in healthcare settings, particularly among adults (17). Data mainly focus on growth decline in children, and research on adults in healthcare settings is scarce (16).

The social determinants of health along with food security are taken into consideration as part of the Right to Health, which dictates their availability and equitable accessibility (18). The Right to Health is recognized as a fundamental part of Human Rights in all international treaties (11). The essential elements of the Right to Health under the Human Rights approach ensure that all people have equal access to the underlying determinants of good health (18). Understanding the relationship between social and economic factors with the risk of malnutrition in hospitalized patients adds an important perspective of strategies targeting the patient's Right to Health (19).

Lebanon is a small country in the Middle East Region that is divided into five main districts with an estimated population of 6,847,712 and 144 hospitals comprising 11,742 beds (20, 21). Studies on the prevalence of malnutrition in hospitalized patients have been modest with a small study reporting a rate of 37.4% in one hospital (22). The country has recently witnessed a severe financial crisis. According to the World Bank, a drop of 36.5% in gross domestic product per capita has reclassified the country as a lower-middle-income country instead of an upper-middle-income country (21). These drastic changes have directly affected employment status impacting household incomes and therefore food security and the extent of healthcare coverage. The aim of this study was to assess the association between indicators of social determinants of health and food security with malnutrition in adult hospitalized patients. We also aimed to determine whether any of these factors are potential predictors of nutritional status. The results of this study would suggest taking a social perspective when identifying malnutrition in hospitalized patients and providing guidance for national policies on including malnutrition in hospitalized patients under the Right to Health framework.

2. Materials and methods

2.1. Study population

Patients were enrolled as a part of a cross-sectional, observational, and multicenter study intended to assess the national prevalence of malnutrition from May to October 2021. They signed an informed consent form after being introduced to the aim and process of the study. A total of five hospitals, one hospital from each of the five districts of Lebanon, were selected by convenience sampling. All adult patients, men and women aged 18 years and above, admitted to the different wards of the hospitals during the period of data collection were recruited within 48 h of admission. Patients with dementia or other cognitive impairment were also included, and the caregivers were approached to sign the consent form and fill the part of the questionnaire. Exclusion criteria included the following wards: gynecology, intensive care unit, psychiatry, and short stay of <48 h because of the inability of conducting questionnaires.

2.2. Data collection and social determinants

The patient's basic characteristics, including age, gender, marital status, and admission diagnosis, were recorded. The World Health Organization and Office of Disease Prevention and Health Promotion identify various indicators as integral to social determinants of health impacting directly health outcomes in their Healthy Report 2030 (13, 23). Four of these indicators were considered, and patients were interviewed accordingly: (1) area of residence (urbanization level), (2) level of education, (3) employment status, and (4) source of health coverage (11, 12). The source of health coverage that applies to the country context includes National Social Security Fund (NSSF), private insurance, and financial aid from governmental and non-governmental organizations.

2.3. Food security

The level of food insecurity was screened using a simplified tool based on two questions adapted from the 2000 United States Department of Agriculture Report on Food Security Measurement Project (24). It was demonstrated that a two-item screening tool has high sensitivity and specificity and is a practical tool for use in surveys conducted in healthcare settings (25–27). The two questions (Q1 and Q4) from the Food Security Scale were selected to focus on the patient's perception of food availability in the household. The first question was "Which of these statements best describes the food eaten in the household in the last 12 months?" The response categories were as follows:

(1) enough of the kinds of food we want to eat
(2) enough but not always the kinds of food we want
(3) sometimes not enough to eat
(4) often not enough to eat.

The second question was "Which of these statements best describes the quality of food eaten in the household in the last 12 months?" The response categories were determined based on the patient's description of the number of food groups they consume as follows (24):

(1) very good
(2) good
(3) average
(4) poor.

2.4. Nutritional status

The Global Leadership Initiative on Malnutrition (GLIM) was used to diagnose malnutrition and its severity in hospitalized patients (5). It is a two-step process by first identifying at least one phenotypic criterion and one etiologic criterion and second assessing the severity of malnutrition as "moderate" and "severe" based on the phenotypic criterion. Anthropometrics, including height, weight, body mass index (BMI), and mid-upper arm muscle circumference (MUAC), were used to evaluate the phenotypic criteria. Patients were interviewed for the history of weight loss, appetite, and record of food intake. Food intake was assessed using the dietary recall of meals consumed before hospital admission and categorized as <50% of estimated needs in >1 week or any reduction for >2 weeks. C-reactive protein levels (CRPs) were retrieved from the available blood tests from the patient's records. Reduced food intake retrieved from the patient's interviews and inflammatory condition assessed by their CRP levels retrieved from the patient's files was the etiologic criteria. Cutoff points of the different etiologic and phenotypic criteria are described in Table 1.

2.5. Statistical analysis

Statistical analysis was performed using STATA v17.1. Descriptive analysis was used to summarize the study variables and to check for out-of-range values. Continuous variables were described using mean and standard deviations, while frequencies and percentages were used to represent categorical variables. Shapiro–Wilk was used to assess data normality. The median and interquartile range (IQR) were used to describe the non-parametric variables. A series of simple logistic regressions were conducted at the bivariate level to identify potential predictors of malnutrition. A multiple logistic regression model was run thereafter to assess the independent associations between malnutrition status and patients' social determinants and food security level. Variables were selected for inclusion in the model based on a p-value of < 0.2 at the bivariate level. All reported p-values were evaluated at a significance level of 5%.

TABLE 1 Global Leadership Initiative on Malnutrition GLIM criteria for the diagnosis of malnutrition (43).

Phenotypic criteria			Etiologic criteria	
Severity level	Moderate	Severe		
Weight loss	>5–10% within past 6 months or 10-20% beyond 6 months	>10% within past 6 months, or >20% beyond 6 months	Reduced food intake	<50% of Estimated Needs in > 1 week or any reduction for >2 weeks
Low BMI	<20 if <70 years, >22 if >70 years	<18.5 if <70 years, <20 if <70 years		any chronic GI condition that adversely impacts food assimilation or absorption
Reduced muscle mass	MUAC[a] < 23	MUAC < 20	Inflammation	Elevated C-Reactive Protein (CRP) levels

[a]Mid-Upper Arm Muscle Circumference.

3. Results

3.1. Sociodemographic characteristics

A total of 343 participants were enrolled in this study from May to October 2021. Demographics and social characteristics are presented in Table 2. The mean age was 60 years (SD: 17 years), and the majority of the patients were <70 years old (65.89%). Almost half of the patients were male (54.81%), and the majority were married (70.55%). The majority of households (62.10%) were located in urban areas. In total, 27.99% of participants had university degrees, but more than half were not working (58.6%).

3.2. Nutritional status of patients

Using the GLIM diagnostic criteria, a total of 35.57% of patients (n = 122) were identified as malnourished, 21.28% (n = 73) had a moderate level of malnutrition, and 14.29% (n = 49) were classified as being severely malnourished. An equal

TABLE 2 Sociodemographic characteristics of patients ($N = 343$).

	N (%)
Age	
<70 years old	226 (65.89%)
≥70 years old	117 (34.11%)
Gender	
Male	188 (54.81%)
Female	155 (45.19%)
Marital status	
Single	45 (13.12%)
Married	242 (70.55%)
Divorced	17 (4.96%)
Widowed	39 (11.37%)
Level of education	
No schooling	32 (9.33%)
Primary school	59 (17.20%)
Intermediate school	66 (19.24%)
High school	64 (18.66%)
Technical diploma	26 (7.58%)
University degree	96 (27.99%)
Work status	
Not working	157 (45.77%)
Employee full time	91 (26.53%)
Employee part time	11 (3.21%)
Self-employed	29 (8.45%)
Retired	55 (16.03%)
Household location	
Urban	213 (62.10%)
Countryside	130 (37.90%)
Health coverage	
None	30 (8.75%)
NSSF[a]	86 (25.07%)
Private insurance	84 (24.49%)
Combination of NSSF1 and insurance	40 (11.66%)
Army or other governmental institution	82 (23.91%)
Non-governmental organization	21 (6.12%)

[a]National social security fund.

proportion (50%) of malnourished patients were distributed in male and female populations. Among the 122 patients identified as malnourished, the most dominant phenotypic criterion was "weight loss" accounting for 76.7% followed by low muscle mass (57.5%) and low BMI (31.2%). Decreased food intake was the most common etiologic criterion identified (88%) followed by inflammatory status (60.7%).

TABLE 3 Distribution of level of food security among patients ($N = 343$).

	N (%)
Food security (quantity)	
Enough of the kinds of food we want to eat	87 (25.36%)
Enough but not always the kinds of food	200 (58.31%)
Sometimes not enough to eat	50 (14.58%)
Often not enough to eat	6 (1.75%)
Food security (quality)	
Very good	80 (23.32%)
Good	111 (32.36%)
Average	131 (38.19%)
Poor	21 (6.12%)

3.3. Level of food security

Referring to the quantity of food consumed in the first question, the majority of the patients (58.31%) described their household food to be "enough but not always the kinds of food we want" as shown in Table 3. Only six patients (1.75%) responded as not having enough food to eat. When referring to the quality of food in the household in the second question, responses were mainly distributed between two categories: good (32.36%) and average (38.19%).

3.4. Association of malnutrition with social determinants

Table 4 describes the bivariate associations between malnutrition and different sociodemographic characteristics. The odds of being malnourished according to the GLIM criteria were higher among patients of older age (≥70 years old, $p < 0.001$) compared to those of younger age. Gender and marital status were not significantly associated. As for the four indicators identified as social determinants, unemployed or retired patients ($p < .001$) and those who had completed basic schooling ($p = 0.004$) or no schooling at all ($p = 0.047$) had higher odds of being malnourished as compared to those employed or had university degrees, respectively. Household location (urban vs. rural) and type of health coverage were not significantly associated with being malnourished.

3.5. Association of malnutrition with the level of food security

Patients who described in the first question the quality of the food eaten to be "poor" compared to "very good" have higher odds of being malnourished ($p = 0.032$). There was no association between malnutrition and the reported description of food quantity in the second question ($p = 0.4234$) as shown in Table 4.

3.6. Multiple logistic regression and potential predictors of malnutrition

Age, work status, district, and type of health coverage were found to be independent predictors of malnutrition diagnosis as shown in Table 5. Specifically, patients of older age (≥70 years old, $p < 0.001$) and unemployed/retired ($p < 0.001$) had higher odds of being diagnosed with malnutrition compared to their counterparts. As for food security, patients who described the quality of the food eaten to be "poor" compared to "very good" in the first question had higher odds of being malnourished ($p = 0.066$), but the results were borderline significant. However, patients who had private insurance as medical coverage means had lower odds of being diagnosed with malnutrition ($p = 0.033$). The Hosmer and Lemeshow goodness-of-fit test indicates that our model fits the data well with p-values of 0.7247.

TABLE 4 Bivariate associations between diagnosis of malnutrition and social determinants and level of food security.

	Odds ratio (OR)	CI	*P*-value
Age[a]			
≥70 years old	4.16	2.58; 6.70	<0.001**
Gender[b]			
Female	1.35	0.86; 2.10	0.184
Employment status[c]			
Not working	4.11	2.43; 6.95	< 0.001**
Level of education[d]			
No schooling	2.33	1.01; 5.39	0.047*
Primary school/intermediate school	2.36	1.32; 4.21	0.004*
High school/technical diploma	1.43	0.75; 2.70	0.276
Marital status[e]			
Married	1.19	0.73; 1.96	0.470
Household location[f]			
Countryside	0.88	0.56; 1.39	0.603
Health coverage[g]			
NSSF	1.03	0.44; 2.40	0.947
Private insurance	0.5	0.21; 1.20	0.123
Combination of NSSF and insurance	0.57	0.21; 1.55	0.273
Army or other governmental institution	1.17	0.50; 2.74	0.712
Non-governmental organization	0.75	0.23; 2.40	0.628
Food Security (Quantity)[h]			
Enough of the kinds of food we want to eat	0.88	0.52; 1.49	0.650
Enough but not always the kinds of food sometimes/often not enough to eat	1.11	0.56; 2.21	0.763
Food security (quality)[i]			
Good	1.24	0.67; 2.28	0.491
Average	1.15	0.64; 2.08	0.643
Poor	2.93	1.09; 7.85	0.032*

[a]reference group "<70 years old", [b]reference group "males", [c]reference group "working", [d]reference group "university degree", [e]reference group "not married", [f]reference group "urban", [g]reference group "none", [h]reference group "Enough of the kinds of food we want to eat", [i]reference group "very good" *$p < 0.05$.

4. Discussion

The nutritional status of hospitalized patients in this study was assessed and diagnosed using the GLIM criteria. It is a newly proposed diagnostic tool based on a global set of criteria that take into consideration different characteristics of malnutrition, including weight loss, muscle mass, and food intake (28). It is considered an evolving concept that was designed to provide a more specific diagnosis of malnutrition and has been validated in numerous studies (28–31). The prevalence rate of malnutrition among hospitalized patients in this study was found to be 36.7% using the GLIM criteria. In an international multicenter study that included two hospitals in Lebanon and was conducted in 2008, nutrition screening was done using Nutrition Risk Screening (NRS) and reported a lower rate of 22% of patients being at risk of malnutrition (32). Although both studies were done on adult hospitalized patients without excluding any medical conditions, they differ in two major criteria. First, the study used a screening tool as compared to the use of a diagnostic tool in our study. In addition, it was carried out in only one district of Lebanon including 273 patients as compared to our study that was carried out in all five districts including 343 patients. However, a notable increase in the prevalence from 22% of patients at risk to 36.7% of patients diagnosed with malnutrition is observed. A possible explanation for this increase is the drop in GDP that the country has experienced leading to a drastic financial crisis (21).

This proposed explanation further supports our hypothesis that malnutrition in hospitalized patients is influenced not only by well-known medical and clinical conditions but also by social and economic factors. As a matter of fact, a financial crisis will affect the ability to purchase enough food of good quality affecting in return the nutritional status of the patients (33). In our study, the risk of food insecurity was screened using a valid adapted tool focusing on both the quantity and quality of food (34). Nearly 60% of patients reported that their food intake was sufficient in quantity but inadequate in variety, as they lacked access to different types of food groups. This lack of adequacy described by the patients in our study was significantly associated with malnutrition despite the food quantity. Other numerous studies have always focused on exploring food insecurity either starvation in the community as a consequence of unavailability of food or obesity as a consequence of unhealthy food choices (16, 35). In our study, we used a regression model and identified the level of food security as a predictor of malnutrition in hospitalized adults. Patients who had a poor level of food security identified by the adapted tool we used had higher odds

10.3389/fnut.2023.1149579

TABLE 5 Adjusted multiple logistics regression model of diagnosis of malnutrition and social determinants and level of food security.

	Odds ratio (OR)	95% CI for OR	*P*-value
Age[a]			
≥70 years old	3.03	1.55; 5.90	0.001**
Gender[b]			
Female	0.88	0.49; 1.57	0.684
Employment status[c]			
Not working	2.50	1.23; 5.09	0.011**
Level of education[d]			
No schooling	1.53	0.46; 5.09	0.481
Primary school/intermediate school	1.10	0.51; 2.42	0.799
High school/technical diploma	0.75	0.35; 1.64	0.473
Health coverage[e]			
NSSF	0.85	0.31; 2.36	0.759
Private insurance	0.30	0.10; 0.90	0.033*
Combination of NSSF and insurance	0.32	0.09; 1.13	0.079
Army or other governmental institution	0.84	0.29; 2.42	0.750
Non-governmental organization	0.69	0.15; 3.19	0.645
Food security (quality)[f]			
Good	1.75	0.82; 3.73	0.151
Average	1.48	0.66; 3.35	0.343
Poor	3.54	0.92; 13.61	0.066

[a]reference group "<70 years old", [b]reference group "males", [c]reference group "working", [d]reference group "university degree", [e]reference group "none", [f]reference group "very good"
*$p < 0.05$.

of 3.56 to being malnourished as compared to patients categorized with a good level.

Food security is recognized as a component of the social determinants of health that include education, economic stability, and access to healthcare (36). These fundamental determinants have been linked to adverse health outcomes and are considered key drivers of health equity. Research has primarily concentrated on the pediatric population in the community and has established a correlation between low income and education levels with child stunting as an indicator of poor nutritional status (37, 38). In our study population in the hospital setting, employment status and education level were highly associated with malnutrition. Patients who were not working or had completed only elementary school had higher odds of being diagnosed with malnutrition. In addition, employment status was considered a predictor of malnutrition in hospitalized patients in our regression model (OR = 4.1). Malnutrition in older people living in the community was also associated with low educational levels in a recent systematic review (39). On the other hand, marital status was not associated with the level of malnutrition in our population and cannot be determined as a risk factor.

Another predictor of malnutrition in our study was the type of health coverage. Patients who had been insured in private insurance had significantly lower odds of being malnourished as compared with patients with no health coverage or relying on social security funds and non-governmental aid. Private insurance in Lebanon is prohibitively expensive and typically only obtained by individuals from higher socioeconomic groups reflecting a correlation between income level and risk of malnutrition. This correlation has also been demonstrated when studying the nutritional status of children and older adults in the community (33, 39). The type of residence area, being urban or rural, was not associated with malnutrition in our model. The small surface area of Lebanon (10,452 km^2) has decreased the differences in the level of urbanization between the cities and rural areas, and therefore, a discrepancy could not be identified.

The association that we have demonstrated between social determinants and food security should alarm healthcare professionals to broaden their perspective when identifying malnutrition in hospitalized patients. When conducting nutritional assessments, including the GLIM criteria or any validated tool, it is advisable to incorporate a social dimension and identify any factors that increase the risk of malnutrition, such as food insecurity, low income, or low literacy levels (29, 40). When developing a management plan for malnutrition in hospitalized patients, it is crucial to address social determinants and food security as essential components. Healthcare professionals are used to focusing primarily on biomedical and clinical care that has been recently described as a downstream approach aiming to treat symptoms of malnutrition without targeting root causes (41, 42). Healthy People 2030 initiative has recently proposed a more proactive approach that targets the causes of diseases at a macro-level. This initiative acknowledges the economic and social factors that are typically beyond the patient's control (36). In order to provide effective nutritional care, healthcare professionals should review the patient's living and working conditions and address the social determinants of health directly (33). Through this tailored approach, healthcare professionals can prioritize enhancing food security, education, and income levels, even for hospitalized patients, as a means of achieving the Right to Health at a broader national level (18).

This study has several strengths. First, it has a heterogeneous population because it included patients from five hospitals across different areas and admitted to various wards. Second, the identification of malnutrition was not done by a screening process but was determined through a systematic nutritional assessment using the new GLIM criteria. Third, it was the first study to our knowledge to investigate the association of social determinants with malnutrition measured in hospitalized patients and to identify potential predictors. This study also has some limitations. First, social and economic indicators were collected from the patients and their caregivers through a questionnaire and they had some reservations while answering the questions. Second, a direct question on income level could not be collected due to the severe devaluation of the national currency and the inadequacy of any

relevant categorization. Third, food security was only addressed at a screening level using a two-item questionnaire as hospitalized patients were less responsive to surveys of longer duration.

5. Conclusion

To conclude, our study found a malnutrition prevalence rate of 35.57% in hospitalized patients in Lebanon. We also identified social determinants of health, including education level, income level, employment status, and health coverage, as factors associated with malnutrition, along with food security. These determinants were also recognized as predictors of malnutrition in hospitalized patients. Our findings suggest that healthcare professionals should consider adopting a broader perspective in targeting malnutrition in their patients. Their approach should aim to address the underlying causes of malnutrition beyond clinical factors by incorporating social determinants into their nutritional care assessments. National authorities should also prioritize addressing the social determinants of health in their policy agenda to improve malnutrition at the clinical level.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the American University of Beirut. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EK, KO, NH, and N-BK: conceptualization and methodology. KO: data collection and writing—original draft preparation. KO and JA: formal analysis. EK, NH, and N-BK: writing—review and editing. EK: supervision. KO and NH: funding acquisition. All authors contributed to the article and approved the submitted version.

Funding

This research study was partially funded by Dietitians in Nutrition Support DNS—Academy of Nutrition and Dietetics in the United States, grant number 104037. Open access funding by American University of Beirut.

Acknowledgments

The authors would like to thank all the hospitals that participated in the study: Saint George Hospital University Medical Center (Beirut), Sacre Coeur (Mount Lebanon), Monla Hospital (North), Raee Hospital (South), and Hospital Libano-Francais (Bekaa). The authors expressed tremendous gratitude to all clinical dietitians who facilitated the process of data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Kirkland LL, Kashiwagi DT, Brantley S, Scheurer D, Varkey P. Nutrition in the hospitalized patient. *J Hosp Med*. (2013) 8:52–8. doi: 10.1002/jhm.1969

2. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. *Int J Environ Res Public Health*. (2011) 8:514–27. doi: 10.3390/ijerph8020514

3. Schneider SM, Veyres P, Pivot X, Soummer AM, Jambou P, Filippi J, et al. Malnutrition is an independent factor associated with nosocomial infections. *Br J Nutr*. (2004) 92:105–11. doi: 10.1079/BJN20041152

4. Corkins MR, Guenter P, DiMaria-Ghalili RA, Jensen GL, Malone A, Miller S, et al. ASPEN data brief 2014: use of enteral and parenteral nutrition in hospitalized patients with a diagnosis of malnutrition: United States. *Nutr Clin Pract*. (2014) 29:698–700. doi: 10.1177/0884533614543834

5. Cederholm T, Jensen GL, Correia MI, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition—A consensus report from the global clinical nutrition community. *Clin Nutr*. (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

6. Cederholm T, Rothenberg E, Barazzoni R. Editorial: a clinically relevant diagnosis code for "malnutrition in adults" is needed in ICD-11. *J Nutr Health Aging*. (2022) 26:314–315. doi: 10.1007/s12603-022-1774-z

7. Cederholm T, Barazzoni RO, Austin P, Ballmer P, Biolo GI, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. (2017) 36:49-64. doi: 10.1016/j.clnu.2016.09.004

8. O'Keeffe M, Kelly M, O'Herlihy E, O'Toole PW, Kearney PM, Timmons S, et al. Potentially modifiable determinants of malnutrition in older adults: a systematic review. *Clin Nutr*. (2019) 38:2477-2498. doi: 10.1016/j.clnu.2018.12.007

9. Reinhardt K, Fanzo J. Addressing chronic malnutrition through multi-sectoral, sustainable approaches: a review of the causes and consequences. *Front Nutr*. (2014) 1:13. doi: 10.3389/fnut.2014.00013

10. Corkins MR, Guenter P, DiMaria-Ghalili RA, Jensen GL, Malone A, Miller S, et al. Malnutrition diagnoses in hospitalized patients: United States. *JPEN J Parenter Enteral Nutr*. (2014) 38:186-95. doi: 10.1177/0148607113512154

11. Costa-Font J, Hernandez-Quevedo C. Measuring inequalities in health: what do we know? What do we need to know? *Health Policy*. (2012) 106:195-206. doi: 10.1016/j.healthpol.2012.04.007

12. Kosaka S, Umezaki M. A systematic review of the prevalence and predictors of the double burden of malnutrition within households. *Br J Nutr*. (2017) 117:1118-1127. doi: 10.1017/S0007114517000812

13. Commission on Social Determinants of Health Final Report. *Closing the Gap in a Generation: Health Equity Through Action on Social Determinants of Health*. Geneva: WHO (2008).

14. Fakir AM, Khan MD. Determinants of malnutrition among urban slum children in Bangladesh. *Health Econ Rev*. (2015) 5:59. doi: 10.1186/s13561-015-0059-1

15. Zhang N, Becares L, Chandola T. Patterns and determinants of double-burden of malnutrition among rural children: evidence from China. *PLoS ONE*. (2016) 11:e0158119. doi: 10.1371/journal.pone.0158119

16. Maitra C. *A Review of Studies Examining the Link Between Food Insecurity and Malnutrition, in Techanical Paper Food*. Rome: Agricuture Organization FAO (2018).

17. Carvajal-Aldaz D, Cucalon G, Ordonez C. Food insecurity as a risk factor for obesity: a review. *Front Nutr*. (2022) 9:1012734. doi: 10.3389/fnut.2022.1012734

18. Willen SS, Knipper M, Abadía-Barrero CE, Davidovitch N. Syndemic vulnerability and the right to health. *Lancet*. (2017) 389:964-977. doi: 10.1016/S0140-6736(17)30261-1

19. Steiber A, Hegazi R, Herrera M, Zamor ML, Chimanya K, Pekcan AG, et al. Spotlight on global malnutrition: a continuing challenge in the 21st century. *J Acad Nutr Diet*. (2015) 115:1335-41. doi: 10.1016/j.jand.2015.05.015

20. Long MW, Gortmaker SL, Ward ZJ, Resch SC, Moodie ML, Sacks G, et al. Cost effectiveness of a sugar-sweetened beverage excise tax in the U.S. *Am J Prev Med*. (2015) 49:112–23. doi: 10.1016/j.amepre.2015.03.004

21. Lebanon Econmic Monitor, in World Bank. (2022). Available online at: https://www.worldbank.org/en/country/lebanon/publication/lebanon-economic-monitor (accessed January 23, 2023).

22. Choueiry G, Fattouh N, Hallit R, Kazour F, Hallit S, Salameh P. Nutritional status of lebanese hospitalized patients with chronic disease: a cross-sectional study. *Hosp Pharm*. (2021) 56:102–8. doi: 10.1177/0018578719867664

23. Healthy People 2030, U.S. *Department of Health and Human Services, Office of Disease Prevention and Health Promotion*. Maryland. (2022).

24. *Guide to Measuring Household Food Security*. Virginia: United States Department of Agriculture. (2000).

25. Hager ER. Development and validity of a 2-item screen to identify families at risk for food insecurity. *Pediatrics*. (2010) 126:e26–32. doi: 10.1542/peds.2009-3146

26. Hager ER, Quigg AM, Black MM, Coleman SM, Heeren T, Rose-Jacobs R. Validity of a single item food security questionnaire in Arctic Canada. *Pediatrics*. (2014) 133:e1616–23. doi: 10.1542/peds.2013-3663

27. Poblacion A, Segall-Corrêa AM, Cook J, Taddei JA. Validity of a 2-item screening tool to identify families at risk for food insecurity in Brazil. *Cad Saude Publica*. (2021) 37:e00132320. doi: 10.1590/0102-311x00132320

28. Correia MI, Tappenden KA, Malone A, Prado CM, Evans DC, Sauer AC, et al. Utilization and validation of the global leadership initiative on malnutrition (GLIM): a scoping review. *Clin Nutr*. (2022) 41:687–97. doi: 10.1016/j.clnu.2022.01.018

29. Schuetz P, Seres D, Lobo DN, Gomes F, Kaegi-Braun N, Stanga Z. Management of disease-related malnutrition for patients being treated in hospital. *Lancet*. (2021) 398:1927–38. doi: 10.1016/S0140-6736(21)01451-3

30. Balci C, Bolayir B, Eşme M, Arik G, Kuyumcu ME, Yeşil Y, et al. Comparison of the efficacy of the global leadership initiative on malnutrition criteria, subjective global assessment, and nutrition risk screening 2002 in diagnosing malnutrition and predicting 5-year mortality in patients hospitalized for acute illnesses. *JPEN J Parenter Enteral Nutr*. (2021) 45:1172–80. doi: 10.1002/jpen.2016

31. da Silva Couto A, Gonzalez MC, Martucci RB, Feijó PM, Rodrigues VD, de Pinho NB, et al. Predictive validity of GLIM malnutrition diagnosis in patients with colorectal cancer. *JPEN J Parenter Enteral Nutr*. (2023) 47:420–8. doi: 10.1002/jpen.2475

32. Sorensen J, Kondrup J, Prokopowicz J, Schiesser M, Krähenbühl L, Meier R, et al. EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. *Clin Nutr*. (2008) 27:340–9. doi: 10.1016/j.clnu.2008.03.012

33. Peregrin T. Social determinants of health: enhancing health equity. *J Acad Nutr Diet*. (2021) 121:1175-—8. doi: 10.1016/j.jand.2021.02.030

34. *Guide to Measuring Household Food Security*. Virginia: U.S. Department of Agriculture. (2000).

35. Tydeman-Edwards R, Van Rooyen FC, Walsh CM. Obesity, undernutrition and the double burden of malnutrition in the urban and rural southern Free State, South Africa. *Heliyon*. (2018) 4:e00983. doi: 10.1016/j.heliyon.2018.e00983

36. Healthy People 2020. *Social Determinants of Health*. Maryland: U.S. Department of Health and Human Services. (2021).

37. Harris J, Nisbett N. The basic determinants of malnutrition: resources, structures, ideas and power. *Int J Health Policy Manag*. (2021) 10:817-827. doi: 10.34172/ijhpm.2020.259

38. Tette E, Sifah EK, Nartey ET, Nuro-Ameyaw P, Tete-Donkor P, Biritwum RB. Maternal profiles and social determinants of malnutrition and the MDGs: what have we learnt? *BMC Public Health*. (2016) 16:214. doi: 10.1186/s12889-016-2853-z

39. Besora-Moreno M, Llauradó E, Tarro L, Solà R. Social and economic factors and malnutrition or the risk of malnutrition in the elderly: a systematic review and meta-analysis of observational studies. *Nutrients*. (2020) 12:737. doi: 10.3390/nu12030737

40. Soriano-Moreno DR, Dolores-Maldonado G, Benites-Bullón A, Ccami-Bernal F, Fernandez-Guzman D, Esparza-Varas AL, et al. Recommendations for nutritional assessment across clinical practice guidelines: a scoping review. *Clin Nutr ESPEN*. (2022) 49:201–7. doi: 10.1016/j.clnesp.2022.04.023

41. Booske BC, Kinding DA. *Different Perspectives for Assigning Weights to Determinants of Health, in County Health Rankings*. Working Paper. Wisconsin: Population of Health Institute. (2010).

42. Lantz PM. The medicalization of population health: Who will stay upstream? *Milbank Q*. (2019). 97:36–9. doi: 10.1111/1468-0009.12363

43. Cederholm T, Jensen GL, Correia MI, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition—A consensus report from the global clinical nutrition community. *Clin Nutr*. (2018) 3:33. doi: 10.1016/j.clnu.2019.02.033

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 24 May 2023
DOI 10.3389/fnut.2023.1149727

OPEN ACCESS

EDITED BY
Barbara Troesch,
Self-Employed, Zurich, Switzerland

REVIEWED BY
Lakshmi Ranganathan,
Senior Researcher, Chennai, India
Iftikhar Alam,
Bacha Khan University, Pakistan

*CORRESPONDENCE
Sarah M. Ajabnoor
✉ smajabnoor@kau.edu.sa

RECEIVED 22 January 2023
ACCEPTED 02 May 2023
PUBLISHED 24 May 2023

CITATION
Ajabnoor SM, Zaher S, Malatani R and Jawa H (2023) Exploring the practice of nutritional support during hospitalization across physicians, dietitians, and pharmacists based in Saudi Arabia.
Front. Nutr. 10:1149727.
doi: 10.3389/fnut.2023.1149727

Exploring the practice of nutritional support during hospitalization across physicians, dietitians, and pharmacists based in Saudi Arabia

Sarah M. Ajabnoor [1]*, Sara Zaher [2], Rania Malatani [3] and Hani Jawa [4]

[1]Clinical Nutrition Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia, [2]Clinical Nutrition Department, Faculty of Applied Medical Sciences, Taibah University, Madinah, Saudi Arabia, [3]Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia, [4]Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Background: Nutritional support has a pivotal role in preventing and treating malnutrition. Recognizing the gaps in nutritional support practice can aid the development of tailored nutritional protocols. Therefore, this study aimed to assess the current practices, attitudes, and perceptions related to nutritional support for hospitalized patients in one of the largest Middle Eastern countries.

Methods: A cross-sectional study was conducted among different healthcare professionals currently working in hospitals in Saudi Arabia and involved in nutritional support practice. Data were collected using convenient sample via a self-administered web-based questionnaire.

Results: A total of 114 participants were included in this study. The majority were dietitians (54%), followed by physicians (33%) and pharmacists (12%), and were from the western region (71.9%). Various attitudes in many practices were observed among the participants. Only 44.7% of the participants had a formal nutritional support team. The mean confidence level of all respondents was significantly higher for enteral nutrition practice (7.7 $\pm$ 2.3) than for parenteral nutrition practice (6.1 $\pm$ 2.5) ($p < 0.01$). The confidence level for enteral nutrition practice was significantly influenced by nutritional qualification ($\beta = 0.202$, $p < 0.05$), type of healthcare facility ($\beta = 0.210$, $p < 0.05$), profession ($\beta = -0.308$, $p < 0.01$), and years of experience ($\beta = 0.220$, $p < 0.05$).

Conclusion: This study comprehensively assessed various aspects of nutritional support practice in Saudi Arabia. Healthcare practice of nutritional support should be guided by evidence-based guidelines. Professional qualification and training in nutritional support are essential for promoting practice in hospitals.

KEYWORDS

nutritional support, enteral nutrition, parenteral nutrition, nutritional support team, practice

Introduction

More than 40% of hospitalized patients are considered malnourished (1). In Saudi Arabia, robust national data on the malnutrition rate in hospitalized patients are lacking. An earlier single-center study that utilized anthropometric data reported malnutrition in up to 34% of hospitalized patients (2). Other studies used the Mini Nutritional Assessment (MNA) tool for reporting malnutrition in hospitalized elderly patients; up to 36.5% of patients were malnourished, while up to 57.8% were at risk for malnutrition (3–5). The malnutrition rate in hospitalized elderly patients was associated with a higher mortality rate and prolonged hospital stay (5). Nevertheless, the prevalence of malnutrition on admission is consistently high (between 40 and 60%) (6). Malnutrition should be identified early during hospital admission, and nutritional care plans should be appropriately initiated. Recently, the American Society for Parenteral and Enteral Nutrition (ASPEN) issued updated evidence-based standards for various nutritional support practices in hospitalized adult patients, which help clinicians deliver safe and efficient nutritional care plans (7). The availability of such guidelines should prevent inappropriate practices of nutritional support, such as late feed initiation, inappropriate parenteral nutrition (PN) prescription for patients who can tolerate enteral nutrition (EN), unmet patient caloric requirements, or poor monitoring of EN/PN-related complications. However, inappropriate practices resulting from insufficient knowledge and nutritional training and poor compliance with available guidelines are still being reported among healthcare professionals (8, 9). In Saudi Arabia, there is a lack of consensus and national guidelines for clinical nutrition practice. Thus, nutritional support protocols for hospitalized patients are warranted.

The efficiency and safety of nutritional support delivery can be optimized with multidisciplinary approaches. Nutritional support teams (NSTs) have been established since 1980 by many hospitals to provide optimal nutrition care for patients receiving EN or PN (10). NSTs usually comprise dietitians, pharmacists, nurses, and physicians. Most assigned leaders for NSTs are either physicians or dietitians (11). All clinicians included in NSTs should gain expertise and undergo training in nutritional support. The recent ASPEN consensus for appropriate PN practices supports the utilization of NSTs comprising healthcare professionals with the expertise to provide proper PN management (12). NST implementation in hospitals is associated with many positive outcomes, including fewer EN/PN-related complications, improved patient safety, and reduced hospital costs (12). NST implementation is also associated with reduced electrolyte abnormalities (i.e., refeeding syndrome) and mortalities in patients receiving PN (13). However, there is a lack of data on NST implementation in hospitals and its outcomes in Saudi Arabia. Another important function of NST implementation is monitoring of patients receiving long-term home nutritional support, which can be complex and challenging (11).

The current nutritional support practices across hospitals in Saudi Arabia are not fully described. There are no national guidelines supporting appropriate nutritional support practice in hospitalized patients. Therefore, this study primarily aimed to assess the current practices, attitudes, and perceptions related to nutritional support for hospitalized patients among physicians, dietitians, and pharmacists in Saudi Arabia.

Materials and methods

Study design

This cross-sectional study used an online survey conducted from August 2020 to February 2021 among healthcare professionals working in hospitals in Saudi Arabia.

Registered dietitians and clinical pharmacists currently practicing and physicians routinely involved in nutritional support (i.e., gastroenterologists, surgeons, and critical care intensivists) were included. Other healthcare professionals were excluded.

Data collection was done using convenience sampling technique. The questionnaire was primarily distributed via several platforms, such as the Saudi Gastroenterology Association, the Saudi General Surgery Society, the Saudi Critical Care Society, the Saudi Society for Clinical Nutrition, the Saudi Society of Clinical Pharmacy, and social media. Members of national associations were invited to participate in the study via email with a link for the questionnaire. Because recruitment was online and open, the response rate was not calculated.

Survey development

The questionnaire comprised six main sections covering 45 items. Included questions were developed by the research team after reviewing previous surveys that investigated different areas of nutritional support practice among physicians and other healthcare professionals working in Canada, the United States, and Europe (14–19). The main sections of the questionnaire were designed to assess the respondent demographic data, structure and performance of the NST, nutritional screening and assessment practices, use of established nutritional support guidelines, attitudes related to initiation and monitoring of nutritional support, and perceptions related to the current knowledge of nutritional support. The questionnaire was electronically created using Google Forms.

For questionnaire validation, pilot testing of the survey was initially conducted among an expert panel, which included one dietitian, two Ph.D holders in clinical nutrition, and two pharmacists. The panel assessed the appropriateness of the questionnaire and the time spent for completing the survey. All feedback was considered by the research investigators. The clinicians who participated in the pilot testing were excluded from the main study survey.

Ethical approval

The study was approved by the Unit of the Biomedical Ethics Research Committee at King Abdulaziz University in Jeddah, Saudi Arabia (HA-02-J-008). All participants provided an electronic informed consent prior to answering the questionnaire. Statements regarding confidentiality and anonymity were included on the first page of the questionnaire.

Statistical analysis

Data were downloaded and analyzed using the Statistical Package for the Social Sciences version 23 (SPSS Inc.). The Shapiro–Wilk test was used to assess the normality of continuous variables. Data were presented as either means ± standard deviations or frequencies and percentages.

The Mann–Whitney U-test was used to compare the confidence score between two variables while the Kruskal–Wallis test was used to compare the confidence score between more than two variables.

A stepwise linear regression analysis was performed to identify the factors influencing the healthcare providers' confidence in practicing nutritional support. The confidence level was used as the outcome variable in the regression models. The dependent variables used in the models were nutritional qualification (yes coded as 1 and no as 0), type of healthcare facility (Ministry of Health hospital coded as 1, military hospital as 2, university teaching hospital as 3, specialized hospital as 4, national guard hospital as 5, medical city as 6, Security Forces Hospital as 7, and private hospital as 8), profession (dietitians coded as 1, pharmacists as 2, and physicians as 3), years of experience (0 years [newly graduated] coded as 1, 2–5 years as 2, 6–10 years as 3, and > 10 years as 4), region (western coded as 1, eastern as 2, central as 3, southern as 4, and northern as 5), and capacity of healthcare facility (<100 beds coded as 1, 100–250 beds as 2, 251–500 beds as 3, and >500 beds as 4).

All performed tests were two-tailed, with a significance level of 95%.

Results

Participant characteristics

A total of 140 respondents agreed to participate in the study; of them, only 117 answered yes when asked whether they were involved in nutritional support for hospitalized patients. Nutritional support was defined in the survey as a part of medical therapy that helps in treating and preventing malnutrition and includes EN and PN. Three responses were excluded owing to duplication and incompletion. The final analysis included 114 participants. Of them, 38 (33%) were physicians; 62 (54%), dietitians; and 14 (12%), pharmacists. The majority (71.9%) were from the western region of Saudi Arabia. The participant demographics are described in **Table 1**.

Roles in nutritional support

The participants were asked to report which nutritional support-related tasks they were involved in. All clinicians were relatively involved in determining patient needs for nutritional support and selecting the appropriate feeding route. All dietitians (100%), 85.7% (n = 12) of the pharmacists, and only 39.5% (n = 15) of the physicians indicated that they participated in estimating the patients' nutritional requirements.

Approximately 80.6% (n = 50) of the dietitians, 60.5% (n = 23) of the physicians, and 14.2% (n = 2) of the pharmacists reported that they were involved in writing EN orders; 22.5% (n = 14), 39.5% (n = 15), and 85.7% (n = 12) reported that they were involved in writing PN orders, respectively.

The majority of the physicians (65.7%, n = 22) and only 12.9% (n = 8) of the dietitians indicated that they were involved in the insertion and administration of EN feeding tubes. Only 13.1% (n = 5) of the physicians indicated that they participated in placing PN access devices.

Most dietitians (91.9%, n = 62) and pharmacists (100%) indicated their involvement in monitoring EN and PN, respectively. However, a smaller proportion of physicians reported their involvement in monitoring. **Figure 1** and **Supplementary Table 1** show the main current roles of the respondents in nutritional support.

Perceptions related to the use of established nutritional support guidelines

Around 78.1% (n = 89) of the respondents indicated that they were familiar with the published international guidelines by the ASPEN and/or European Society for Clinical Nutrition and Metabolism (ESPEN). The dietitians and pharmacists expressed greater familiarity with these guidelines.

Approximately 62.3% (n = 71) of the participants indicated that written policies for nutritional support provision were available in their institutions. Of them, 45 (63.4%) were involved in writing and updating these policies. The dietitians were highly involved (73%) in updating such policies, while the pharmacists (54.5%) and physicians (33.3%) were relatively less involved. The participants involved in writing policies and protocols for nutritional support reported that the most frequently used guidelines as reference were the ASPEN (47.4%) and ESPEN (38.6%) guidelines. **Table 2** shows the physicians', dietitians', and pharmacists' perceptions toward the use of established guidelines.

Nutritional screening practices

Approximately 35.96% of the participants were not aware of the screening tool that was routinely used in their hospitals. The Nutrition Risk Screening (NRS 2002) and Malnutrition Universal Screening Tool (MUST) were used routinely by 28.07 and 22.8% of the respondents. Other screening tools, including the MNA, Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Screening Tool (MST), and Subjective Global Assessment (SGA), were used routinely by fewer respondents.

Only 55 (48.2%) participants reported that screening for malnutrition was routinely conducted in their institutions. Of them, 45.4% selected dietitians as the key persons primarily responsible for the initial screening; 38.2%, nurses; and 16.4%, physicians. The majority (76.4%) reported that screening was routinely initiated on admission with periodic re-screening. **Supplementary Table 2** illustrates all participants' nutritional screening and assessment practices.

Nutritional assessment practices

The nutritional assessment practices varied among the respondents. Regarding referral to dietitians, 42.1% answered that

TABLE 1 Demographics of the study participants.

Demographic characteristics		Physicians (*n* = 38)	Dietitians (*n* = 62)	Pharmacists (*n* = 14)	Total (*n* = 114)
		n (%)			
Region	Western region	22 (57.9%)	48 (77.4%)	12 (85.7%)	82 (71.9%)
	Eastern region	3 (7.9%)	5 (8.1%)	2 (14.3%)	10 (8.8%)
	Central region	13 (34.2%)	6 (9.7%)	0 (0.0%)	19 (16.6%)
	Southern region	0 (0.0%)	3 (4.8%)	0 (0.0%)	3 (2.6%)
	Northern region	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Years of experience	Newly graduated	1 (2.6%)	3 (4.8%)	0 (50.0%)	4 (3.5%)
	2–5 years	8 (21.1%)	28 (45.2%)	7 (50.0%)	43 (37.7%)
	6–10 years	4 (10.5%)	20 (32.3%)	5 (35.7%)	29 (25.4%)
	More than 10 years	25 (65.8%)	11 (17.7%)	2 (14.3%)	38 (33.3%)
Type of health care facility	Medical cities (e.g., Prince Sultan Medical City)	1 (2.6%)	5 (8.1%)	0 (0.0%)	6 (5.3%)
	Military hospitals	0 (0.0%)	8 (12.9%)	4 (28.6%)	12 (10.5%)
	Ministry of Health (MOH) hospitals	7 (18.4%)	24 (38.7%)	0 (0.0%)	31 (27.2%)
	National guard hospitals	3 (7.9%)	3 (4.8%)	1 (7.1%)	7 (6.1%)
	Private hospitals	10 (26.3%)	8 (12.9%)	0 (0.0%)	18 (15.8%)
	Security Forces Hospital	2 (5.3%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
	Specialized hospitals (King Faisal Specialist Hospital and Research Centre)	6 (15.8%)	6 (9.7%)	3 (21.4%)	15 (13.2%)
	University teaching hospitals	9 (23.7%)	8 (12.9%)	6 (42.9%)	23 (20.2%)
Capacity of health care facility	<100 beds	4 (10.5%)	5 (8.1%)	2 (14.3%)	11 (9.6%)
	100–250 beds	8 (21.1%)	8 (12.9%)	1 (7.1%)	17 (14.9%)
	251–500 beds	8 (21.1%)	29 (46.8%)	4 (28.6%)	41 (36.0%)
	>500 beds	16 (42.1%)	13 (21.0%)	7 (50.0%)	36 (31.6%)
	Don't know	2 (5.3%)	7 (11.3%)	0 (0.0%)	9 (7.9%)
Nutritional support qualification	ASPEN nutrition support certification	0 (0.0%)	5 (8.1%)	0 (0.0%)	5 (4.4%)
	ESPEN diploma in clinical nutrition and metabolism	0 (0.0%)	3 (4.8%)	0 (0.0%)	3 (2.6%)
	Fellowship in clinical nutrition	2 (5.3%)	6 (9.7%)	1 (7.1%)	9 (7.9%)
	Master of clinical nutrition with focus on nutrition support	0 (0.0%)	10 (16.1%)	0 (0.0%)	10 (8.8%)
	More than one certificate	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Nutrition support training in their local hospital	1 (2.6%)	0 (0.0%)	3 (21.4%)	4 (3.5%)
	Others	1 (2.6%)	3 (4.8%)	0 (0.0%)	4 (3.5%)
	None	33 (86.8%)	35 (56.5%)	10 (71.4%)	78 (68.4%)

Data are presented as numbers and percentages.

it was ordered by physicians and 17.5% by nurses after the initial screening. However, 30.7% reported that dietitians assessed all newly admitted patients.

The majority of the respondents (58.8%) relied on anthropometric data (i.e., weight and height) as clinical indicators of nutritional status, while only 28.9% used albumin levels. Few (7.9%) used pre-albumin levels. A small proportion (16.7%) reported that they were not involved in calculating caloric needs. Conversely, 62.3% reported their use of simple weight-based equations, and 18.4% used predictive equations. Only 2.6% indicated that they had access to indirect calorimetry. Supplementary Table 3 shows the nutritional assessment practices by each profession.

Initiation, monitoring, and documentation of nutritional support plans

Initiation practices

Approximately 28.9 and 12.3% of the participants waited 1 and 2 days, respectively, before starting nutritional support for critically ill and hemodynamically stable patients with nil per oral status. Meanwhile, 39.5% waited 3 days. Nearly half (43.9%) of the participants waited 3–5 days before starting PN for well-nourished and stable patients with minimal oral intake or EN (<50% of requirements). Few waited 7–14 days.

Monitoring practices

The most common practices for patients on gastric feeding who were complaining of nausea and vomiting were slowing tube feeding (70.2%) and checking the gastric residual volume (GRV) (63.2%). Stopping tube feeding was indicated by 21.9% of the participants. Other practices were also reported by the participants. Nevertheless, about half (51.8%) reported that they routinely measured the GRV to assess EN intolerance.

Documentation practices

Only 15.8% indicated that nutritional data were documented manually in their institutions. Meanwhile, data related to nutritional assessment and care plan were documented electronically by 64% of the respondents. Prescription orders for EN and PN were electronically documented by 59.6% and 53.5%, respectively. Table 3 illustrates the main nutritional support practices in Saudi hospitals by each profession.

Availability of NSTs

The majority of the participants (93.9%) agreed that NSTs were important to the accuracy and efficacy of EN/PN prescription. The next question in the survey aimed to identify the proportion of participants working in hospitals with established NSTs. Approximately 44.7% (n = 51) of the clinicians had a formal NST, while 31.5% had none-formal NST (nutritional management was aided by regular communication between disciplines). Fewer participants either had no NST (13.2%) or were not aware (10.5%).

The 51 clinicians who had a formal NST indicated the following as members of the team: dietitians (100%), physicians (96.1%), pharmacists (84.3%), and nurses (74.5%). Conversely, the

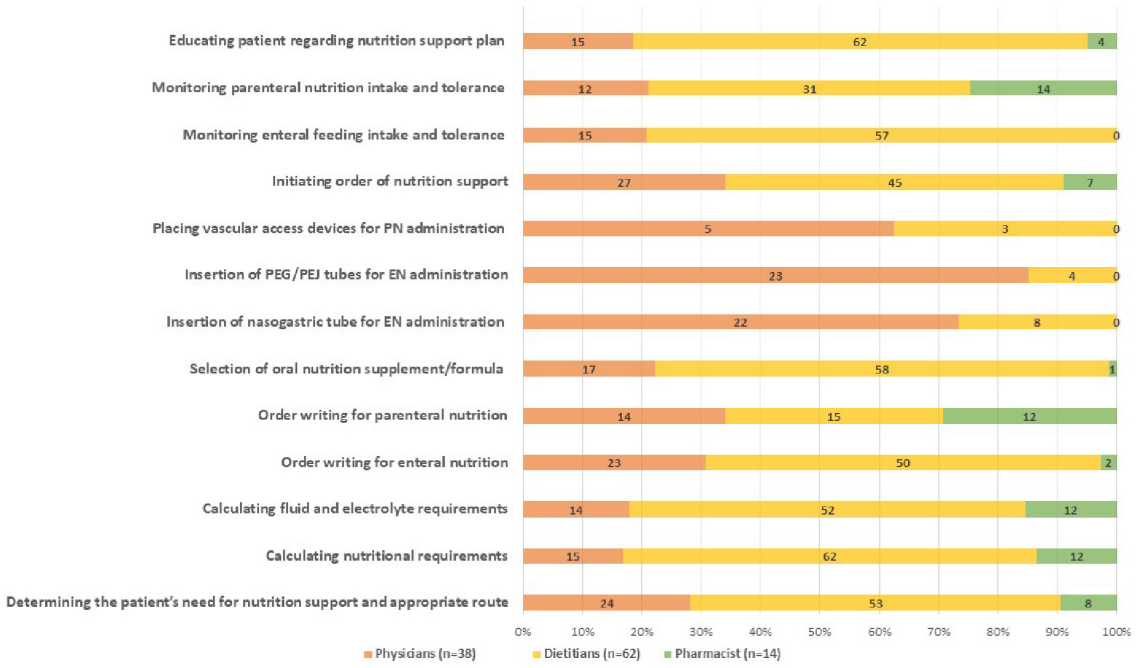


FIGURE 1
Nutrition support related activities performed by health care providers. This figure shows the frequencies of the nutrition support tasks performed by each profession. Numbers represents the number of participants.

TABLE 2 Perception of health care providers regarding the use of established nutrition support guidelines.

Questions	Answers	Physicians (*n* = 38)	Dietitians (*n* = 62)	Pharmacists (*n* = 14)	Total (*n* = 114)
		n (%)			
(1) Familiar with ASPEN and/or ESPEN guidelines	Familiar	18 (47.3%)	59 (95.1%)	12 (85.7%)	89 (78.1%)
	Not familiar	20 (52.6%)	3 (4.8%)	2 (14.2%)	25 (21.9%)
(2) Availability of written policies and procedures for the provision of nutrition support in my facility (i.e., timing and route of feed initiation, formula selection, assessing patient's nutrient requirements, and assessing feeding intolerance)*	Available	12 (31.5%)	48 (77.4%)	11 (78.5)	71 (62.3%)
	Not available	10 (26.3%)	8 (12.90%)	0 (0.0%)	18 (15.8%)
	Don't know	16 (42.1%)	6 (9.67%)	3 (21.4%)	25 (21.9%)
		Physicians (n = 12)	Dietitians (n = 48)	Pharmacists (n = 11)	Total (n = 71)
		n (%)			
(3) Involvement in writing and updating the hospital's nutrition support policies	Involved	4 (33.3%)	35 (73%)	6 (54.5%)	45 (63.4%)
	Not involved	8 (66.7%)	13 (27%)	5 (45.5%)	26 (36.6%)
(4) Type of guidelines used as a reference in my institution**	ASPEN	2 (5.3%)	43 (68.3%)	9 (64.3%)	54 (47.4%)
	ESPEN	2 (5.3%)	40 (63.5%)	2 (14.3%)	44 (38.6%)
	Other	8 (21.1%)	3 (4.8%)	2 (14.3%)	13 (11.4%)
	Don't know	0 (0.0%)	2 (3.2%)	0 (0.0%)	2 (1.8%)

Data are presented as numbers and percentages.
*Only participants who answered Yes (n = 71) to this question were allowed to proceed to the following questions: participants who answered No or I don't know were exempted from questions 3 and 4.
**Percentages for each column don't add to 100 because participants were allowed to choose more than one option. ASPEN, American Society for Parenteral and Enteral Nutrition; ESPEN, European Society of Clinical Nutrition and Metabolism.

frequency of NST meetings greatly varied. Approximately 72.5% indicated that NSTs reviewed and reported service performance data. The most common barriers for developing a dedicated NST were a lack of physicians with interest (100%), qualified pharmacist (92.2%), and incentives by hospital administrations (96.1%). Meanwhile, over half (66.7%) indicated no barriers. Table 4 provides an overview of the current practices for NSTs in Saudi hospitals.

Confidence level in practicing nutritional support

When the participants were asked to rate their confidence level in practicing EN, the dietitians had the highest score (8.66 ± 1.63). The confidence level for practicing EN significantly differed ($p < 0.01$) between the professions (Table 5). Meanwhile, the pharmacists had the highest confidence score (7.36 ± 1.27) in practicing PN; however, no significant difference in the confidence score was observed across the professions ($p > 0.05$). The mean confidence level of all respondents was significantly higher for EN practice (7.7 ± 2.3) than for PN practice (6.1 ± 2.5) ($p < 0.01$).

Factors influencing the confidence level

In the univariate analysis (Table 5), the confidence level for practicing EN and PN significantly differed between the participants with and without nutritional qualification ($p < 0.01$). To evaluate the association between the demographics and confidence level, we conducted a multiple linear regression analysis (Table 6). The regression analysis indicated that the confidence level for practicing EN was significantly influenced by nutritional qualification ($\beta = 0.202$, $p < 0.05$), type of healthcare facility ($\beta = 0.210$, $p < 0.05$), profession ($\beta = -0.308$, $p < 0.01$), and years of experience ($\beta = 0.220$, $p < 0.05$). The participants with nutritional qualifications and more years of experience had a higher confidence level for practicing EN than the other participants. Conversely, the confidence level for practicing PN was significantly associated with nutritional qualification ($\beta = 0.398$, $p < 0.01$) and region ($\beta = -0.197$, $p < 0.05$).

TABLE 3 Nutrition support initiation, monitoring and hospital documentation practices in Saudi hospitals as reported by health care providers.

Questions	Answers	Physicians (*n* = 38)	Dietitians (*n* = 62)	Pharmacists (*n* = 14)	Total (*n* = 114)
		n (%)			
(1) In your practice, in a critically ill and hemodynamically stable patient, after how many days of nil per oral (NPO) status, would you wait before the use of artificial nutrition support?	*1 Day*	8 (21.1%)	22 (35.5%)	3 (21.4%)	33 (28.9%)
	2 Days	5 (13.2%)	8 (12.9%)	1 (7.1%)	14 (12.3%)
	3 Days	22 (57.9%)	17 (27.4%)	6 (42.9%)	45 (39.5%)
	Not applicable in my practice	1 (2.6%)	11 (17.7%)	4 (28.6%)	16 (14.0%)
	Other	2 (5.3%)	4 (6.5%)	0 (0%)	6 (5.3%)
(2) In your practice, after how many days of minimal oral intake or enteral nutrition (less than 50% of estimated caloric requirements) by a well-nourished, stable patient, would you initiate parenteral nutrition?	*3-5 Days*	12 (31.5%)	23 (37.0%)	2 (14.2%)	37 (32.4%)
	7 Days	20 (52.6%)	22 (35.4%)	7 (50.0%)	49 (42.9%)
	14 Days	1 (2.6%)	9 (14.5%)	0 (0.0%)	10 (8.7%)
	I don't know	1 (2.6%)	3 (4.83%)	3 (21.4%)	7 (6.1%)
	Not applicable in my practice	4 (10.5%)	5 (8.1%)	2 (14.3%)	11 (9.6%)
(3) In your practice, what would you do if a patient experiences a few nauseas or vomiting with gastric tube feeding?*	*Stop tube feeding*	6 (15.8%)	18 (29.0%)	1 (7.1%)	25 (21.9%)
	Slow tube feeding	30 (78.9%)	46 (74.2%)	4 (7.1%)	80 (70.2%)
	Give promotility agent	21 (55.3%)	31 (50.0%)	4 (7.1%)	56 (49.1%)
	Check gastric residual volume	24 (63.2%)	44 (71.0%)	4 (7.1%)	72 (63.2%)
	Check tube placement	28 (73.7%)	28 (45.2%)	2 (7.1%)	58 (50.9%)
	Place tube to suction	3 (7.9%)	10 (16.1%)	0 (7.1%)	13 (11.4%)
	Advance tube	4 (10.5%)	2 (3.2%)	0 (7.1%)	6 (5.3%)
	Switch to parenteral feeding	2 (5.3%)	3 (4.8%)	1 (7.1%)	6 (5.3%)
	Consult a specialist	6 (15.8%)	21 (33.9%)	1 (7.1%)	28 (24.6%)
	Perform a physical examination	19 (50.0%)	1 (1.6%)	1 (7.1%)	21 (18.4%)
	Elevate the head of the bed	18 (47.4%)	48 (77.4%)	0 (7.1%)	66 (57.9%)
	Check gastric emptying study	8 (21.1%)	21 (33.9%)	1 (7.1%)	30 (26.3%)
	Give IV fluids	12 (31.6%)	5 (8.1%)	4 (7.1%)	21 (18.4%)

(Continued)

TABLE 3 (Continued)

Questions	Answers	Physicians (*n* = 38)	Dietitians (*n* = 62)	Pharmacists (*n* = 14)	Total (*n* = 114)
		n (%)			
	Other	2 (5.3%)	5 (8.1%)	0 (7.1%)	7 (6.1%)
	I Don't know	0 (0.0%)	1 (1.6%)	9 (7.1%)	10 (8.8%)
(4) In your practice, do you routinely measure gastric residual volume (GRV) in patients receiving enteral nutrition as a measure of enteral feeding intolerance?	*Yes*	19 (50.0%)	34 (54.8%)	6 (42.9%)	59 (51.8%)
	No	10 (26.3%)	26 (41.9%)	0 (0.00%)	36 (31.6%)
	I Don't know	9 (23.7%)	2 (3.2%)	8 (57.1%)	19 (16.7%)
(5) At your institution, which of the following nutritional data is documented or carried out using the hospital's electronic health record system?*	*Nutrition screening data*	14 (36.8%)	40 (64.5%)	6 (42.9%)	60 (52.6%)
	Nutrition assessment data	23 (60.5%)	45 (72.6%)	5 (35.7%)	73 (64.0%)
	Nutrition care plan	19 (50.0%)	49 (79.0%)	5 (35.7%)	73 (64.0%)
	Enteral nutrition order entry	19 (50.0%)	45 (72.6%)	4 (28.6%)	68 (59.6%)
	Parenteral nutrition order entry	21 (55.3%)	30 (48.4%)	10 (71.4%)	61 (53.5%)
	Nutrition monitoring and evaluation data	15 (39.5%)	39 (62.9%)	7 50.0%)	61 (53.5%)
	None of the above (all are done manually)	8 (21.1%)	8 (12.9%)	2 (14.3%)	18 (15.8%)

Data are presented as numbers and percentages.
*Participants were allowed to choose more than one option.

Discussion

The present study aimed to explore various aspects of nutritional support practice in Saudi Arabia. The majority of the participants were dietitians, followed by physicians and pharmacists. Various attitudes in practices across the clinicians were observed. A main finding herein shows that professional qualification and training in nutritional support are essential for promoting practice in hospitals.

Roles and responsibilities of healthcare professionals in providing nutritional support for hospitalized patients

All participants were relatively involved in determining patient need for nutritional support and selecting the appropriate feeding route. With the application of appropriate nutritional screening, nutritional support clinicians are able to select the correct route of nutritional support without delay. However, the study participants contributed differently to other tasks. Implementing a good nutritional care plan for hospitalized patients greatly depends on the clinician's ability to determine an adequate caloric and nutritional requirement. The limited involvement of physicians in many tasks found herein could be explained by the lack of knowledge in nutritional support practices. Insufficient nutritional knowledge among Saudi physicians has been previously reported by Alkhaldy (20). Moreover, the pharmacists in this study mainly wrote and monitored PN orders with a minimal role in other tasks. In a previous investigation in Kuwait, pharmacists working at hospitals primarily contributed to technical tasks, such as PN compounding, with limited contribution in direct patient care (21). The role of pharmacists in PN is well recognized. However, pharmacists play different roles in the provision of PN. Their inclusion to NSTs has been reported to reduce metabolic and catheter-related issues compared with PN management by physicians only (22, 23).

Regarding insertion of nutritional support access devices, we found that a large proportion of physicians were involved in

TABLE 4 Nutrition support team in Saudi hospitals.

Questions	Answers	Total (n = 114)
(1) In your opinion, how important is having nutrition support team to the accuracy and efficacy of nutritional prescription for hospitalized patients?	*Very important*	107 (93.9%)
	Somewhat important	7 (6.1%)
	Not important	0 (0.0%)
(2) Does your hospital have an established multidisciplinary nutrition support team that is currently active?*	*Yes*	51 (44.7%)
	No	15 (13.2%)
	No formal team exists but nutritional management is aided by regular communication between disciplines	36 (31.5%)
	I Don't know	12 (10.5%)
Questions	**Answers**	**Total (n = 51)**
(3) Which of the following members included in the nutrition support team in your hospital?**	*Physician*	49 (96.1%)
	Dietitian	51 (100.0%)
	Pharmacist	43 (84.3%)
	Nurses	38 (74.5%)
(4) How frequent does the nutrition support team meet to discuss patient management?	*Daily*	17 (33.3%)
	Once a week	13 (25.5%)
	Once every other week	3 (5.9%)
	Once monthly	5 (9.8%)
	Only as needed and case by case	7 (13.7%)
	I Don't know	6 (11.8%)
(5) Does your hospital's nutrition support team review and report on service performance, quality indicators, patient's outcome data, and adverse events related to nutrition support therapies?	*Yes*	37 (72.5%)
	No	4 (7.8%)
	I don't Know	10 (19.6%)
(6) In your opinion, what are the important barriers in forming a dedicated nutrition support team at your institution?**	*Lack of physicians with interest and qualifications to direct such team*	51 (100.0%)
	Lack of qualified and dedicated nutrition support pharmacists	47 (92.2%)
	Lack of qualified and dedicated nutrition support dietitians	27 (52.9%)
	No or little incentives and appreciation of the value of such team by the hospital administration	49 (96.1%)
	None	34 (66.7%)

Data are presented as numbers and percentages. *Only participants who answered Yes (n = 51) to this question were allowed to proceed to the following questions related to nutrition support team. **Percentages don't add to 100 because participants were allowed to choose more than one option.

inserting EN feeding tubes. Practically, the limited number of personnel privileged to secure nutritional access in hospitals can delay nutritional support initiation as soon as it is needed, which can have detrimental effects especially for patients at a high nutritional risk. Guidelines recommend that enteral feeding tubes or PN vascular accesses should be inserted only by privileged healthcare professionals with appropriate training and qualification (24, 25). Dietitian-led bedside small bowel feeding tube placement and nurse-led PICC line insertion have been described and may improve efficiency and prevent delays in achieving appropriate access especially in hospitals with large volumes of cases and limited resources (24–26). Implementing such concepts requires advanced training, competency, and hospital-specific credentialling to ensure patient safety.

Awareness and utilization of nutritional support guidelines and protocols

Herein, both ASPEN and ESPEN guidelines were frequently recognized and used in writing nutritional support policies and protocols. Feeding protocols especially in critical illness have been shown to enhance nutritional delivery that meets requirements, resulting in improved outcomes (27). For hospitalized medical inpatients with malnutrition, individualized nutritional support therapy has led to better clinical outcomes and survival compared with standard protocols (28). Among our participants, more dietitians and fewer physicians and pharmacists were involved in writing and updating hospital nutritional support policies and procedures. For such policies to achieve optimal care delivery, involvement of all members of an NST/committee (physicians, nurses, dietitians, and pharmacists) is recommended as a hospital standard by professional societies.

TABLE 5 Comparison of the perception of health care providers related to their confidence level in practicing nutrition support based on their profession, nutritional qualifications, region, years of experience type and capacity of health care facility they work in.

Profession	Physicians(n = 38)	Dietitians(n = 62)	Pharmacist(n = 14)	p-value
	Mean (± SD)			
(1) Confidence score in practicing EN	7.74 (± 1.82)	8.66 (± 1.63)	3.86 (± 2.24)	0.001*
(2) Confidence score in practicing PN	6.10 (± 2.57)	5.85 (± 2.85)	7.36 (± 1.27)	0.140

Nutritional Qualification*	Yes(n = 36)	No(n = 78)	0-Value
	Mean (± SD)		
(1) Confidence score in practicing EN	8.8 (± 1.8)	7.2 (± 2.4)	0.001*
(2) Confidence score in practicing PN	7.5 (± 1.9)	5.4 (± 2.5)	0.001*

Region	Western (n = 82)	Eastern(n = 10)	Central (n = 18)	Southern(n = 3)	Northern(n = 0)	p-Value
	Mean (± SD)					
(1) Confidence score in practicing EN	7.7 (± 2.4)	8.2 (± 1.7)	7 (± 2.8)	9.0 (± 0.0)	-	0.638
(2) Confidence score in practicing PN	6.1 (± 2.6)	6.0 (± 2.8)	5.4 (± 2.1)	7 (0.0)	-	0.743

Years of experience	Newly graduate(n = 11)	2–5 years(n = 43)	6–10 years(n = 29)	More than 10 years(n = 38)	p-Value
	Mean (± SD)				
(1) Confidence score in practicing EN	7.7 (± 1.7)	7.1 (± 2.5)	7.9 (± 2.2)	8.2 (± 2.1)	0.155
(2) Confidence score in practicing PN	5.7 (± 3.0)	5.3 (± 2.5)	6.8 (± 2.4)	6.3 (± 2.5)	0.086

Type of health care facility	MOH (n = 31)	Military hospitals (n = 12)	University teaching hospitals (n = 23)	Specialized hospitals (n = 15)	National guard hospitals (n = 7)	Medical cities (n = 6)	Security Forces Hospital (n = 2)	Private hospitals (n = 18)	p-Value
	Mean (± SD)								
(1) Confidence score in practicing EN	7.7 (± 1.9)	7.4 (± 2.6)	6.8(± 2.7)	7.6 (± 2.7)	7.5 (± 2.9)	8.6 (± 1.6)	9(0.0)	8.9 (± 1.4)	0.202
(2) Confidence score in practicing PN	5.1 (± 3.0)	7.5 (± 2.5)	6.8(± 1.5)	5.8 (± 2.1)	6.4 (± 2.0)	6.0 (± 1.5)	2(0.0)	5.8 (± 3.1)	0.128

Capacity of health care facility	<100 beds(n = 11)	100–250 beds (n = 17)	251–500 beds(n = 41)	>500 bed(n = 36)	Don't know(n = 9)	p-Value
	Mean (± SD)					
(1) Confidence score in practicing EN	6.7 (± 2.6)	8.1 (± 1.8)	8.2 (± 2.2)	7.2 (± 2.5)	8.3 (± 1.8)	0.127
(2) Confidence score in practicing PN	6.5 (± 1.6)	5.2 (± 3.6)	5.5 (± 2.2)	6.9 (± 2.2)	6.1(± 3.2)	0.131

Participants were asked to rate their confidence in practicing nutrition support and discussing the patient suitability for it with other clinicians on a scale of 1–10. Kruskal–Wallis test was conducted to compare the mean confidence score between the categories. Mann–Whitney U-test was conducted to compare the mean confidence score between the two categories. *p-value is statistically significant at <0.05 level.

10.3389/fnut.2023.1149727

Nutritional screening and assessment practices for hospitalized patients

All hospitalized patients with poor nutritional intake should have their nutritional risk evaluated before the start of specialized nutritional therapy using a validated screening tool (29). Herein, the awareness and practice of a specific screening tool were low, and most dietitians identified themselves as being involved in screening and assessment. A large cross-sectional survey in the United States found that although hospitals were compliant to malnutrition screening within 24 h of admission, there was variation in the screening tools used (19). Nurses were mostly responsible for screening and dietitians for assessments (19). Although screening is a critical step in the nutritional care algorithm for hospitalized patients, it is the simplest step that can be performed by any trained healthcare professionals. The lack of trained personnel or delay in screening is problematic because it could negatively impact patient outcomes. Additionally, referral for dietetic assessment after screening should be well recognized by most healthcare professionals (i.e., physicians and nurses). The present findings suggest that nurses need to be empowered to refer patients for nutritional assessment.

For nutritional assessment, many respondents used anthropometric measurements, while small proportion, mainly including physicians, reported their use of albumin levels as a nutritional indicator. Regarding the estimation of nutritional requirements, the physicians had minimal involvement in this important step. This could be explained by expectations that clinical dietitians calculate nutritional requirements because of their skillset; however, physicians should play an important role in complementing this step by assessing and communicating patient-related factors that might affect nutritional requirements.

Nutritional support initiation and monitoring practices

We detected variations in the practitioners' practices regarding the initiation and monitoring of nutritional support, including the timing and use of the GRV, which can affect optimal provision of nutrition. According to the ASPEN guidelines, early EN must be started within 24–48 h among hemodynamically stable patients in the ICU but who are unable to maintain oral intake (30). However, 39.5% of the respondents waited 3 days. Evidence has shown that early nutritional support in critically ill patients is associated with reduced mortality and infection (30). In terms of PN initiation for well-nourished and stable patients with minimal oral or EN intake, we found that many practitioners waited 3–5 days. Clinical recommendations often advise starting PN (total or supplemental) after 7 days in patients with unmet nutritional requirements (12).

Gastric feeding intolerance is common in critically ill patients. Therefore, monitoring of EN tolerance is essential. Although the GRV is commonly used by many practitioners, it is a poor indicator of EN intolerance (31). The use of multiple parameters, including the GRV and presence of diarrhea, vomiting, and abdominal

TABLE 6 Regression analysis to identify the factors influencing the health care providers confidence when dealing with nutrition support.

Model 1 Outcome variable: Confidence score in practicing enteral nutrition	*R*	R^2	Adjusted R^2
	0.465	0.216	0.187
Dependent variable (n = 114)	*Beta*	*p-Value*	*Partial correlation*
Nutritional qualification (Yes/No)[a]	0.202	0.027*	0.304
Type of health care facility[a]	0.210	0.022*	0.203
Profession (dietitians, pharmacists, physicians)[a]	−0.308	0.002*	−0.234
Years of experience[a]	0.220	0.023*	0.181
Region[b]	0.77e	0.372	−0.086
Model 2 Outcome variable: Confidence score in practicing parenteral nutrition	***R***	**R^2**	**Adjusted R^2**
	0.427	0.182	0.167
Dependent variable (n = 114)	*Beta*	*p-Value*	*Partial correlation*
Nutritional qualification (Yes/No)[a]	0.398	0.001*	0.402
Region[a]	−0.197	0.024*	−0.212
Profession (dietitians, pharmacists, physicians)[a]	0.171c	0.057	0.18
Years of experience[b]	0.155c	0.071	0.171
Type of health care facility[b]	0.054c	0.531	0.06

[a]Predictors: (constant).
[b]Excluded variables.
*p-Value is statistically significant at <0.05 level. All models were adjusted for hospital capacity.

distention, has been recommended by the ASPEN for evaluating EN intolerance (32).

Nutritional support plan documentation practices

Data related to nutritional assessment and care plan were the most commonly documented data by the participants. Documentation of nutritional assessment, including nutritional requirements, is a key step and directly affects patient outcomes. Nutritional support process is complex and has many steps that need proper documentation. Improving the documentation quality can help prevent EN/PN-related errors.

NSTs in Saudi hospitals

The delivery of optimal nutritional support needs a multidisciplinary care team. In this study, the majority of the participants reported that NSTs were very important to the accuracy and efficacy of EN and PN prescription. The existence of NSTs helps improve the quality of care among patients receiving nutritional support. A recent systematic review found that NSTs relatively reduced the rate of catheter-related infections and were significantly correlated with decreased metabolic complications, mortality, and inappropriate utilization of PN (33). Nonetheless, the prevalence of NST implementation in hospitals is decreasing as a result of cutting or saving budgets by healthcare organizations (10). In the United Kingdom, only 60% of hospitals provide nutritional support through a multidisciplinary NST (34). Nearly half of the respondents in the current study had a formal NST comprising physicians, dietitians, pharmacists, and nurses. Typically, NSTs might hold weekly meetings to talk about their operations, specific patients, reported data, and journals (34). The current study reported a great variability in the frequency of NST meetings.

Although NSTs are cost effective (35), their implementation is challenging. The main barriers for implementing NSTs in this study included the lack of physicians with interest, qualified pharmacists, and incentives by hospital administrations. DeLegge et al. reported similar barriers associated with the initiation of NSTs (36). Such barriers must be addressed by future hospitals' strategies for NST implementation in Saudi Arabia.

Confidence level among nutritional support practitioners

The confidence level of all study participants was significantly higher for EN practice than for PN practice. It also varied between the healthcare professions. Moreover, the present study identified nutritional qualification and more years of experience as factors enhancing the confidence level in practice. Promoting nutritional support education among healthcare practitioners is important. According to the ASPEN standards of practice, certain minimum qualifications are required for all nutritional support physicians to demonstrate competence to practice in the field of nutrition (37). These qualifications include board certification in a primary specialty, training/experience or certification in nutritional support, participation in institutional nutritional support activities, current clinical responsibility for patients requiring nutritional support therapy, and active membership in a nutritional support professional society. For pharmacists, nutritional support practices vary with the position, education, and practice environment. Certain minimum qualifications are required for all pharmacists involved in nutritional support.

Strengths and limitations

To our knowledge, this study is the first to describe nutritional support practices in different regions in Saudi Arabia and to identify the factors influencing the confidence of healthcare professionals in practicing EN and PN. In addition, the questionnaire used captured various aspects related to practice. However, a possible limitation of this study is that participation was mostly by dietitians followed by physicians and pharmacists. This could indicate a relatively small number of physicians and pharmacists involved in hospital nutritional support. Therefore, it might be difficult to generalize the results to other healthcare professionals.

Conclusion

This study explored the current nutritional support practices in Saudi Arabia and identified the factors influencing the confidence of clinicians in practicing EN and PN. It also identified areas where the current hospital standards in Saudi Arabia might be improved and evaluated them against international nutritional support standards. Further, the study provided insights into what Saudi hospitals as a stakeholders can do to improve nutritional support practices. These included using evidence-based hospital-specific protocols, increasing physicians' awareness about nutritional support guidelines and policies, enhancing nutritional support education and certification among physicians, funding nutritional support committees and national nutritional support training programs, and implementing NSTs in accordance with evidence-based practice guidelines. Clearly, dietitians play a key role in nutritional support; however, the safety and efficacy of care are improved when pharmacists, doctors, and nurses are all involved in the process.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Unit of the Biomedical Ethics Research Committee at

King Abdulaziz University in Jeddah, Saudi Arabia (HA-02-J-008). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SA: conceptualization, methodology, formal analysis, and writing–original draft. SZ: conceptualization, methodology, formal analysis, investigation, and writing—review and editing. RM: methodology, investigation, and writing—review and editing. HJ: conceptualization, investigation, and writing—review and editing. All authors critically revised the manuscript and approved the final version of the manuscript.

Acknowledgments

We would like to thank all clinicians who kindly agreed to participate in the study, the expert panel for their effort and time in revising the questionnaire and for their helpful feedback, and national societies for their support in the survey distribution.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1149727/full#supplementary-material

References

1. Inciong J, Chaudhary A, Hsu H, Joshi R, Seo J, Trung L, et al. Hospital malnutrition in northeast and southeast Asia: a systematic literature review. *Clin Nutr ESPEN.* (2020) 39:30–45. doi: 10.1016/j.clnesp.2020.06.001

2. Bani I, Al-Kanhal M. Malnutrition among hospitalized patients in King Khalid university hospital, Riyadh. *Saudi J Gastroenterol.* (1998) 4:172–5.

3. Alhamdan A, Alsaif A. The nutritional, glutathione and oxidant status of elderly subjects admitted to a university hospital. *Saudi J Gastroenterol.* (2011) 17:58–63. doi: 10.4103/1319-3767.74474

4. Elmadbouly M, AbdElhafez A. Assessment of nutritional status of hospitalized elderly patients in Makkah governorate. *Pak J Nutr.* (2012) 11:886–92.

5. Alzahrani S, Alamri S. Prevalence of malnutrition and associated factors among hospitalized elderly patients in King Abdulaziz University Hospital, Jeddah, Saudi Arabia. *BMC Geriatr.* (2017) 17:136. doi: 10.1186/s12877-017-0527-z

6. Correia M, Perman M, Waitzberg D. Hospital malnutrition in Latin America: a systematic review. *Clin Nutr.* (2017) 36:958–67.

7. Ukleja A, Gilbert K, Mogensen K, Walker R, Ward C, Ybarra J, et al. Standards for nutrition support: adult hospitalized patients. *Nutr Clin Pract.* (2018) 33:906–20.

8. Lyu Y, Chen G, Shen L, Liu Y, Gao F, He X, et al. Knowledge, attitudes, clinical practice and perceived barriers with nutrition support among physicians and nurses in the emergency department: a national cross-sectional survey. *Int Emerg Nurs.* (2021) 55:100973. doi: 10.1016/j.ienj.2021.100973

9. Abi Saleh W, Bou Khalil P, Ouaijan K, Abillama F, Akiki S, Ahmad N, et al. Evaluation of nutrition support practices: results from a nationwide survey. *Clin Nutr.* (2018) 37:1976–9.

10. DeLegge M, True Kelley A. State of nutrition support teams. *Nutr Clin Pract.* (2013) 28:691–7.

11. Force A, DeLegge M, Wooley J, Guenter P, Wright S, Brill J, et al. The state of nutrition support teams and update on current models for providing nutrition support therapy to patients. *Nutr Clin Pract.* (2010) 25:76–84. doi: 10.1177/0884533609354901

12. Worthington P, Balint J, Bechtold M, Bingham A, Chan L, Durfee S, et al. When is parenteral nutrition appropriate? *JPEN J Parenter Enteral Nutr.* (2017) 41:324–77. doi: 10.1177/0148607117695251

13. Braun K, Utech A, Velez M, Walker R. Parenteral nutrition electrolyte abnormalities and associated factors before and after nutrition support team initiation. *JPEN J Parenter Enteral Nutr.* (2018) 42:387–92.

14. Senkal M, Dormann A, Stehle P, Shang E, Suchner U. Survey on structure and performance of nutrition-support teams in Germany. *Clin Nutr.* (2002) 21:329–35. doi: 0.054/clnu.2002.0551

15. Shang E, Hasenberg T, Schlegel B, Sterchi A, Schindler K, Druml W, et al. An European survey of structure and organisation of nutrition support teams in Germany, Austria and Switzerland. *Clin Nutr.* (2005) 24:1005–13. doi: 10.1016/j.clnu.2005.07.005

16. Singh H, Duerksen D. Survey of clinical nutrition practices of Canadian gastroenterologists. *Can J Gastroenterol Hepatol.* (2006) 20:527–30. doi: 10.1155/2006/835462

17. Behara A, Peterson S, Chen Y, Butsch J, Lateef O, Komanduri S. Nutrition support in the critically ill: a physician survey. *JPEN J Parenter Enteral Nutr.* (2008) 32:113–9. doi: 10.1177/0148607108314763

18. Cahill N, Narasimhan S, Dhaliwal R, Heyland D. Attitudes and beliefs related to the Canadian critical care nutrition practice guidelines: an international survey of critical care physicians and dietitians. *JPEN J Parenter Enteral Nutr.* (2010) 34:685–96. doi: 10.1177/0148607110361908

19. Patel V, Romano M, Corkins M, DiMaria-Ghalili R, Earthman C, Malone A, et al. Nutrition screening and assessment in hospitalized patients: a survey of current practice in the United States. *Nutr Clin Pract.* (2014) 29:483–90. doi: 10.1177/0884533614535446

20. Alkhaldy A. Nutritional knowledge and self-reported nutritional practice against malnutrition among physicians in Jeddah, Saudi Arabia. *Healthcare.* (2019) 7:149. doi: 10.3390/healthcare7040149

21. Katoue M, Al-Taweel D. Role of the pharmacist in parenteral nutrition therapy: challenges and opportunities to implement pharmaceutical care in Kuwait. *Pharm Pract.* (2016) 14:680. doi: 10.18549/PharmPract.2016.02.680

22. Giancarelli A, Davanos E. Evaluation of nutrition support pharmacist interventions. *JPEN J Parenter Enteral Nutr.* (2015) 39:476–81. doi: 10.1177/0148607114551025

23. Katoue M. Role of pharmacists in providing parenteral nutrition support: current insights and future directions. *Integr Pharm Res Pract.* (2018) 7:125–40. doi: 10.2147/IPRP.S117118

24. Brown B, Hoffman S, Johnson S, Nielsen W, Greenwaldt H. Developing and maintaining an RDN-Led bedside feeding tube placement program. *Nutr Clin Pract.* (2019) 34:858–68. doi: 10.1002/ncp.10411

25. Scimò M, Vallecorsa I, Cini A, Cabelguenne D, Piriou V. Vascular access unit: six-years experience report in France. *J Vasc Access.* (2022). doi: 10.1177/11297298221080228 [Epub ahead of print].

26. Corrigan M, Bobo E, Rollins C, Mogensen K. Academy of nutrition and dietetics and American society for parenteral and enteral nutrition: revised 2021 standards of practice and standards of professional performance for registered dietitian nutritionists

(competent, proficient, and expert) in nutrition support. *Nutr Clin Pract.* (2021) 36:1126–43. doi: 10.1002/ncp.10774

27. O'Leary-Kelley C, Bawel-Brinkley K. Nutrition support protocols: enhancing delivery of enteral nutrition. *Crit Care Nurse.* (2017) 37:e15–23.

28. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet.* (2019) 393:2312–21. doi: 10.1016/S0140-6736(18)32776-4

29. McClave S, DiBaise J, Mullin G, Martindale R. ACG clinical guideline: nutrition therapy in the adult hospitalized patient. *Am J Gastroenterol.* (2016) 111:315–34. doi: 10.1038/ajg.2016.28

30. McClave S, Taylor B, Martindale R, Warren M, Johnson D, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (ASPEN). *JPEN J Parenter Enteral Nutr.* (2016) 40:159–211. doi: 10.1177/0148607115621863

31. Jenkins B, Calder P, Marino L. A systematic review of the definitions and prevalence of feeding intolerance in critically ill adults. *Clin Nutr ESPEN.* (2022) 49:92–102. doi: 10.1016/j.clnesp.2022.04.014

32. Boullata J, Carrera A, Harvey L, Escuro A, Hudson L, Mays A, et al. ASPEN safe practices for enteral nutrition therapy. *JPEN J Parenter Enteral Nutr.* (2017) 41:15–103. doi: 10.1177/0148607116673053

33. Eriksen M, Crooks B, Baunwall S, Rud C, Lal S, Hvas C. Systematic review with meta-analysis: effects of implementing a nutrition support team for in-hospital parenteral nutrition. *Aliment Pharmacol Ther.* (2021) 54:560–70. doi: 10.1111/apt.16530

34. Nightingale J. Nutrition support teams: how they work, are set up and maintained. *Front Gastroenterol.* (2010) 1:171–7. doi: 10.1136/fg.2009.000224

35. Hollingworth T, Oke S, Akbar T, McKee R, Rochford A, Relph W, et al. The composition of nutrition support teams in the UK. *Clin Nutr ESPEN.* (2019) 29:269–70. doi: 10.1016/j.clnesp.2018.12.051

36. Delegge M, Wooley J, Guenter P, Wright S, Brill J, Andris D, et al. The state of nutrition support teams and update on current models for providing nutrition support therapy to patients. *Nutr Clin Pract.* (2010) 25:76–84. doi: 10.1177/0884533609354901

37. Mascarenhas M, August D, DeLegge M, Gramlich L, Iyer K, Patel V, et al. Standards of practice for nutrition support physicians. *Nutr Clin Pract.* (2012) 27: 295–9.

frontiers | Frontiers in Nutrition

TYPE Clinical Trial
PUBLISHED 25 May 2023
DOI 10.3389/fnut.2023.1164722

OPEN ACCESS

EDITED BY
Barbara Troesch,
Self-employed, Switzerland

REVIEWED BY
Enza D'Auria,
Ospedale dei Bambini Vittore Buzzi, Italy
Sabina Fijan,
University of Maribor, Slovenia

*CORRESPONDENCE
Jean-Pierre Chouraqui
✉ chouraquijp@wanadoo.fr

RECEIVED 13 February 2023
ACCEPTED 09 May 2023
PUBLISHED 25 May 2023

CITATION
Chouraqui J-P, Brancato S, Delmas B and Hanh T (2023) Effectiveness of a starch thickened infant formula with reduced lactose content, probiotics and prebiotics on quality of life and clinical outcome in infants with regurgitation and/or colic.
Front. Nutr. 10:1164722.
doi: 10.3389/fnut.2023.1164722

Effectiveness of a starch thickened infant formula with reduced lactose content, probiotics and prebiotics on quality of life and clinical outcome in infants with regurgitation and/or colic

Jean-Pierre Chouraqui[1]*, Sandra Brancato[2], Berenice Delmas[3] and Thierry Hanh[3]

[1]Pediatric Gastroenterology and Nutrition, University Hospital Grenoble-Alpes, La Tronche, France, [2]Association Française de Pédiatrie Ambulatoire (AFPA), Brignon, France, [3]Département Médical Nutrition Infantile, Nestlé France, Issy-les-Moulineaux, France

Background: Regurgitation and colic are quite common in young infants, leading to a reduced quality of life (QoL) and to parental distress. Their management is challenging and aims to effectively reassure and relieve symptoms. This study aimed to assess the effectiveness over 30days of a starch thickened formula with a reduced lactose content, *Limosilactobacillus reuteri* (*Lactobacillus reuteri*) DSM 17938 and FOS/GOS.

Methods: A real-world prospective multicenter experimental study was conducted in a before-after design within subject. Full term infants 0–5 months with regurgitation or colic or both symptoms and without intercurrent illness were included after parental informed consent and received the studied formula. The primary endpoint was the improvement in QoL using the QUALIN infant's questionnaire. Secondary endpoints were the symptoms outcome and the formula tolerance.

Results: Of the 101 infants included (age: 6.2 ± 4.3 weeks), 33 had regurgitation, 34 colic and 34 had both. At D30, the QoL score was improved in 75% of infants in per protocol analysis (n=68; +8.2 ± 13.7; p<0.001), more in those with colic or both symptoms. Meanwhile, in intention to treat analysis (all p<0.001), the daily number of regurgitations decreased by 61% and the weekly number of days with colic by 63% while the daily cumulative duration of crying decreased by 82 ± 106 mn. These improvements were observed within the first week by 89 and 76% of parents, respectively.

Conclusion: The study formula associated with reassurance is shown to be quickly effective in the management of infant's regurgitation or/and colic in routine clinical practice.

Clinical trial registration: https://clinicaltrials.gov/, identifier NCT04462640.

KEYWORDS

functional gastro-intestinal disorders, infants, regurgitation, colic, comfort formula, thickened formula, *Limosilactobacillus reuteri*

Introduction

Functional gastrointestinal disorders (FGIDs) are frequent in otherwise healthy infants and include a variable combination of recurrent or chronic symptoms (1). The global prevalence of at least one FGID in infants has been estimated between 25% and 30% in European studies (2, 3) and above 50% in Italian infants under 6 months (4). Regurgitation, and colic are the most frequent FGIDs in infants and often coexist (2, 3, 5–7). The pathophysiology of these symptoms is far from being able to be explained whereas they should naturally resolve over time (1). Their respective prevalence varies among the different studies due to differences in diagnostic criteria, study design, data collection methods, cultural habits, availability of health centers, and diet (7). The formal consensus diagnosis of these disorders relies on the symptom-based Rome criteria that have evolved over time until the latest ones established in 2016 as the Rome IV criteria (1). In infants 0–6 months, a recent review reported a prevalence of colic of 10%–15%, of regurgitation of 34% and constipation of 1.5% according either to Rome III or Rome IV criteria (7). In France, according to two studies using Rome III and Rome IV criteria, the respective prevalence of regurgitation, colic, and constipation in infants have been estimated 17%−41%, 18%−19%, and 6%−9% (2, 8). Frequently infants may have multiple FGIDs, notably both colic and regurgitation (3, 9, 10). Formula-fed infants are more likely to suffer from FGIDs, mainly functional constipation, than breastfed infants (3, 9, 10).

Frequent regurgitation and unexplained and inconsolable crying display distressing and anxiety-provoking for parents, driving them to seek frequent medical advice (5, 11–14). Parents are all the more worried, desperate and demanding when the infant display a reduced quality of life (QoL) (5, 9, 13, 15, 16). The Rome IV consensus statement stipulate that physicians should be aware of the impact of the FGIDs symptoms on the infant's QoL in addition to their clinical assessment (1).

Parents are understandably eager for a quick and easy fix and will often opt for medication in hopes of quick symptom relief (17). Clinicians depend on the reports and interpretation of the parents regarding the symptoms and must meet their expectations. Together, this leads to numerous changes in infant formula, the use of over-the-counter medications, an over-prescription of drugs despite recommendations regarding their uselessness, and therefore an increase in healthcare costs (13, 15, 18). In particular, despite their lack of efficacy in this indication, proton pump inhibitors are increasingly used in infants presenting with unexplained regurgitation or crying, restlessness and irritability that define colic (19–22).

The natural history of infant colic and regurgitation is a spontaneous gradual improvement from the age of 4 and 6 months, respectively (3, 9, 10). In the meantime, the management goals are to provide effective reassurance and symptom relief without requiring medication (1). Therefore, conservative measures such as a dietary approach and/or the use of probiotics are attractive as a first-line management of these common FGIDs (12). Both measures are the most frequently prescribed by French practitioners (8, 9, 15). According to the report of the parents of the 8,865 French infants aged 2 months included in the ELFE study, either a thickened formula, or a thickened formula plus pre- and/or probiotics or a regular formula enriched with pre- and/or probiotics were, respectively, used in 9, 44, and 17% of infants with regurgitation ($n = 1,098$; 12.4%) and 6, 37, and 26% of infants with colic ($n = 1,921$; 21.7%) (23). The use of a thickened formula is the optimal initial management of uncomplicated regurgitation recommended by the joint committee of the North American and the European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN/ESPGHAN) and in the National Institute for Health and Care Excellence (NICE) guideline (24, 25). The management of infants with colic may be more challenging insofar as the level of evidence of the different approach proposed is low (26–30). The strongest evidence for the treatment of infantile colic is with probiotics, i.e., live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (31), primarily probiotic strains of *Limosilactobacillus reuteri* previously named *Lactobacillus reuteri* (26, 30, 32, 33). Several randomized controlled trials found that, *Limosilactobacillus reuteri* DSM 17938 (LrD), can reduce crying and/or fussing time in breastfed infants with colic whereas the results of the scarce studies in formula-fed infants are contradictory as reported in systematic reviews and meta-analysis (16, 30, 32, 34–37). The Rome IV recommendations already concluded on the "need for prospective studies to show the efficacy of different diets in infants with FGIDs" leading to new studies considering the specific composition of the formula (1).

The current study aimed at assessing the effectiveness in routine clinical practice of a thickened formula with reduced lactose content and supplemented with LrD and a prebiotic mixture of fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) on QoL and on the symptom relief in infants with regurgitation and/or colic. As the probiotics, the prebiotic mixture was thus considered according to the definition set by the International Scientific Association for Probiotics and Prebiotics (ISAPP) (31).

Methods

Study design

This open real-world prospective multicenter experimental study was conducted to assess the effectiveness of the study formula over 30 days in exclusively formula-fed infants 0–5 months with regurgitation or colic or both. The composition of the formula used is detailed in Table 1 in accordance with EFSA recommendations and the European Commission Delegated Regulation 2016/127 (38, 39). The study formula contained *L. reuteri* DSM 17938 at concentration that guarantee a daily intake of approximately 10^8 colony-forming unit (CFU). The method used a pretest-posttest within-subjects design.

The study protocol, the parents' information sheet and the informed consent form were reviewed and approved by the Subject Protection Review Board "Sud Mediterrannée III" (Nimes 2020/03/18, no. 2020.01.07 bis_19.12.26.60314). The study was registered in the Clinical Trials Protocol Registration System at ClinicalTrials.gov with the identifier NCT04462640. It was conducted in full agreement with

Abbreviations: FGIDs, Functional gastrointestinal disorders; FOS, Fructo-oligosaccharides; GOS, Galacto-oligosaccharides; ITT, Intention to treat; LrD, *Limosilactobacillus reuteri* DSM 17938; PP, Per protocol; QoL, Quality of life.

TABLE 1 Composition of the study infant formula per 100mL and 100kJ.

	Study formula		EFSA recommendations (38)
	/100mL	/100kJ	
Energy	67 kcal (280.3 kJ)	100 kJ	250–293 kJ/100 mL
Protein	1.2 g	0.43 g	0.43–0.60 g /100 kJ
Casein	0.36 (30%)	0.13 g	
Whey protein	0.84 (70%)	0.30 g	
Total fat	3.6 g	1.3 g	1.1–1.4 g/100 kJ
DHA[a]	16.8 mg	6 mg	4.8–12 mg/100 kJ
ARA[b]	16.8 mg	6 mg	
Carbohydrates	7.2 g	2.53 g	2.2–3.3 g/100 kJ
Lactose	5.2 g	1.84 g	≥1.1 g/100 kJ
Starch (95% potato, 5% rice)	2 g		≤2/100 mL
FOS[c]/GOS[d]	0.04/0.36 g		
Magnesium	6.2 mg	2.2 mg	≥1.2 mg/100 kJ
Osmolarity	21.1 m0sm		

[a]DHA, docosahexaenoic acid.
[b]ARA, arachidonic acid.
[c]FOS, fructo-oligosaccharides.
[d]GOS, galacto-oligosaccharides.

the guidelines laid down in the Declaration of Helsinki and the French data protection act (*Loi* "*Informatique et Libertés*"), ensuring that respondents' personal identity is withheld. The study was carried out in collaboration with a group of family paediatricians.

Participants

The parents consulting for regurgitation and/or colic in their exclusively formula-fed infant were invited to participate in the study by their pediatrician, provided that they had a sufficient French language competency and that they were able to use a computer.

Otherwise, healthy infants under six months whose parents were worried about frequent regurgitations or/and crying, irritability, and fussing that start and stop without obvious cause, which are considered as colic in routine practice, were eligible for inclusion. They did not have to fulfill Rome IV criteria (1) since this was a real-world experimental study. They must also have been born at term (≥37 weeks of gestation) with a birth weight ≥2,500 g. The exclusion criteria were: intercurrent acute or chronic illness including suspected or confirmed food allergy; current drug treatment or food supplement other than vitamins; feeding with a partially or extensively hydrolyzed protein formula; failure to thrive. All this information was known to the pediatrician who the infant's usual doctor was. Each paediatrician had to include all consecutive infants fulfilling inclusion and exclusion criteria and was asked to include, as much as possible, the same number of children with regurgitation or colic. After offering a fully informed description of the survey, parents gave their consent to participate, without any financial incentive.

Course of the study

The initial consultation (D0) consisted of verifying that the infant met the above inclusion criteria, examining the infant and obtaining the parental informed consent. The paediatricians had to collect anamnestic data and to assess the health status of the infant. Baseline data included date of birth and of the visit, gestational age, gender, birth and current weight and length, number of children in the family, current and previous type of feeding, number and volume of daily feeding in the previous 3 days, previous treatment, and the detailed description of the FGIDs symptoms. These data were reported by the practitioners in an online specific clinical chart derived from the one developed by the Rome Foundation (40). Parents were asked to complete the QoL questionnaire, that was the validated QUALIN questionnaire specifically designed for infants (41). At the end of the visit, parents were asked to move their infant feeding to the study formula for one month.

One month (±3 days) after inclusion (D30), the same charts were completed by the paediatricians and the parents, respectively. Data concerning the course of FGIDs, as well as the efficacy and tolerance of the prescribed infant formula, including the possible adverse effects, were recorded. Parents also had to testify to the doctor about their degree of satisfaction.

All data (D0 and D30) were reported by the physician on an electronic patient reported outcomes software (DACIMA ePRO, Montreal, Quebec, Canada). Data were collected and analyzed by a Clinical Research Organization (CRO, Keyrus Life Science, Levallois Perret, France).

Data and statistical analysis

The primary endpoint was the outcome of the infants QoL as assessed by parents. Secondary endpoints were the outcome of the symptoms and anthropometric data as well as the tolerance of the study formula and the parents' satisfaction assessment.

Sample size was calculated with respect to the primary outcome and according to the results of a previous study leading to expect an improvement of 13.5 points in the QoL score with a standard deviation (SD) of 20 (15). Also considering a correlation coefficient of 0.5 between QoL scores at D0 and D30 with an α level of 0.05 and a power $(1 - \beta)$ of 0.95 and assuming a dropout rate up to 40%, we calculated that 90 infants equally divided between regurgitation and colic should be included.

The QUALIN questionnaire (Supplementary File) includes 34 items with 6 possible answers, which were definitely false, mostly false, both true and false, mostly true, definitely true and do not know (41). The answers were scored from −2 (definitely false) to +2 (definitely true) when it is a positive question, whereas negative items are reverse-scored, from −2 "definitely true" to +2 "definitely false." As a result, the overall score might range from −68 (worst QoL) and + 68 (best QoL). Following the results of the principal component analysis performed during the validation study, some answers have been grouped in four topics, namely behavior and communication (items no. 3, 5, 8, 13, 16, 18, 21, 22, 24, 32, 33), ability to remain alone (items no. 7, 10, 15, 17, 23), family environment (items no. 11, 26, 29, 31), and psychological and somatic well-being (items no. 4, 6, 14, 19, 27, 30), leaving 8 items out (items no. 1, 2, 9, 12, 20, 25, 28, 34) (41).

All reasons for dropping out including lost to follow-up, stopping or not taking the formula and/or adding a drug treatment, and all adverse effects had to be collected. The analysis of primary outcome was performed on the per protocol population (PP), i.e., the infants who completed the study without violation of the protocol and for which the QoL questionnaire was completed at D0 and D30. The analyses of secondary outcomes were performed first on the intention to treat population (ITT), i.e., all infants included at D0 who were not lost to follow-up and therefore have consulted again at D30, and second on per protocol population.

At each visit the symptoms were assessed according to their frequency and characteristics during the week prior to the visit as reported by parents. Dichotomous variables were described as numbers and percentages, and continuous variables by the mean ± SD and by median, interquartile range (*Q*1–*Q*3) and range (minimum-maximum) listed in brackets. The assessment of stool consistency was adapted from the Bristol stool form scale (42).

Statistical analyses were done using SAS software version 9.4 (SAS Institute Inc., Cary, NC, United States). Means of quantitative variables were compared using the Student's *t*-test for paired normally distributed data, otherwise the paired non-parametric Wilcoxon signed-rank test was used. Linear regression was used to test independence between the total QoL score and the evolution of symptoms (number of regurgitations/day and number of days with crying) and the Pearson correlation coefficient was calculated. The two-sided alpha level of significance was set at 5%.

Results

Participant flow and baseline characteristics

Of the 68 paediatricians contacted, 53 were initially interested in the study and 28, who were distributed throughout the national territory, finally voluntarily actively participated in the study. Between end of august 2020 and end of October 2021, they included 101 infants presenting regurgitation or excessive crying or both [number of inclusions/pediatrician: mean: 3.6 ± 2.4 (4.0; 2.0–5.0; 1.0–10.0)]. Figure 1 shows the subjects' flow during the study. Of the included infants, 7 were lost to follow up before D30 (ITT, $n = 94$). For the per protocol analysis ($n = 68$), 16 infants were dropped out because of violation of protocol (3 formula change, 7 drug added, 6 both) and 10 infants because of an uncompleted QUALIN questionnaire.

Baseline characteristics of the population

They are showed in Table 2, with no difference between the ITT and PP populations or between gender. All infants were born at term, with a normal birth weight. Their median age at inclusion was 5 weeks. Only 13% of infants were older than 3 months, with the oldest one aged 18 weeks. Among included infants, 33 presented with regurgitation only, 34 with colic only and 34 with both regurgitation and colic leading to a sum of prevalence of the two FGIDs over 100%. All the 67 infants with regurgitation had fulfilled the Rome IV criteria ($n \geq 2$/ day), whereas among the 68 colic infants 95.6% had excessively cried or fussed for more than 3 days a week, but only 22% had presented it during more than 3 h per day and had thus met the full Rome IV criteria (1). According to the Rome IV criteria, five infants could be considered as constipated (≤2 bowel movements/day), and none had a functional diarrhea (≥4 large, unformed stools).

All infants included were fully formula-fed except for one who had started few complementary foods. From birth to D0, 89% of infants were always fed the same formula, 6% had changed formula once, 3% twice, and 2% four times. No infant was fed a formula with all the same characteristics as the study formula. The formula used prior to inclusion were: standard formula ($n = 1$); standard formula with probiotics ($n = 45$), or prebiotics ($n = 32$), or both ($n = 1$); formula with reduced content of lactose only ($n = 2$) or with additionally probiotics and prebiotics ($n = 13$); thickened formula with probiotics ($n = 5$) or with prebiotics ($n = 2$). Moreover 11 infants had received treatment with probiotics, which was LrD in 10. Thus, in total, 55 infants had received LrD before D0, including 45 for whom it was administered as a component of a formula.

On average the final visit (D30) occurred 30.1 ± 2.2 days (30; 29–32; 21–36) after D0.

Primary outcome

The QoL of 75% of infants in the PP analysis improved at D30 without difference between gender or age, although colicky infants tended to be slightly younger. The mean improvement in the global score was +8.2 ± 13.7 (8; 1–18; −23 to 40; $p < 0.001$) (Table 3). The prevalence of infants with an improved score tended to be higher in the group with only colic (77%) and in the group with colic and regurgitation (89%) than in the group with only regurgitation (62.5%). The QUALIN score significantly increased in infants with colic alone (+9.7 ± 13.8; 10; 1–18; −18 to 40; $p = 0.001$) or in association with regurgitation (+13.3 ± 13.9; 16; 6–24; −15 to 33; $p < 0.001$) and not in infants with only regurgitation (+2.7 ± 11.9; 4; −4 to 10; −23 to 24). This improvement was mainly due to items related to behavior and communication and well-being (66.2% of infants) among which the question related to crying (no. 30) most often got an improved response (54.4% of infants), followed by items no. 5, 13, 21 for about 40% of infants. This group of items accounted, in median value (*Q*1–*Q*3), for 36.4% (28.1–42.5) of the global result at D0 and 37.1% (33.3–42.6) at D30. Worsening of the score was noted in 19% of infants, mainly in the items related to the ability to remain alone (39% of infants), which accounted for less than 5% of the total score. In linear regression, no relationship between the global QoL score and the improvement in the daily number of regurgitations or the weekly number of days with colic was found.

Secondary outcomes (regurgitation and colic)

Table 4 shows the different outcomes.

Overall, the daily number of regurgitations decreased from 4.8 ± 2.0 at D0 to 1.7 ± 1.2 at D3O (ITT, $n = 61$; $p < 0.001$), and from 4.7 ± 1.9 to 1.7 ± 1.2 (PP, $n = 42$; $p < 0.001$) in ITT, the decrease was–3.1 ± 2 (−3; −4; −2; −8 to 2) regurgitations per day, i.e., minus 60.7 ± 26.3% (66.7; 50–80; 20–88). The number of infants in ITT analysis meeting the Rome IV criteria for regurgitation decreased

10.3389/fnut.2023.1164722

TABLE 2 Baseline characteristics of the population.

	Included	PP
n	101	68
Male *n* (%)	50/101 (49.5)	34/68 (50.0)
Rank in siblings	(*n* = 99)	(*n* = 67)
% as no. 1; 2; 3; 4; 5	56.6; 26.3; 15.2; 1.0; 1.0	56.7; 25.4; 17.9; 0.0; 0.0
Gestational age	(*n* = 100)	(*n* =68)
Mean week (SD)	39.3 (1.1)	39.3 (1.1)
Median (Q1−Q3; range)	39.0 (39.0−40.0; 37.0−41.0)	39.0 (38.0−40.0; 37.0−41.0)
Birth weight	(*n* = 100)	(*n* = 68)
Mean kg (SD)	3.30 (0.40)	3.31 (0.42)
Median (Q1−Q3; range)	3.33 (3.00−3.50; 2.50−4.34)	3.35 (3.04−3.56; 2.50−4.34)
Birth length	(*n* = 100)	(*n* = 68)
Mean cm (SD)	49.3 (2.1)	49.2 (2.2)
Median (Q1−Q3; range)	50.0 (48.0−51.0; 44.0−54.0)	50.0 (48.0−51.0; 44.0−54.0)
Age at inclusion	(*n* = 100)	(*n* = 68)
Mean weeks (SD)	6.2 (4.3)	6.3 (4.3)
Median (Q1−Q3; range)	5.0 (3.0−9.0; 0.3−18.0)	5.0 (3.0−8.0; 0.3−18.0)
Weight	(*n* = 100)	(*n* = 68)
Mean kg (SD)	4.74 (1.11)	4.69 (1.11)
Median (Q1−Q3; range)	4.45 (3.97−5.30; 2.70−7.80)	4.45 (3.90−5.28; 2.70−7.80)
Length	(*n* = 100)	(*n* = 68)
Mean cm (SD)	55.2 (4.4)	55.0 (4.2)
Median (Q1−Q3; range)	54.0 (52.0−58.0; 48.0−67.0)	54.0 (52.0−58.0; 48.0−65.0)
Head circumference, cm	(*n* = 100)	(*n* = 68)
Mean cm (SD)	37.8 (2.1)	37.8 (2.1)
Median (Q1−Q3; range)	37.0 (37.0−39.0; 34.0−44.0)	37.0 (37.0−39.0; 34.0−43.0)
Number (%) of infants with regurgitations	67 (66.4)	42 (61.8)
Number (%) of infants with colic	68 (67.3)	44 (64.7)
Number (%) of infants with both FGIDs	34 (33.7)	18 (26.5)
Number (%) of infants with mostly regurgitation[a]	50 (49.5)	33 (48.5)
Number (%) of infants with mostly colic[a]	46 (45.5)	35 (51.5)
Number (%) of infants with as much regurgitation as colic[a]	5 (5)	0 (0)
Number of bowel movements/week[b]		
Mean (SD)	9.3 (5.3)	9.7 (5.3)
Median (Q1−Q3; range)	7 (6–14; 1–21)	7 (6–14; 2–21)
Number (%) of infants with hard stool[b]	12 (11.9)	7 (10.3)
Number (%) of infants with normal stool[b]	31 (30.7)	21 (30.9)
Number (%) of infants with smooth or lumpy stool[b]	45 (44.6)	31 (45.6)
Number (%) of infants with curdy or liquid stool[b]	13 (12.9)	9 (13.2)

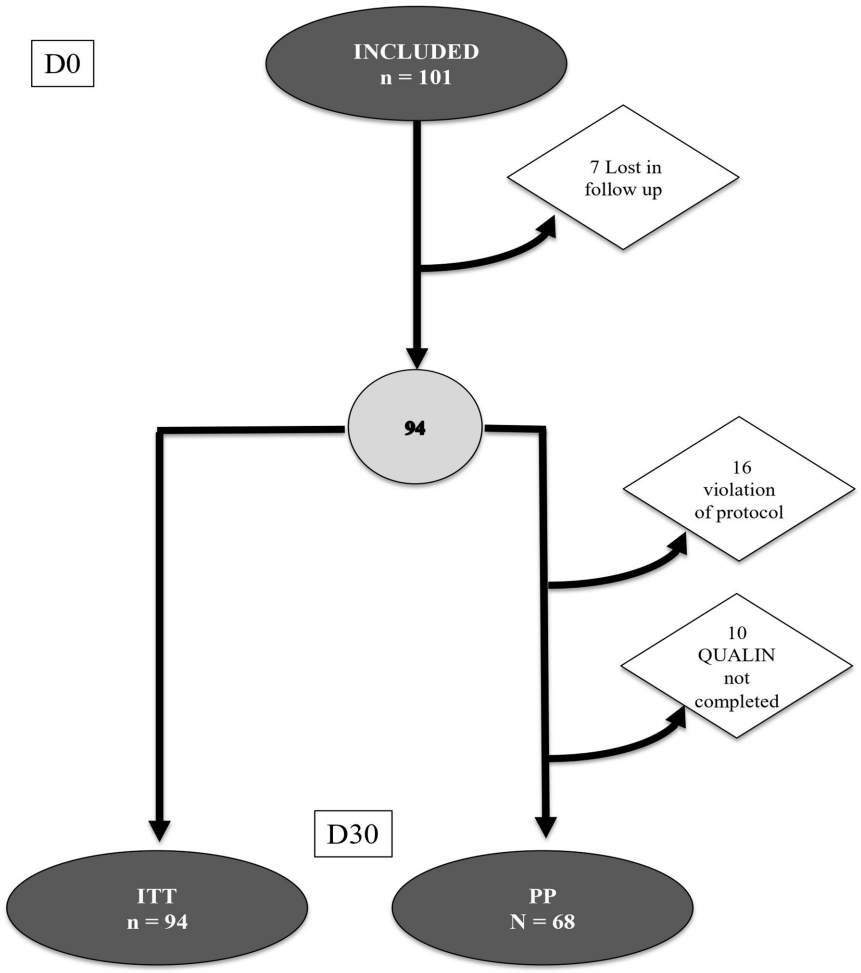
[a]According to pediatrician's assessment.
[b]As reported by parents during the previous week.

from 100 to 38% at D30. In ITT analysis, 91.8% of parents have noticed a decrease in regurgitation in less than 4 days for 59% of them and within one week for 89%. In PP analysis the decrease in the daily number of regurgitations was of 63.4 ± 17.8% (66.7; 50–80; 20–88); of parents, 98% noticed such an improvement, within one week for 95% of them.

In infants with colic, the weekly number of days with crying or fussing decreased from 5.8 ± 1.5 to 2.0 ± 2.0 in ITT analysis ($n = 65$; $p < 0.001$) and from 6.3 ± 1.1 to 1.5 ± 1.6 in PP analysis ($n = 44$; $p < 0.001$). This corresponded to a decrease of 63.4 ± 37.5% (71; 50–100; 75–100) and 73.6 ± 27.8% (82; 59–100; 0–100) respectively. Of parents 89% (ITT) and 95% (PP) noticed a decrease in number of crying/fussing; it was within 3 days for 36 and 45% and within one week for 76 and 83% of parents, respectively. In PP analysis, parents reported 100% of infants with colic had 3 or more days with crying per week at D0 and 22% at D30. On the other hand, they reported 27% of infants who cried for ≥3 h /day at D0 and 2% at D30. Overall, the cumulative daily crying duration decreased from 120.0 ± 100.5 mn to 38.1 ± 46.3 mn in ITT analysis ($n = 65$; $p < 0.001$), i.e., a decrease of 82 ± 106 mn, and from 124.5 ± 108.5 mn to 28.7 ± 38.3 mn in PP analysis ($n = 44$; $p < 0.001$). Specifically, 90% of the 32 infants with colic who previously to inclusion received LrD, either as drops or in a formula, had improved. In these 32 infants, the number of days per week with colic decreased from 6.1 ± 1.4 to 2.1 ± 2.4 ($p < 0.001$); the median value decreased from 7 (5–7; 2–7) to 1 (0–3; 0–7). In these infants the crying duration per day decreased from 131.4 ± 121.2 mn (90; 60–180; 4–600) to 42.3 ± 51.7 (30; 0–60; 0–240) ($p < 0.001$).

Evolution of stool frequency and consistency

Little change in the number of bowel movements per week was shown from 9.3 ± 5.3 (7; 6–14; 1–21) at D0 to 8.2 ± 4.0 (7; 6–10; 1–21) at D30. At D30 there was a trend for fewer infants with hard or liquid/curdy stool and for more infants with normal stools, and no more infants who could be considered constipated (Figure 2). These changes in stool consistency were noticed by 45.7% of parents, of whom 41.9% noticed it within 3 days after introduction of the study formula and 80.5% within one week.



ITT: Intention to treat analysis; PP: Per protocol analysis

FIGURE 1
Flow chart.

Satisfaction, tolerance and adverse events

Of parents in ITT analysis ($n = 94$) and PP analysis ($n = 68$), 84 and 85% considered that the comfort of the infant had been improved during the study period and 78.7% and 83% asked to continue with the study formula, respectively. Of the 20 and 11 parents who in each analysis did not ask to continue, 13 and 8 considered the formula to be ineffective, and 7 and 3 that the problems were resolved, respectively.

The quantity of formula consumed at D30 was 798.4 ± 99.4 mL/day (750; 720–900; 540–1,080), without difference between infant with regurgitations and infants with colic. Solid foods were introduced in 4 more infants than at D0. The weight gain during the study period in the PP population was 28.8 ± 8.2 g/day (27.1; 23.8–33.4; 11.3–49.7). The length gain was 3.3 ± 1.3 cm (3; 2–4; 1–8) and that of head circumference 1.8 ± 0.8 cm (2; 1–2; 1–5).

Seven adverse events were reported including two constipations (as assessed by parents but not in accordance with Rome IV criteria), two increases in regurgitation, one worsening of colic, one urine tract infection and one gastroenteritis.

Discussion

This multicenter prospective experimental study was conducted in routine circumstances leading to include infants who did not all meet the Rome IV criteria. Such infants precisely represent the target population concerned by such a dietary approach in current pediatric practice. Such a real-life study is better able to inform on the effectiveness of a management (43). The completion of recruitment has required an unusually relatively long time of over 14 months due to three waves of COVID epidemic (44). The physician's goal as well as the parents' expectations in the management of infant's regurgitations and colic are to improve the comfort of the infant as evidenced by the QoL score by ensuring an alleviation of the symptoms, what were the criteria adopted to judge the effectiveness.

TABLE 3 Evolution of the QUALIN scores from baseline to day 30 according to the symptoms presented in per protocol analysis.

	Infants with regurgitations		Infants with colic		Infants with regurgitations and colic		All infants	
n	24	26	18	68	*n*	24	26	18
	D0	D30	D0	D30		D0	D30	D0
Total score								
Mean (SD)	37.7 (9.9)	40.3 (12.2)	29.0 (14.1)	38.7 (10.4)***	30.9 (12.6)	44.3 (8.4)***	32.6 (12.7)	40.8 (10.7)***
Median (Q1–Q3)	39 (30–47)	43 (34–50)	30 (18–41)	39 (33–47)	28 (20–40)	47 (42–49)	35 (23–42)	44 (35–49)
[Range]	[20–55]	[8–60]	[5–55]	[16–60]	[14–54]	[24–56]	[5–55]	[8–60]
Behavior and communication								
Mean (SD)	13.4 (6.0)	14.6 (5.5)	10.0 (7.4)	14.7 (5.4)	10.9 (7.0)	16.8 (4.6)	11.5 (6.9)	15.2 (5.2)
Median (Q1–Q3)	14 (9–19)	15 (12–19)	11 (6–16)	16 (12–19)**	11 (5–18)	18 (15–21)**	12 (7–18)	16 (12–20)***
[Range]	[0–22]	[1–22]	[−9 to 22]	[0–22]	[−2 to 21]	[6–22]	[−9 to 22]	[0–22]
Ability to remain alone								
Mean (SD)	1.6 (1.6)	1.7 (1.7)	1.5 (2.0)	1.7 (1.7)	2.1 (1.5)	2.2 (1.4)	1.7 (1.7)	1.8 (1.6)
Median (Q1–Q3)	2 (1–3)	2 (0–3)	2 (0–3)	2 (0–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (0–3)
[Range]	[−2 to 4]	[−2 to 5]	[−2 to 5]	[−2 to 5]	[0–5]	[0–4]	[−2 to 5]	[−2 to 5]
Family environment								
Mean (SD)	6.6 (1.4)	6.6 (1.6)	6.1 (1.5)	6.6 (1.4)	6.1 (2.1)	7.0 (1.3)	6.3 (1.6)	6.7 (1.4)
Median (Q1–Q3)	7 (6–8)	7 (6–8)	6 (5–7)	7 (6–8)	7 (5–8)	8 (6–8)	7 (5–8)	7 (6–8)
[Range]	[4–8]	[4–8]	[2–8]	[4–8]	[2–8]	[4–8]	[2–8]	[4–8]
Psychological and somatic well-being								
Mean (SD)	4.6 (2.5)	6.0 (3.1)	1.2 (4.8)	3.8 (4.0)**	1.5 (4.2)	5.4 (3.0)***	2.5 (4.2)	5.0 (3.5)***
Median (Q1–Q3)	4 (3–6)	6 (3–9)	0 (−3 to 4)	4 (1–7)	1 (−2 to 4)	7 (2–8)	3 (−1 to 6)	5 (2–8)
[Range]	[−1 to 9]	[0–11]	[−5 to 11]	[−5 to 10]	[−6 to 10]	[2–10]	[−6 to 11]	[−5 to 11]

**$p < 0.01$, ***$p \leq 0.001$.

Effectiveness of the study formula on infants'quality of life and clinical outcome

At inclusion the QoL score in our population of infants with colic or regurgitation was much lower than the one originally reported in healthy 1–3 years children (~53) but higher than that reported in chronic diseases (~23) (41). It is comparable to that already reported in infants with FGIDs (27.2 ± 15.1) (15). In studied infants, the QoL score was lower in those with colic or with both symptoms than in those with regurgitations only, confirming how stressing and depressing the crying/fussing problems could be for parents and for the perception of their infant's QoL (45). Just over a third of the included infants presented with both FGIDs. Infants presenting multiple FGIDs have already been reported as having a lower QoL score and a slower recovery than those with a single symptom (9).

The results of our study suggest that a starch thickened "comfort formula" containing the probiotic *Limosilactobacillus reuteri* DSM 17938, a mixture of prebiotics FOS/GOS and a reduced content of lactose is effective in the management of infant's regurgitation and/or colic. The findings were an improvement of the quality of life in three quarters of infants and a decrease in the daily number of regurgitations and in the number of days with colic as well as of daily cumulative duration of crying. The improvement in QoL was more frequently observed in infants with colic, even if they were associated with regurgitations. A greater improvement in QoL score in case of combined FGIDs was previously shown (9). As shown by others, no relationship between the improvement in QoL and that of symptoms could be demonstrated by linear regression (16). The rapid improvement of the symptoms certainly contributes greatly to reassuring parents, what is the cornerstone in the management of these two FGIDs, especially in case of colic (1, 46). It certainly increased "free time" and improved "sleep time" of parents what participated in the perception of better QoL.

Both FGIDs are time-limited conditions. However, age at inclusion (75% of infants were younger than 9 weeks and the oldest included infant was 18 weeks old) and duration of the trial (4 weeks) make the possibility of a natural temporal evolution unlikely to explain the improvements observed (47, 48). The natural evolution of

10.3389/fnut.2023.1164722

TABLE 4 Outcome of regurgitation or colic from day 0 to day 30 in intention to treat (ITT) and per protocol (PP) analyses.

		Infants with regurgitations		Infants with colic		Infants with regurgitations and colic	
Analysis		ITT	PP	ITT	PP	ITT	PP
n		29	24	33	26	32	18
Number of regurgitations/day							
D0	Mean (SD)	5.4 (2.2)	5.0 (2.0)	–	–	4.3 (1.8)	4.4 (1.8)
	Median (Q1–Q3)	5 (4–6)	5 (3–6)	–	–	4 (3–6)	5 (3–5)
	[Range]	[2–9]	[2–9]	–	–	[2–8]	[2–8]
D30	Mean (SD)	1.8 (1.3)***	1.9 (1.4)***	–	–	1.7 (1.0)***	1.3 (0.6)***
	Median (Q1–Q3)	1 (1–2)	1 (1–3)	–	–	1 (1–2)	1 (1–2)
	[Range]	[1–5]	[1–5]	–	–	[1–5]	[1–5]
Number of days per week with crying or fussing							
D0	Mean (SD)	–	–	6.0 (1.2)	6.2 (1.0)	5.7 (1.9)	6.3 (1.2)
	Median (Q1–Q3)	–	–	6 (5–7)	7 (6–7)	7 (4–7)	7 (6–7)
	[Range]	–	–	[3–7]	[3–7]	[1–7]	[4–7]
D30	Mean (SD)	–	–	2.1 (2.0)***	1.7 (1.8)***	2.0 (2.0)***	1.5 (1.6)***
	Median (Q1–Q3)	–	–	2 (0–3)	2 (0–2)	2 (0–3)	1 (0–2)
	[Range]	–	–	[0–7]	[0–7]	[0–7]	[0–4]
Daily crying duration (mn)							
D0	Mean (SD)	–	–	152.3 (116.2)	150.3 (121.2)	86.7 (68.1)	87.1 (75.4)
	Median (Q1–Q3)	–	–	120 (90–180)	120 (90–180)	60 (48–120)	60 (50–120)
	[Range]	–	–	[4–600]	[4–600]	[3–300]	[3–600]
D30	Mean (SD)	–	–	39.2 (44.1)***	35.1 (45.8)***	37.0 (49.1)***	19.4 (21.8)***
	Median (Q1–Q3)	–	–	30 (0–60)	25 (0–55)	20 (5–60)	15 (0–30)
	[Range]	–	–	[0–180]	[0–180]	[0—240]	[0–60]

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

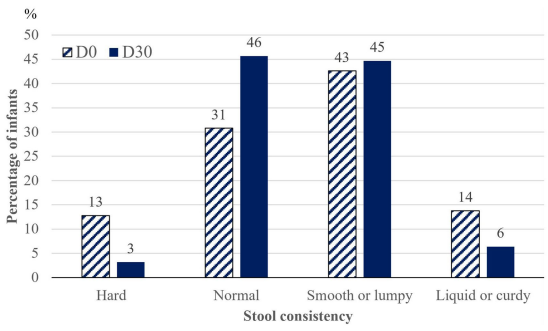


FIGURE 2
Evolution in stool consistency from inclusion (D0) to endpoint (D30) (*n*=94). Prevalence of infants with each type of stool.

regurgitation shows indeed a peak around 4 months of age and a tapering from 6 months onwards (1, 49, 50). On the other hand, the literature displays substantial variation in the reported age at which the excessive crying stopped, ranging from 9 to 104 weeks (median 19 weeks) with a consensus to consider it after 6 months (1, 9, 46, 51). At the end of our study the oldest infant was 22 weeks old. Therefore, the hypothesis of a formula-specific effect on symptoms outcome seems more than likely in most infants, whereas a spontaneous evolution during the study period seems less likely but cannot be completely excluded in the infants older than 4 months.

The tested formula was well-tolerated and supported adequate infant growth. It has satisfied the vast majority of parents.

Contribution of the different ingredients to the explanation of the results

Given the diversity of modifications made in the composition of the study formula compared to a standard formula, it is difficult to assess the contribution of each to the observed improvement. Obviously, the thickening of the formula with starch contributed largely to the alleviating of regurgitation as generally admitted (24, 25, 52–55). On the other hand, LrD has been shown to accelerate gastric emptying and improve regurgitation in infants (56). Regarding the improvement in colic, whose etiology remains elusive, our results are consistent with those from studies using formulas also containing LrD but with partially hydrolyzed protein (16, 35, 36). In exclusively breastfed colic infants, the use of LrD is supported by RCTs and meta-analysis, whereas studies in formula fed colic infants are rare and inconsistent and often performed with LrD given as drops and not as an ingredient of the formula (30, 32, 34, 37). In their recent position

paper, the ESPGHAN Special Interest Group on Gut Microbiota and Modifications considered that no recommendation could be made so far for or against its use in colic formula fed infants due to insufficient evidence (32). However, the group stated that LrD as well as *B. lactis* BB-12 may be recommended for the management of colic in breastfed infant. The rationality of using LrD is based on the demonstrated notion of an imbalanced microbiota colonization in infants with colic (11, 57, 58). A low intestinal concentration of lactobacilli genera would have an important role in the pathophysiology of infantile colic and, on the other hand, LrD would reduce inflammation, gas production, and pain perception (37). Besides this probiotic, the study formula, like the one used by Vandenplas et al. with partially hydrolyzed protein, contained FOS/GOS leading to consider the possibility of a synbiotic effect (16), as defined by the ISAPP consensus statement (31). This might participate in explaining the improvement of infants having previously received LrD but then without effectiveness. In addition, a fermented formula for which the bacterial fermentation process is followed by mild heat treatment and that contained FOS/GOS has been shown to be more effective in preventing infant's colic than the same formula without FOS/GOS or an unfermented formula containing FOS/GOS (59). The role of excess lactose in the onset of colic has been questioned and related to a transient low lactase activity in young infants (27). The undigested lactose then reaches the colon where its bacterial fermentation produces gas including hydrogen, and intestinal distension that possibly triggers crying (11). Greater baseline breath hydrogen excretion at baseline as well as after a lactose meal have been reported in some infants with colic compared with healthy infants, but this may have been contradicted by others (27, 60). Randomized clinical trials of oral lactase administration as well as trials with reduced lactose content have shown conflicting results in the management of infantile colic (27, 60–62). A reduced lactose content (5.0 g/100 mL) in the study formula may thus have contributed to alleviation of crying. In total, the combination of all the changes made to the formula studied is presumably at the origin of the results observed, without it being possible to formally conclude on the interest of each of them. This would require randomized studies comparing formulas with an isolated modification and then combining them in different ways. Such studies are almost impossible.

Strengths and limitations

The strength of our study is that effectiveness assessment was based on both clinical outcome and QoL as recommended by Rome IV consensus (1). Of included infants only 7% were lost to follow-up and full adherence to protocol was observed in more than 67% of parents. The main advantage of such a pragmatic real-life study is its natural practice setting, mimicking every day clinical practice which provides high external validity (43). The possibility of having an overestimation of the number of regurgitations or of the amounts of crying by the parents is counterbalanced by the fact that the evaluation of their evolution was carried out within the subject in a pre- post-test.

Some limitations must be acknowledged. The report of data by parents lead to a few rare outliers that sometimes constitute the extreme data of the ranges. Some questions of the QUALIN questionnaire might not be well suited to very young infants or may have embarrassed some parents, which could explain the number of uncompleted questionnaires. Finally, the absence of randomization with a control group leads to consider the possibility of a placebo effect. Colic was shown to be highly responsive to placebo in different studies (63, 64). The parents' awareness of the potential effect of the formula as well as the reassurance measures provided by the pediatrician probably interacted in the improvements observed (13, 37, 46). However, the placebo and reassurance effects are components of the response to treatment normally present in clinical practice and were certainly acting before inclusion, especially since 11% of infants had previously changed from formula, 68% had already received a probiotic, and 45% prebiotics, but without effectiveness. This leads to the conclusion that the study formula is effective as a whole.

Conclusion

This study shows that, in routine clinical practice, a starched thickened formula with reduced lactose content and supplemented with *Limosilactobacillus reuteri* DSM 17938 and a mixture of fructo-oligosaccharides and galacto-oligosaccharides has more than likely helped improve quality of life of young infants with regurgitation or colic or both and alleviate the underlying symptoms. As a consequence, such a formula deserves to be prescribed, in association with reassurance to parents, in the management of these infants without waiting for a possible spontaneous improvement which can be much later. On the other hand, the study confirms the absolute non-necessity of drugs in the management of these FGIDs. However, none of the specific ingredients of the test formula can be directly associated with the observed improvement, but the formula as a whole, unless separate RCTs are carried out in the future with each of them.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Subject Protection Review Board "Sud Mediterrannée III" (Nimes 2020/03/18, no. 2020.01.07 bis_19.12.26.60314). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

J-PC, SB, BD, and TH contributed equally to the conception and design of the study, as well as analysis, and interpretation of data; they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J-PC wrote the original draft. SB, BD, and TH revised it critically. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by Nestlé France, Département Médical Nutrition Infantile, Issy-les-Moulineaux, France.

Acknowledgments

The authors thank all the families who participated in the study, as well as all the paediatricians who contributed to it. We also thank the collaborators of Keyrus CRO who were involved in collecting data and performing statistical analysis.

Conflict of interest

J-PC served as consultant for this study. SB received honoraria for her contribution to the conduct of the study, fees from Bledina for writing a leaflet and from the AFPA for expert testimony. BD and TH are employees of Nestlé France.

The authors declare that this study received funding from Nestlé. The funder had the following involvement in the study: participation in the study design and in reviewing the final manuscript to approve it without involvement in data analysis, discussion nor conclusion.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1164722/full#supplementary-material

References

1. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. (2016) 150:1443–1455.e2. doi: 10.1053/j.gastro.2016.02.016

2. Chouraqui JP, Brancato S, Rubio A, Bousquet P. Prevalence of functional intestinal disorders in infants and young children. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; 44th Annual Meeting, Sorrento, Italy. (2011). Poster PO-G-258

3. Steutel NF, Zeevenhooven J, Scarpato E, Vandenplas Y, Tabbers MM, Staiano A, et al. Prevalence of functional gastrointestinal disorders in European infants and toddlers. *J Pediatr*. (2020) 221:107–14. doi: 10.1016/j.jpeds.2020.02.076

4. Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, di Prima L, et al. Paediatric study group on gastrointestinal symptoms in infancy. Gastrointestinal symptoms in infancy: a population-based prospective study. *Dig Liver Dis*. (2005) 37:432–8. doi: 10.1016/j.dld.2005.01.009

5. van Tilburg MA, Hyman PE, Walker L, Rouster A, Palsson OS, Kim SM, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. *J Pediatr*. (2015) 166:684–9. doi: 10.1016/j.jpeds.2014.11.039

6. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Çokura F, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. *J Pediatr Gastroenterol Nutr*. (2015) 61:531–7. doi: 10.1097/MPG.0000000000000949, Erratum in: J Pediatr Gastroenterol Nutr (2016) 62:516

7. Muhardi L, Aw MM, Hasosah M, Ng RT, Chong SY, Hegar B, et al. A narrative review on the update in the prevalence of infantile colic, regurgitation, and constipation in young children: implications of the ROME IV criteria. *Front Pediatr*. (2022) 9:778747. doi: 10.3389/fped.2021.778747

8. Campeotto F, Barbaza MO, Hospital V. Functional gastrointestinal disorders in outpatients aged up to 12 months: a French non-interventional study. *Int J Environ Res Public Health*. (2020) 17:4031. doi: 10.3390/ijerph17114031

9. Bellaiche M, Oozeer R, Gerardi-Temporel G, Faure C, Vandenplas Y. Multiple functional gastrointestinal disorders are frequent in formula-fed infants and decrease their quality of life. *Acta Paediatr*. (2018) 107:1276–82. doi: 10.1111/apa.14348

10. Beser OF, Cullu Cokugras F, Dogan G, Akgun O, Elevli M, Yilmazbas P, et al. The frequency of and factors affecting functional gastrointestinal disorders in infants that presented to tertiary care hospitals. *Eur J Pediatr*. (2021) 180:2443–52. doi: 10.1007/s00431-021-04059-2

11. Lifschitz C. Prevention of excessive crying by intestinal microbiota programming. *J Pediatr*. (2013) 163:1250–2. doi: 10.1016/j.jpeds.2013.06.034

12. Salvatore S, Abkari A, Cai W, Catto-Smith A, Cruchet S, Gottrand F, et al. Review shows that parental reassurance and nutritional advice help to optimise the management of functional gastrointestinal disorders in infants. *Acta Paediatr*. (2018) 107:1512–20. doi: 10.1111/apa.14378

13. Vandenplas Y, Hauser B, Salvatore S. Functional gastrointestinal disorders in infancy: impact on the health of the infant and family. *Pediatr Gastroenterol Hepatol Nutr*. (2019) 22:207–16. doi: 10.5223/pghn.2019.22.3.207

14. Botha E, Joronen K, Kaunonen M. The consequences of having an excessively crying infant in the family: an integrative literature review. *Scand J Caring Sci*. (2019) 33:779–90. doi: 10.1111/scs.12702

15. Jung C, Beck L, Hanh T, Bellaiche M. Quality of life of infants with functional gastrointestinal disorders: a large prospective observational study. *Int J Child Health Nutr*. (2017) 6:62–9. doi: 10.6000/1929-4247.2017.06.02.2

16. Vandenplas Y, Gerlier L, Caekelbergh KNan-Study-Group, Possner M. An observational real-life study with a new infant formula in infants with functional gastrointestinal disorders. *Nutrients*. (2021) 13:3336. doi: 10.3390/nu13103336

17. Saps M, Di Lorenzo C. Pharmacotherapy for functional gastrointestinal disorders in children. *J Pediatr Gastroenterol Nutr*. (2009) 48:S101–3. doi: 10.1097/MPG.0b013e3181a15f49

18. Mahon J, Lifschitz C, Ludwig T, Thapar N, Glanville J, Miqdady M, et al. The costs of functional gastrointestinal disorders and related signs and symptoms in infants: a systematic literature review and cost calculation for England. *BMJ Open*. (2017) 7:e015594. doi: 10.1136/bmjopen-2016-015594

19. Mouterde O, Chouraqui JP, Ruemmele F, Mas E, Bellaïche M, Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatriques; Comité de relecture du manuscritet al. Cessons de prescrire des inhibiteurs de pompe à proton pour suspicion de reflux gastro-œsophagien, en dehors des indications justifiées ! [Let's stop proton pump inhibitor prescriptions for suspected GERD in non-validated indications!]. *Arch Pediatr*. (2014) 21:686–9. doi: 10.1016/j.arcped.2014.04.030

20. Gieruszczak-Białek D, Konarska Z, Skórka A, Vandenplas Y, Szajewska H. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. *J Pediatr*. (2015) 166:767–70.e3. doi: 10.1016/j.jpeds.2014.11.030

21. Lyamouri M, Mårild K, Nielsen RG, Størdal K. Proton pump inhibitors for infants in three Scandinavian countries increased from 2007 to 2020 despite international recommendations. *Acta Paediatr*. (2022) 111:2222–8. doi: 10.1111/apa.16491

22. Yang S, Trinh NTH, Chalumeau M, Kaguelidou F, Ruemmele FM, Milic D, et al. Pediatric prescriptions of proton pump inhibitors in France (2009–2019): a time-series analysis of trends and practice guidelines impact. *J Pediatr*. (2022) 245:158–64.e4. doi: 10.1016/j.jpeds.2022.01.041

23. de Lauzon-Guillain B, Davisse-Paturet C, Lioret S, Ksiazek E, Bois C, Dufourg MN, et al. Use of infant formula in the ELFE study: the association with social and health-related factors. *Matern Child Nutr*. (2018) 14:e12477. doi: 10.1111/mcn.12477

24. Rosen R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the north American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. (2018) 66:516–54. doi: 10.1097/MPG.0000000000001889

25. National Institute for Health and Care Excellence (NICE), London. Gastro-oesophageal reflux disease in children and young people: diagnosis and management. *NICE guideline*, 1.) (2019). https://www.ncbi.nlm.nih.gov/books/NBK552673/ (Accessed October 17, 2022).

26. Daelemans S, Peeters L, Hauser B, Vandenplas Y. Recent advances in understanding and managing infantile colic. *F1000Res*. (2018) 7:Faculty Rev-1426. doi: 10.12688/f1000research.14940.1

27. Gordon M, Biagioli E, Sorrenti M, Lingua C, Moja L, Banks SS, et al. Dietary modifications for infantile colic. *Cochrane Database Syst Rev*. (2018) 2019:CD011029. doi: 10.1002/14651858.CD011029.pub2

28. Gordon M, Gohil J, Banks SS. Parent training programmes for managing infantile colic. *Cochrane Database Syst Rev*. (2019) 2019:CD012459. doi: 10.1002/14651858.CD012459.pub2

29. Hjern A, Lindblom K, Reuter A, Silfverdal SA. A systematic review of prevention and treatment of infantile colic. *Acta Paediatr*. (2020) 109:1733–44. doi: 10.1111/apa.15247

30. Ellwood J, Draper-Rodi J, Carnes D. Comparison of common interventions for the treatment of infantile colic: a systematic review of reviews and guidelines. *BMJ Open*. (2020) 10:e035405. doi: 10.1136/bmjopen-2019-035405

31. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The international scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol*. (2020) 17:687–701. doi: 10.1038/s41575-020-0344-2

32. Szajewska H, Berni Canani R, Domellöf M, Guarino A, Hojsak I, Indrio F, et al. Working group on probiotics and prebiotics of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN special interest group on gut microbiota and modifications. *J Pediatr Gastroenterol Nutr*. (2023) 76:232–47. doi: 10.1097/MPG.0000000000003633

33. Zheng J, Wittouck S, Salvetti E, Franz CMAP, Harris HMB, Mattarelli P, et al. A taxonomic note on the genus *Lactobacillus*: description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. *Int J Syst Evol Microbiol*. (2020) 70:2782–858. doi: 10.1099/ijsem.0.004107

34. Sung V, D'Amico F, Cabana MD, Chau K, Koren G, Savino F, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. *Pediatrics*. (2018) 141:e20171811. doi: 10.1542/peds.2017-1811

35. Dadan S, Higuera M, Daza W. Improvement of digestive symptoms with a partially hydrolyzed serum, reduced lactose and *Lactobacillus reuteri* DSM 17938—based functional infant formula in infants younger than 5months old with infantile colic, in outpatient pediatric centers of Bogota, Colombia. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; 52nd Annual Meeting, Glasgow, 5–8 June 2019. (2019). Poster G-P-253.

36. Turco R, Russo M, Bruzzese D, Staiano A. Efficacy of a partially hydrolysed formula, with reduced lactose content and with *Lactobacillus reuteri* DSM 17938 in infant colic: a double blind, randomised clinical trial. *Clin Nutr*. (2021) 40:412–9. doi: 10.1016/j.clnu.2020.05.048

37. Pereira AR, Rodrigues J, Albergaria M. Effectiveness of probiotics for the treatment of infantile colic. *Aust J Gen Pract*. (2022) 51:573–6. doi: 10.31128/AJGP-07-21-6062

38. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies). Scientific opinion on the essential composition of infant and follow-on formulae. *EFSA J*. (2014) 12:3760. doi: 10.2903/j.efsa.2014.3760

39. Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing regulation (EU) no 609/2013 of the European Parliament and of the council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0127&from=FR (Accessed July 16, 2022).

40. Whitehead WE, Drossman DA, Chang L, Kellow J, Chey WD, Tack J. *Rome IV diagnostic questionnaire for pediatric gastrointestinal disorders for neonates and toddlers* 1 Rome Foundation (2017); 289 https://romeonline.org/product/rome-iv-diagnostic-questionnaires-and-tables-for-investigators-and-clinicians-first-edition/ (Accessed August 16, 2019).

41. Manificat S, Dazord A, Langue J, Danjou G, Bauche P, Bovet F, et al. Evaluation de la qualité de vie du nourrisson et du très jeune enfant: validation d'un questionnaire. Etude multicentrique européenne [Evaluation of the quality of life of infants and very young children: validation of a questionnaire. Multicenter European study]. *Arch Pediatr*. (2000) 7:605–14. doi: 10.1016/s0929-693x(00)80127-x

42. National Institute for Health and Care Excellence (NICE), London. London. Constipation in children and young people: diagnosis and management. (2017). Available at: https://www.nice.org.uk/guidance/cg99/evidence/full-guidance-pdf-245466253 (Accessed October 17, 2022).

43. Saturni S, Bellini F, Braido F, Paggiaro P, Sanduzzi A, Scichilone N, et al. Randomized controlled trials and real life studies. Approaches and methodologies: a clinical point of view. *Pulm Pharmacol Ther*. (2014) 27:129–38. doi: 10.1016/j.pupt.2014.01.005

44. Costemalle V, Gaini M, Hazo JB, Naouri D. En quatre vagues, l'épidémie de Covid-19 a causé 116 000 décès et lourdement affecté le système de soins. [In four waves, the Covid-19 epidemic has caused 116,000 deaths and heavily affected the healthcare system]. *INSEE References* (2021). https://www.insee.fr/fr/statistiques/5432509?sommaire=5435421 (Accessed December 6, 2022).

45. Wake M, Morton-Allen E, Poulakis Z, Hiscock H, Gallagher S, Oberklaid F. Prevalence, stability, and outcomes of cry-fuss and sleep problems in the first 2 years of life: prospective community-based study. *Pediatrics*. (2006) 117:836–42. doi: 10.1542/peds.2005-0775

46. St James-Roberts I, Garratt R, Powell C, Bamber D, Long J, Brown J, et al. A support package for parents of excessively crying infants: development and feasibility study. *Health Technol Assess*. (2019) 23:1–144. doi: 10.3310/hta23560

47. Iacovou M. Editorial: interventions in infantile colic—can efficacy be attributed to treatment or to time? *Aliment Pharmacol Ther*. (2020) 51:397–8. doi: 10.1111/apt.15599

48. Nocerino R, de Filippis F, Cecere G, Marino A, Micillo M, di Scala C, et al. Editorial: interventions in infantile colic—can efficacy be attributed to treatment or to time? Authors' reply. *Aliment Pharmacol Ther*. (2020) 51:398–9. doi: 10.1111/apt.15627

49. Curien-Chotard M, Jantchou P. Natural history of gastroesophageal reflux in infancy: new data from a prospective cohort. *BMC Pediatr*. (2020) 20:152. doi: 10.1186/s12887-020-02047-3

50. Hegar B, Dewanti NR, Kadim M, Alatas S, Firmansyah A, Vandenplas Y. Natural evolution of regurgitation in healthy infants. *Acta Paediatr*. (2009) 98:1189–93. doi: 10.1111/j.1651-2227.2009.01306.x

51. Wolke D, Bilgin A, Samara M. Systematic review and meta-analysis: fussing and crying durations and prevalence of colic in infants. *J Pediatr*. (2017) 185:55–61.e4. doi: 10.1016/j.jpeds.2017.02.020

52. Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Guarino A, et al. Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. *Acta Paediatr*. (2016) 105:244–52. doi: 10.1111/apa.13270

53. Kwok TC, Ojha S, Dorling J. Feed thickener for infants up to six months of age with gastro-oesophageal reflux. *Cochrane Database Syst Rev*. (2017) 12:CD003211. doi: 10.1002/14651858.CD003211

54. Salvatore S, Savino F, Singendonk M, Tabbers M, Benninga MA, Staiano A, et al. Thickened infant formula: what to know. *Nutrition*. (2018) 49:51–6. doi: 10.1016/j.nut.2017.10.010

55. Lopez RN, Lemberg DA. Gastro-oesophageal reflux disease in infancy: a review based on international guidelines. *Med J Aust*. (2020) 212:40–4. doi: 10.5694/mja2.50447

56. Foster JP, Dahlen HG, Fijan S, Badawi N, Schmied V, Thornton C, et al. Probiotics for preventing and treating infant regurgitation: a systematic review and meta-analysis. *Matern Child Nutr*. (2022) 18:e13290. doi: 10.1111/mcn.13290

57. Dubois NE, Gregory KE. Characterizing the intestinal microbiome in infantile colic: findings based on an integrative review of the literature. *Biol Res Nurs*. (2016) 18:307–15. doi: 10.1177/1099800415620840

58. Johnson JM, Adams ED. The gastrointestinal microbiome in infant colic: a scoping review. *MCN Am J Matern Child Nurs*. (2022) 47:195–206. doi: 10.1097/NMC.0000000000000832

59. Vandenplas Y, Ludwig T, Bouritius H, Alliet P, Forde D, Peeters S, et al. Randomised controlled trial demonstrates that fermented infant formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides reduces the incidence of infantile colic. *Acta Paediatr*. (2017) 106:1150–8. doi: 10.1111/apa.13844

60. Mai T, Fatheree NY, Gleason W, Liu Y, Rhoads JM. Infantile colic: new insights into an old problem. *Gastroenterol Clin N Am*. (2018) 47:829–44. doi: 10.1016/j.gtc.2018.07.008

61. Ahmed M, Billoo AG, Iqbal K, Memon A. Clinical efficacy of lactase enzyme supplement in infant colic: a randomised controlled trial. *J Pak Med Assoc*. (2018) 68:1744–7.

62. Narang M, Shah D. Oral lactase for infantile colic: a randomized double-blind placebo-controlled trial. *BMC Pediatr*. (2022) 22:468. doi: 10.1186/s12887-022-03531-8

63. O'Donovan JC, Bradstock AS Jr. The failure of conventional drug therapy in the management of infantile colic. *Am J Dis Child*. (1979) 133:999–1001. doi: 10.1001/archpedi.1979.02130100023003

64. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. *J Paediatr Child Health*. (2012) 48:128–37. doi: 10.1111/j.1440-1754.2011.02061.x

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 10 July 2023
DOI 10.3389/fnut.2023.1172610

OPEN ACCESS

EDITED BY
Barbara Troesch,
Danone/Nutricia, Switzerland

REVIEWED BY
Fangyao Chen,
Xi'an Jiaotong University, China
Wei Chen,
Peking Union Medical College Hospital (CAMS), China

*CORRESPONDENCE
Wei Li
✉ liwei66@jlu.edu.cn
JiuWei Cui
✉ cuijw@jlu.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 23 February 2023
ACCEPTED 19 June 2023
PUBLISHED 10 July 2023

CITATION
Ji W, Liu X, Liu P, He Y, Zhao Y, Zheng K, Cui J and Li W (2023) The efficacy of fat-free mass index and appendicular skeletal muscle mass index in cancer malnutrition: a propensity score match analysis. *Front. Nutr.* 10:1172610. doi: 10.3389/fnut.2023.1172610

The efficacy of fat-free mass index and appendicular skeletal muscle mass index in cancer malnutrition: a propensity score match analysis

Wei Ji[1†], XiangLiang Liu[1†], Pengfei Liu[2], YuWei He[1], YiXin Zhao[1], Kaiwen Zheng[1], JiuWei Cui[1]* and Wei Li[1]*

[1]Center of Cancer, The First Affiliated Hospital of Jilin University, Changchun, China, [2]Cancer Department, Longyan First Hospital, Fujian, Longyan, China

Background: Reduced muscle mass (RMM) is a phenotypic criterion for malnutrition; the appendicular skeletal muscle mass index (ASMI) and fat-free mass index (FFMI) are both applicable indicators in the global leadership initiative on malnutrition (GLIM) guideline. However, their sensitivity and prognostic effect remain unclear.

Methods: Clinical data of 2,477 patients with malignant tumors were collected. Multi-frequency bioelectrical impedance analysis was used to obtain ASMI and FFMI. RMM was confirmed by ASMI (<7.0 kg/m^2 for men and <5.7 kg/m^2 for women) or FFMI (<17 kg/m^2 for men and <15 kg/m^2 for women). Propensity score match analysis and logistic regression analysis were used to evaluate the efficacy of FFMI and ASMI in diagnosing severe malnutrition and multivariate Cox regression analysis to determine the efficacy of RMM in predicting survival.

Results: In total, 546 (22.0%) and 659 (26.6%) participants were diagnosed with RMM by ASMI (RMM.ASMI group) and FFMI (RMM.FFMI group); 375 cases overlapped. Body mass index (BMI), midarm circumference, triceps skinfold thickness, and maximum calf circumference were all significantly larger in the RMM.FFMI group for both sexes ($P < 0.05$). A 1:1 matched dataset constructed by propensity score match contained 810 cases. RMM.FFMI was an influential factor of severe malnutrition with HR = 3.033 (95% CI 2.068–4.449, $P < 0.001$), and RMM.ASMI was a predictive factor of overall survival (HR = 1.318, 95% CI 1.060–1.639, $P = 0.013$ in the RMM.ASMI subgroup, HR = 1.315, 95% CI 1.077–1.607, $P = 0.007$ in the RMM.FFMI subgroup).

Conclusion: In general, RMM indicates negative clinical outcomes; when defined by FFMI, it predicts nutritional status, and when defined by ASMI, it is related to poor survival in cancer patients.

KEYWORDS

cancer, nutrition, malnutrition, skeletal muscle, prognosis

1. Introduction

In 2018, the number of cancer patients and cancer-related deaths increased by 18.1 million and 9.6 million globally, respectively (1). According to previous research, the incidence of malnutrition in patients with malignant cancers is 15–40% at initial diagnosis and up to 40–80% during treatment (2). Malnutrition leads to functional decline, reduces

the quality of life, increases hospital costs, and even causes mortality, which explains why it has become the focus of recent research interest (3).

Cancer-related malnutrition results in changes in body composition, mainly muscle depletion, and deteriorating biological function. A decreasing food intake or absorption and inflammation are the main reasons (4–7). In fact, 55% of patients reported reduced dietary intake after suffering from cancer (8). Inflammation, a hallmark of cancer, is involved in malnutrition through multiple mechanisms (9, 10). Interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-γ are demonstrated to contribute to anorexia (11, 12). For instance, Han et al. (13) reported that IL-6 and TNF-α could regulate white adipose tissue lipolysis browning, resulting in the development of malnutrition. Negative nitrogen balance and muscle wasting are significant characteristics of cancer-related malnutrition (14). In addition, IL-6 overexpression increases muscle proteolysis through both ubiquitin-dependent and autophagy-related pathways (15) and can affect mitochondrial dynamics, increasing the oxidative metabolism of skeletal muscle (16).

Cancer-related malnutrition is related to frequent use of antibiotics and long hospitalization, resulting in decreased quality of life and increased cost and psychological pressure (17). Accordingly, screening and assessment of malnutrition are important. The patient-generated subjective global assessment (PG-SGA) is the gold standard in evaluating the nutritional status of cancer patients (18). However, in 2018, the Global Clinical Nutrition Community released a consensus proposing a global screening and diagnostic guideline on malnutrition called the global leadership initiative on malnutrition (GLIM), which includes phenotypic and etiologic criteria (19). Muscle reduction is one of the phenotypic criteria. Both the appendicular skeletal muscle mass index (ASMI) and fat-free mass index (FFMI) are parameters used to evaluate muscle mass, and their cutoff values depend on ethnicities and evaluation tools. However, the diagnostic sensitivity and prognostic effectiveness of the two parameters have not been fully compared. Hence, the study was designed to clarify this point. In this study, we included 2,477 cancer cases. Taking PG-SGA as a gold standard, the diagnostic values of ASMI and FFMI were compared by propensity score match analysis. In addition, the prognostic effectiveness of the two parameters was compared considering overall survival (OS) as an endpoint.

2. Patients and methods

The study protocol adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the First Hospital of Jilin University (2017-362).

2.1. Patients

The clinical data of patients with malignant tumors admitted to the First Affiliated Hospital of Jilin University from November 2011 to December 2018 were collected. Inclusion criteria were as follows: (1) age > 18 years old and (2) pathological diagnosis of malignant tumors. Exclusion criteria were as follows: (1) ≥2 coexisting types of tumors; (2) suffering from server pleural effusion and/or ascites; (3) under regular hemodialysis; or (4) death within 3 days after admission.

Clinical data for each participant were collected by trained personnel. Laboratory examinations, anthropometric measurements, and bioelectric impedance analysis (BIA) were completed within 3 days of admission. Operating details are displayed in Supplementary material 1. Data included the following: (1) General characteristics: age, sex, smoking history, alcohol drinking, comorbidities (diabetes and hypertension), tumor site (the lung, digestive tract, liver, breast, and gynecological), and metastasis. (2) Laboratory examinations: serum albumin concentration, serum C-reaction protein (CRP), leukocyte, neutrophils, lymphocytes, platelets, neutrophils to lymphocytes ratio (NLR), platelets to lymphocytes ratio (PLR), and systematic inflammation index (SII). (3) Evaluation scales: PG-SGA. (4) Anthropometric measurements: body mass index (BMI), mid-arm circumference (MAC), triceps skinfold thickness (TSF), maximum calf circumference (CC), and hand-grip strength (HGS). (5) BIA indices: measured by a multi-frequency bioelectrical impedance body composition analyzer (InbodyS10; Biospace Co.®). Both ASM and FFM were recorded. (6) Survival data: OS was recorded from diagnosis to mortality due to any cause. The corresponding formulas used are as follows:

$$\mathrm{BMI} = \mathrm{weight(kg)/height^2\ (m^2)}$$
$$\mathrm{FFMI} = \mathrm{FFM/height\ (m^2)}$$
$$\mathrm{ASMI(kg/m^2)} = \mathrm{ASM/height^2\ (m^2)}$$
$$\mathrm{SII} = (\mathrm{platelets} \times \mathrm{neutrophils/lymphocytes})/1,000$$

2.2. Reduced muscle mass

GLIM recommends measurement by dual-energy absorptiometry or other validated body composition measures including BIA for detecting reduced muscle mass (RMM). In this study, RMM was confirmed based on ASMI (<7.0 kg/m^2 for men and <5.7 kg/m^2 for women) or FFMI (<17 kg/m^2 for men and <15 kg/m^2 for women) as measured by BIA.

2.3. Statistical analysis

Data were analyzed using SPSS for Windows version 26.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY) and R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria).

A Venn plot was drawn to depict the overlap and division of RMM diagnosed by FFMI and ASMI. The Kolmogorov–Smirnov test was used to confirm normal distributions of continuous data. An independent *t*-test was used for normally distributed data. Counting data were analyzed using the chi-square test, and the *z*-test with Bonferroni adjustment was adopted for multiple comparisons. Next, propensity score match (PSM) analysis was performed. Multicollinearity was tested by linear regression analysis; a variance inflation factor (VIF) >10 was considered to indicate collinearity. Conditional logistic regression analysis was adopted to evaluate the efficacy of FFMI and ASMI in diagnosing

10.3389/fnut.2023.1172610

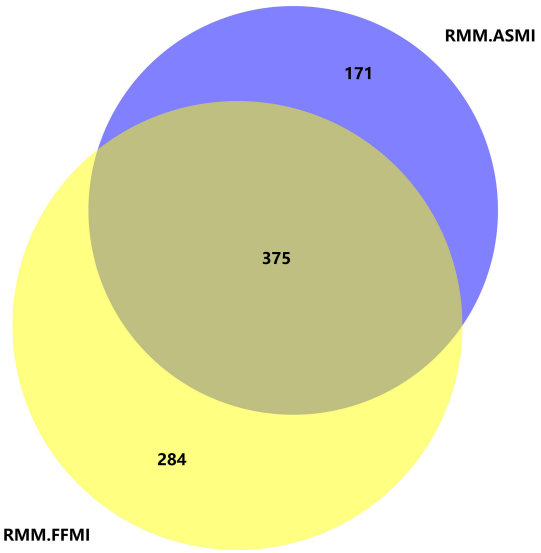


FIGURE 1
RMM diagnosed with ASMI and FFMI. RMM, reduced muscle mass; ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index.

severe malnutrition (PG-SGA $\geq$ 9). The shared frailty model for survival analysis was then performed to determine the efficacy of RMM in predicting survival benefit. A *P*-value of < 0.05 was considered to indicate statistical significance.

3. Results

3.1. RMM detected by ASMI and FFMI

Among the 2,477 participants involved, 546 (22.0%) and 659 (26.6%) participants were diagnosed with RMM by ASMI (RMM.ASMI group) or FFMI (RMM.FFMI group), respectively. There was an overlap of 375 cases, comprising 68.7% of the RMM.ASMI group and 56.9% of the RMM.FFMI group (Figure 1). In total, 33.3% of patients in the RMM.ASMI group were men, significantly less than in the RMM.FFMI group (46.9%, $P < 0.001$). Age, smoking history, drinking history, comorbidities, tumor sites, and metastasis did not differ between the groups ($P > 0.05$) (Supplementary material 2).

3.2. Characteristics of RMM as defined by AMSI and FFMI

No significant difference was detected in albumin, CRP, leukocytes, neutrophils, lymphocytes, platelets, NLR, PLR, and SII between the groups ($P > 0.05$). Then, the anthropometric measurements were compared after stratifying by sex. BMI, MAC, TSF, and CC were all significantly larger in the RMM.FFMI group for both sexes ($P < 0.05$) (Table 1). HGS did not differ between the groups in both sexes ($P > 0.05$).

TABLE 1 Serum nutrition, inflammation indices, and anthropometric measurements of RMM defined by ASMI and FFMI (mean ± SD)/[*n* (%)].

Variables	RMM		*t*	*P*
	ASMI	FFMI		
Albumin (g/L)	37.84 ± 5.27	38.24 ± 5.26	−1.325	0.186
CRP (mg/L)	19.93 ± 35.75	19.25 ± 32.62	0.276	0.782
Leukocyte ($*10^9$/L)	6.94 ± 3.97	6.76 ± 3.08	0.829	0.407
Neutrophils ($*10^9$/L)	4.89 ± 3.81	4.70 ± 3.22	0.953	0.341
Lymphocytes ($*10^9$/L)	1.53 ± 0.69	1.96 ± 0.80	−1.017	0.309
Platelets ($*10^9$/L)	243.03 ± 97.28	240.82 ± 93.35	0.401	0.689
NLR	4.11 ± 4.40	3.89 ± 4.33	0.886	0.376
PLR	188.51 ± 110.87	184.25 ± 151.30	0.546	0.585
SII[#]	1,020.45 ± 466.66	939.08 ± 181.74	1.064	0.288
Female				
BMI (kg/m^2)	19.60 ± 1.89	20.53 ± 2.76	−5.210	< 0.001
MAC (cm)	23.92 ± 2.59	24.62 ± 3.10	−3.282	0.001
TSF (mm)	15.14 ± 5.52	16.79 ± 6.21	−3.740	< 0.001
CC (cm)	30.54 ± 3.14	31.19 ± 3.38	−2.684	0.007
HGS (kg)	17.52 ± 6.12	17.50 ± 6.01	0.033	0.974
Male				
BMI (kg/m^2)	18.63 ± 1.14	20.11 ± 2.07	−10.222	< 0.001
MAC (cm)	23.64 ± 2.14	24.66 ± 2.58	−4.718	< 0.001
TSF (mm)	11.33 ± 4.54	13.44 ± 5.31	−4.662	< 0.001
CC (cm)	30.82 ± 3.14	32.07 ± 3.87	−3.653	< 0.001
HGS (kg)	26.03 ± 7.75	26.89 ± 7.73	−1.199	0.231

[#]SII = platelets*neutrophils/lymphocytes. RMM, reduced muscle mass; ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index; CRP, C-reaction protein; NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; SII, systematic inflammation index; MAC, mid-arm circumference; TSF, triceps skinfold thickness; CC, maximum calf circumference; HGS, hand-grip strength.

3.3. Malnutrition in the RMM.ASMI and RMM.FFMI groups

A 1:1 matched dataset was constructed by PSM for further analysis. Baseline information (age, smoking history, drinking history, comorbidities, tumor sites, and metastasis) was matched considering severe malnutrition (PG-SGA $\geq$ 9) as a dependent variable. The matched dataset contained 810 cases; all basic characteristics were comparable ($P > 0.05$) (Table 2; Supplementary material 3). Leukocyte data were excluded due to collinearity (Supplementary material 4). A conditional logistic

TABLE 2 Characteristics of the involved population before and after propensity score matching.

Variables	Before			After		
	PG-SGA 0–8	PG-SGA ≥9	*P*	PG-SGA 0–8*n* = 405	PG-SGA ≥ 9 *n* = 405	*P*
Age (year)			<0.001			0.880
<65	1,661 (81.0)	286 (67.1)		276 (68.1)	274 (67.7)	
≥65	390 (19.0)	140 (32.9)		129 (31.9)	131 (32.3)	
Sex			<0.001			0.779
Male	805 (39.1)	214 (50.2)		206 (50.9)	202 (49.9)	
Female	1,246 (60.8)	212 (49.8)		199 (49.1)	203 (50.1)	
Smoking			0.001			0.888
Yes	782 (38.1)	200 (46.9)		221 (54.6)	219 (54.1)	
No	1,269 (61.9)	226 (53.1)		184 (45.4)	186 (45.9)	
Drinking			0.050			0.933
Yes	369 (18.0)	94 (22.1)		91 (22.5)	90 (22.2)	
No	1,682 (82.0)	332 (77.9)		314 (77.5)	315 (77.8)	
Comorbidity			0.887			0.270
No	1,939 (79.9)	336 (78.9)		316 (78.0)	321 (79.3)	
Hypertension	308 (15.0)	67 (15.7)		57 (14.1)	63 (15.6)	
Diabetes	104 (5.1)	23 (5.4)		32 (7.9)	21 (5.2)	
Tumor site			<0.001			0.464
Lung	740 (36.1)a	128 (30.0)b		126 (31.1)	120 (29.6)	
Digestive tract	398 (19.4)a	178 (41.8)b		180 (44.4)	172 (42.5)	
Liver	111 (5.4)a	55 (12.9)b		35 (8.6)	51 (12.6)	
Breast	660 (32.2)a	39 (9.2)b		41 (10.1)	37 (9.1)	
Gynecology	142 (6.9)a	26 (6.1)a		23 (5.7)	25 (6.2)	
Metastasis			<0.001			0.533
M0	1,529 (78.7)	286 (70.6)		294 (72.6)	286 (70.6)	
M1	415 (21.3)	119 (29.4)		111 (27.4)	119 (29.4)	

PG-SGA, Patient-Generated Subjective Global Assessment.

regression showed that RMM.ASMI was not an influential factor in the univariate model ($P = 0.122$). However, RMM.FFMI was an influential factor of severe malnutrition even in the multivariate model, with HR = 4.070 (95% CI 2.753–6.019, $P < 0.001$) after adjusting all involved characteristics (Table 3).

3.4. Efficacy of RMM in survival prediction

To determine the efficacy of RMM as detected by ASMI and FFMI, survival analysis was performed in the whole 2,477 cases, followed by sensitivity analysis in subgroups. In the general population, RMM.ASMI was a predictive factor (HR = 1.301, 95% CI 1.034–1.635, $P = 0.025$) in the univariate Cox regression analysis but not in the multivariate analysis (Forward: Wald). Apart from the baseline factors, albumin (HR = 0.953, 95% CI 0.924–0.982, $P = 0.001$), neutrophils (HR = 1.071, 95% CI 1.020–1.126, $P = 0.006$), and TSF (HR = 0.959, 95% CI 0.936–0.982, $P = 0.001$) were considered as influential factors of OS (Table 4).

Next, two 1:1 matched subgroups were constructed, which were adjusted by all baseline factors (age, smoking history, drinking history, comorbidities, tumor sites, and metastasis) and took RMM.FFMI and RMM.ASMI as the dependent variables, respectively. The RMM.ASMI subgroup contained 1,034 cases and the RMM.FFMI subgroup contained 1,232 cases. Since the baseline characteristics were already matched, shared frailty survival analysis was performed in each subgroup. As shown in Figure 2, RMM.ASMI behaved as a predictive factor of OS in both subgroups (HR = 1.318, 95% CI 1.060–1.639, $P = 0.013$ in the RMM.ASMI subgroup, HR = 1.315, 95% CI 1.077–1.607, $P = 0.007$ in the RMM.FFMI subgroup) but RMM.FFMI did not in any subgroup ($P > 0.05$). Thus, Cox regression was performed in the subgroups to further clarify the role of RMM.ASMI in predicting OS (Table 5). In both subgroups, only albumin (HR = 0.961, 95% CI 0.931–0.992, $P = 0.015$; HR = 0.941, 95% CI 0.912–0.970, $P <$

10.3389/fnut.2023.1172610

TABLE 3 Conditional logistic regression analysis for malnutrition.

Variables	Univariable		Multivariable	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Albumin (g/L)	0.923 (0.868–0.982)	<0.001	0.937 (0.906–0.968	<0.001
CRP (mg/L)	1.004 (0.994–1.014)	0.452		
Neutrophils ($*10^9$/L)	1.391 (1.024–1.889)	0.035		
Lymphocytes ($*10^9$/L)	0.763 (0.418–1.393)	0.379		
Platelets ($*10^{10}$/L)	1.002 (0.995–1.009)	0.595		
NLR	0.877 (0.656–1.174)	0.378		
PLR	1.007 (0.998–1.016)	0.109		
SII.Model[#]	0.905 (0.819–1.000)	0.049		
BMI (kg/m^2)	1.003 (0.850–1.183)	0974		
MAC (cm)	0.963 (0.840–1.103)	0.586		
TSF (mm)	1.024 (0.985–1.066)	0.231		
CC (cm)	0.954 (0.855–1.065)	0.404		
HGS (kg)	0.972 (0.935–1.011)	0.158		
RMM.ASMI	2.094 (0.821–5.343)	0.122		
RMM.FFMI	3.675 (1.627–8.302)	0.002	4.070 (2.753–6.019)	<0.001

[#]SII.Model=SII/100, which is calculated merely for model input given practical clinical practice. CRP, C-reaction protein; NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; SII, systematic inflammation index; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold thickness; CC, maximum calf circumference; HGS, hand-grip strength; RMM, reduced muscle mass; ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index. ∗means multiplication.

0.001) and platelets (HR = 1.004, 95% CI 1.002–1.006, $P = 0.026$; HR = 1.003, 95% CI 1.002–1.004, $P = 0.002$) were maintained in the Cox regression model. RMM.ASMI was not retained in both models.

4. Discussion

RMM, measured by FFMI and ASMI, was considered a phenotypic criterion for malnutrition in the GLIM guideline. The prevalence of RMM diagnosed by FFMI and ASMI was 22.0 and 26.2%, respectively, with approximately three-fifths overlapping. As shown by sensitive analysis, FFMI was significant in diagnosing severe malnutrition. However, in survival analysis, although the effect of ASMI was always significant in univariate regression,

TABLE 4 Cox regression analysis for overall survival in the general population.

Variables	Univariable		Multivariable	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Age (year)	1.176 (0.926–1.494)	0.184		
Sex	0.763 (0.606–0.962)	0.022		
Smoking	1.453 (1.155–1.827)	0.001		
Drinking	1.050 (0.801–1.377)	0.724		
Comorbidity				
Hypertension	1.092 (0.798–1.496)	0.582		
Diabetes	1.156 (0.732–1.826)	0.535		
Tumor site				
Digestive tract	0.421 (0.324–0.547)	<0.001	0.524 (0.367–0.748)	<0.001
Liver	1.050 (0.750–1.470)	0.777	1.149 (0.728–1.813)	0.552
Breast	0.156 (0.079–0.306)	<0.001	0.450 (0.193–1.051)	0.065
Gynecology	0.233 (0.114–0.476)	<0.001	0.414 (0.166–1.031)	0.058
Metastasis	3.745 (2.967–4.728)	<0.001	3.349 (2.443–4.592)	<0.001
Albumin (g/L)	0.951 (0.931–0.973)	<0.001	0.953 (0.924–0.982)	0.001
CRP (mg/L)	1.005 (1.002–1.009)	0.003		
Neutrophils ($*10^9$/L)	1.058 (1.023–1.094)	0.001	1.071 (1.020–1.126)	0.006
Lymphocytes ($*10^9$/L)	0.833 (0.704–0.986)	0.033		
Platelets ($*10^{10}$/L)	1.016 (1.004–1.027)	0.008		
NLR	1.001 (0.993–1.009)	0.815		
PLR	1.000 (1.000–1.001)	0.058		
SII.Model[#]	1.002 (0.999–1.006)	0.226		
BMI (kg/m^2)	0.928 (0.894–0.962)	<0.001		
MAC (cm)	0.939 (0.905–0.973)	0.001		
TSF (mm)	0.960 (0.941–0.979)	<0.001	0.959 (0.936–0.982)	0.001
CC (cm)	0.962 (0.933–0.992)	0.012		
HGS (kg)	0.995 (0.983–1.007)	0.420		
RMM.ASMI	1.301 (1.034–1.635)	0.025		
RMM.FFMI	1.141 (0.905–1.440)	0.265		

[#]SII.Model=SII/100, which is calculated merely for model input given practical clinical practice. CRP, C-reaction protein; NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; SII, systematic inflammation index; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold thickness; CC, maximum calf circumference; HGS, hand-grip strength; RMM, reduced muscle mass; ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index.

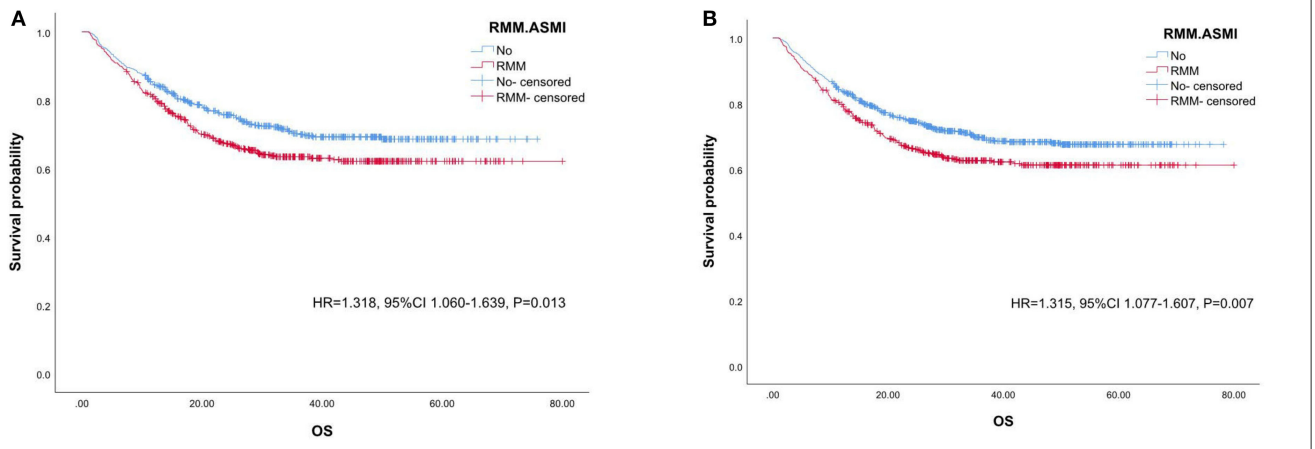


FIGURE 2
Kaplan–Meier survival analysis of RMM.ASMI in OS. **(A)**. the RMM.ASMI subgroup, **(B)**. the RMM.FFMI subgroup. RMM, reduced muscle mass; ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index; OS, overall survival.

neither FFMI nor ASMI was retained in multivariate regressions. These results are due to intrinsic differences between FFMI and ASMI and implied their discrimination in clinical utility, which should be paid attention.

Chronic inflammation and depletion accompany cancer over the whole process (20). Infection and non-infectious inflammation are the initial stages of malignant lesions (21), with persistent crosstalk between inflammation and cancer, mainly converging at the level of the transcription factors such as signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB (NF-κB). Downstream cytokines including IL-6, TNF-α, and TGF-beta also deteriorate energy and protein metabolism (22). The increased metabolism and deteriorated catabolism induce changes in body composition, especially to the muscle tissue, and induce even the occurrence of sarcopenia and cachexia. In addition, treatment-related adverse events, especially nausea, vomiting, and other gastrointestinal symptoms, aggravate the situation.

The FFMI is calculated based on the FFM, which represents the body composition except fat including muscle and bone mass, and organs such as the liver. The ASMI, calculated based on the ASM, merely refers to the skeletal muscle mass in the limbs. Thus, the FFM is more consistent with the weight and BMI, as supported by the present results. PG-SGA is the gold standard of malnutrition assessment for cancer patients, based on weight loss, symptoms, activities and function, metabolic demand (largely refers to inflammation), and physical examinations. As a part of the latter, the muscle assessment includes parts of the torso such as the temples (temporalis muscle), clavicle (pectoralis and deltoids), shoulders (deltoids), interosseous muscles, scapula (latissimus dorsi, trapezius, and deltoids), and a small part of the muscles in the thigh (quadriceps) and calf (gastrocnemius). Therefore, RMM as measured by FFMI closely relates to the severe malnutrition detected by PG-SGA $\geq$ 9. ASM can be persevered by physical activity, especially resistance exercises, as recommended by the guidelines in sarcopenia (23). A detectable ASM loss implies more severe exhaustion. In the updated guidelines, HGS, the functional parameter of ASM, has a higher priority than absolute ASM in diagnosing sarcopenia. HGS was significantly, and similarly, reduced in both RMM groups diagnosed by FFMI and ASMI. However, BMI, MAC, TSF, and CC were all significantly lower in the RMM.ASMI group for both sexes, which suggested that ASM loss indicates a worse situation of depletion. That is why the RMM diagnosed by ASMI and not the RMM diagnosed by FFMI is an influential factor in survival.

However, the decreased ASMI was not included in the multivariate regression model. Parameters such as platelets, neutrophils, TSF, and BMI were unstable in a sensitivity analysis. In contrast, albumin always contributed to nutritional status and survival. Gupta et al. (24) performed a systematic review and found that albumin was of predictive value in survival in various cancer types. Albumin, accounting for approximately 50% of the total protein content, is the most common clinical indicator of nutritional status and is involved in the inflammatory response, acting as an acute-phase protein (25, 26). In addition, serum albumin allows a simple estimation of visceral protein function. Suppressed albumin synthesis is partly due to the activation of cytokines such as IL-1, IL-6, and TNF-α (27), a common observation in cancer, resulting in hypoalbuminemia. This increases the demand for certain amino acids, which, in case of inadequate dietary intake, may mobilize the breakdown of skeletal muscle (28). Alternatively, the oxidative stress induced by cytokines may increase the permeability of the microvascular barriers, thus allowing an increased albumin leakage through capillaries (29, 30). Furthermore, the presence of metastatic tumor cells in the liver may induce the Kupffer cells to produce inflammatory cytokines and chemokines, which foster monocyte infiltration into the liver. These may modulate albumin synthesis by hepatocytes and support tumor development by angiogenesis and T-cell suppression (31). Thus, albumin levels can serve as good indicators of nutritional status and cancer prognosis.

There are some limitations to this study. First, selection bias might exist because this was a retrospective study and the demand for complete clinical data. Second, despite adopting PSM and sensitive analyses, the value of unstable parameters such as platelets,

TABLE 5 Cox regression analysis for overall survival in subgroups[#].

Variables	RMM.ASMI		RMM.FFMI	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Albumin (g/L)	0.961 (0.931–0.992)	0.015	0.941 (0.912–0.970)	<0.001
Platelets (*10^{10}/L)	1.004 (1.002–1.006)	0.026	1.003 (1.002–1.004)	0.002

[#]CRP, Neutrophils, Lymphocytes, NLR, PLR, SII, BMI, MAC, TSF, CC, HGS, RMM.ASMI, and RMM.FFMI were also involved as covariates but not displayed in the table since they were not retained in the multivariable Cox regression models ($P > 0.05$). CRP, C-reaction protein; NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; SII, systematic inflammation index; BMI, body mass index; MAC, mid-arm circumference; TSF, triceps skinfold thickness; CC, maximum calf circumference; HGS, hand-grip strength; RMM, reduced muscle mass; ASMI, appendicular skeletal muscle mass index; FFMI, fat-free mass index.

neutrophils, TSF, and BMI requires further analysis to provide a confidential reference.

In conclusion, this study revealed that RMM indicates negative clinical outcomes and highlighted the intrinsic differences between FFM and ASM, suggesting the need for rational choice in clinical practices to support future decision-making in cancer patients. More importantly, RMM as defined by FFMI predicts nutritional status, whereas when defined by ASMI, it is related to poor survival in cancer patients. In addition, serum albumin appeared to be an influential factor for both malnutrition and survival. The instability of other parameters revealed by sensitive analysis reminds clinical practitioners of precious opinions on these parameters.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Hospital of Jilin University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors made a significant contribution to the study reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas took part in drafting, revising, or critically reviewing the article gave final approval of the version to be published have agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the study.

Funding

WJ was funded by the Doctor of Excellence Program, The First Hospital of Jilin University (JDYY-DEP-2022024).

Acknowledgments

The authors would like to thank the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) Project of China (registered at chictr.org.cn, ChiCTR1800020329) for the substantial study on data collection and patient follow-up.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1172610/full#supplementary-material

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2018) 68:394–424. doi: 10.3322/caac.21492

2. Ravasco P. Nutrition in Cancer Patients. *J Clin Med.* (2019) 8:1211. doi: 10.3390/jcm8081211

3. Zhang X, Pang L, Sharma SV Li R, Nyitray AG, Edwards BJ. Malnutrition and overall survival in older patients with cancer. *Clin Nutr.* (2021) 40:966–77. doi: 10.1016/j.clnu.2020.06.026

4. Kiss N, Curtis A. Current insights in nutrition assessment and intervention for malnutrition or muscle loss in people with lung cancer: a narrative review. *Adv Nutr.* (2022) 13:2420–32. doi: 10.1093/advances/nmac070

5. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr.* (2017) 36:49–64. doi: 10.1016/j.clnu.2016.09.004

6. Soeters PB, Reijven PL, Schols JM, Halfens RJ, Meijers JM, van Gemert WG. A rational approach to nutritional assessment. *Clin Nutr.* (2008) 27:706–16. doi: 10.1016/j.clnu.2008.07.009

7. Chinese Society of Nutritional Oncology. Characteristics of malnutrition in malignant cancer patients. *Electron J Metab Nutr Cancer*, (2020) 7:276–82. doi: 10.16689/j.cnki.cn11-9349/r.2020.03.006

8. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J Parenter Enteral Nutr.* (2014) 38:196–204. doi: 10.1177/0148607113502674

9. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol.* (2014) 15:e493–503. doi: 10.1016/S1470-2045(14)70263-3

10. Nilsson A, Wilhelms DB, Mirrasekhian E, Jaarola M, Blomqvist A, Engblom D. Inflammation-induced anorexia and fever are elicited by distinct prostaglandin dependent mechanisms, whereas conditioned taste aversion is prostaglandin independent. *Brain Behav Immun.* (2017) 61:236–43. doi: 10.1016/j.bbi.2016.12.007

11. Matsuwaki T, Shionoya K, Ihnatko R, Eskilsson A, Kakuta S, Dufour S, et al. Involvement of interleukin-1 type 1 receptors in lipopolysaccharide-induced sickness responses. *Brain Behav Immun.* (2017) 66:165–76. doi: 10.1016/j.bbi.2017.06.013

12. Laviano A, Meguid M M, Rossi-Fanelli F. Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. *Lancet Oncol.* (2003) 4:686–94. doi: 10.1016/S1470-2045(03)01247-6

13. Han J, Meng Q, Shen L, Wu G. Interleukin-6 induces fat loss in cancer cachexia by promoting white adipose tissue lipolysis and browning. *Lipids Health Dis.* (2018) 17:14. doi: 10.1186/s12944-018-0657-0

14. Schmidt SF, Rohm M, Herzig S, Diaz MB. Cancer cachexia: more than skeletal muscle wasting. *Trends Cancer.* (2018) 4:849–60. doi: 10.1016/j.trecan.2018.10.001

15. White JP, Puppa MJ, Sato S, Gao S, Price RL, Baynes JW, et al. IL-6 regulation on skeletal muscle mitochondrial remodeling during cancer cachexia in the ApcMin/+ mouse. *Skelet Muscle.* (2012) 2:14. doi: 10.1186/2044-5040-2-14

16. Ding H, Jiang N, Liu H, Liu X, Liu D, Zhao F, et al. Response of mitochondrial fusion and fission protein gene expression to exercise in rat skeletal muscle. *Biochim Biophys Acta.* (2010) 1800:250–6. doi: 10.1016/j.bbagen.2009.08.007

17. Pressoir M, Desné S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer.* (2010) 102:966–71. doi: 10.1038/sj.bjc.6605578

18. De Groot LM, Lee G, Ackerie A, van der Meij BS. Malnutrition screening and assessment in the cancer care ambulatory setting: mortality predictability and validity of the patient-generated subjective global assessment short form (PG-SGA SF) and the GLIM Criteria. *Nutrients.* (2020) 12:2287. doi: 10.3390/nu12082287

19. Jensen GL, Cederholm T, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. *JPEN J Parenter Enteral Nutr.* (2019) 43:32–40. doi: 10.1002/jcsm.12383

20. Coussens L M, Werb Z. Inflammation and cancer. *Nature.* (2002) 420:860–7. doi: 10.1038/nature01322

21. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer.* (2013) 13:759–71. doi: 10.1038/nrc3611

22. Nishikawa H, Goto M, Fukunishi S, Asai A, Nishiguchi S, Higuchi K. Cancer cachexia: its mechanism and clinical significance. *Int J Mol Sci.* (2021) 22:8491. doi: 10.3390/ijms22168491

23. Gharahdaghi N, Rudrappa S, Brook MS, Idris I, Crossland H, Hamrock C, et al. Testosterone therapy induces molecular programming augmenting physiological adaptations to resistance exercise in older men. *J Cachexia Sarcopenia Muscle.* (2019) 10:1276–94. doi: 10.1002/jcsm.12472

24. Gupta D, Lis C G. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J.* (2010) 9:69. doi: 10.1186/1475-2891-9-69

25. Zhou QP, Li XJ. C-reactive protein to albumin ratio in colorectal cancer: a meta-analysis of prognostic value. *Dose Response.* (2019) 17:1559325819889814. doi: 10.1177/1559325819889814

26. Yu YT, Liu J, Hu B, Wang RL, Yang XH, Shang XL, et al. Expert consensus on the use of human serum albumin in critically ill patients. *Chin Med J (Engl).* (2021) 134:1639–54. doi: 10.1097/CM9.0000000000001661

27. Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. *J Clin Gastroenterol.* (2005) 39:S143–6. doi: 10.1097/01.mcg.0000155514.17715.39

28. Peterson S J, Mozer M. Differentiating sarcopenia and cachexia among patients with cancer. *Nutr Clin Pract.* (2017) 32:30–9. doi: 10.1177/0884533616680354

29. He P, Talukder M A H, Gao F. Oxidative stress and microvessel barrier dysfunction. *Front Physiol.* (2020) 11:472. doi: 10.3389/fphys.2020.00472

30. Van Loo G, Bertrand MJM. Death by TNF: a road to inflammation. *Nat Rev Immunol.* (2022) 23:289–303. doi: 10.1038/s41577-022-00792-3

31. Tacke F. Targeting hepatic macrophages to treat liver diseases. *J Hepatol.* (2017) 66:1300–12. doi: 10.1016/j.jhep.2017.02.026

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 20 July 2023
DOI 10.3389/fnut.2023.1128864

OPEN ACCESS

EDITED BY
Barbara Troesch,
Nutricia/Danone, Switzerland

REVIEWED BY
Sven Dittrich,
Friedrich-Alexander University Erlangen-Nürnberg, Germany
Xiangjun Han,
China Medical University, China

*CORRESPONDENCE
Zhiyu Liu
✉ lzydoct@163.com
Jing Jiang
✉ jujube521@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 21 December 2022
ACCEPTED 30 June 2023
PUBLISHED 20 July 2023

CITATION
Wang K, Xiao J, Li L, Li X, Yang Y, Liu Z and Jiang J (2023) The application of a medium-chain fatty diet and enteral nutrition in post-operative chylous leakage: analysis of 63 patients. *Front. Nutr.* 10:1128864. doi: 10.3389/fnut.2023.1128864

The application of a medium-chain fatty diet and enteral nutrition in post-operative chylous leakage: analysis of 63 patients

Ke Wang[1†], Jiaming Xiao[2†], Li Li[1], Xu Li[1], Yilun Yang[1], Zhiyu Liu[3*] and Jing Jiang[4*]

[1]Department of Clinical Nutrition, Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China, [2]Department of Nutrition and Food Hygiene, School of Public Health, Dalian Medical University, Dalian, Liaoning, China, [3]Department of Urological Surgery, Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China, [4]Department of Nursing, Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

Background: Post-operative chylous leakage (CL) is the pathologic leakage of chylomicron fluid after surgery. This retrospective study was performed to evaluate a uniform oral nutrition management strategy on the post-operative CL.

Methods: We retrospectively reviewed patients who developed post-operative CL and received consultation from a clinical nutritionist in seven departments of the Second Affiliated Hospital of Dalian Medical University from May 2020 to April 2022. We designed the oral nutrition intervention program which mainly standardized the type and amount of foods contained in the medium-chain triglyceride (MCT) diet. The influencing factors of curative efficacy were analyzed. Finally, binary logistic regression analysis was conducted to observe the relationship between curative efficacy and potentially predictive variables, including post-operative albumin, post-operative hemoglobin, surgical procedure, and drainage volume at consultation.

Results: Sixty-three patients with post-operative CL were included in this analysis. Of this number, 58 patients were cured successfully without other treatments. Three patients had a significantly prolonged recovery period, and the remaining two cases were treated by reoperation therapy. The leakage volume at the initiation of enteral intervention had no statistically significant difference in seven surgical departments and surgical sites (left, right, median, and bilateral). The length of stay (LOS) of patients with CL after the intervention was not significantly increased in cardiac, hepatobiliary, gastrointestinal, and urological surgeries. Patients with CL had longer LOS than those without CL in gynecology (P=0.044) and thyroid surgery departments (P=0.008). Each unit increase in post-operative hemoglobin would increase the probability of an effective outcome by 8%, which was statistically significant ($P = 0.037$).

Conclusion: In treating patients with post-operative CL, we recommend the MCT diet and EN as the first option, rather than fasting, parenteral nutrition (PN), or octreotide.

KEYWORDS

chylous leakage, nutritional intervention, medium-chain fatty diet, enteral nutrition, post-operation

1. Introduction

Chylous leakage (CL) is a pathological status in which chylomicron fluid leaks from the lymphatic vessels (1). CL is commonly associated with surgical trauma, abdominal malignancies, cirrhosis, and infection (2–4). In clinical settings, CL occurs mostly in patients after surgical trauma, and the incidence of CL is higher in tumor resection with lymphadenectomy (5). The incidence of CL after thyroid surgery is approximately 0.5–1.4% (6, 7). The incidence of CL after general thoracic surgery ranges from 0.4% to 3.9% (8, 9). CL may occur in 1–16% of patients after pancreatectomy (10, 11). CL occurs in ∼3.8%−5.1% of nephrectomy (12, 13) and approximately 0.3–7.4% in gynecology (14, 15). Patients with post-operative CL are often in a state of high energy expenditure and protein requirements due to traumatic stress. CL may lead to decreased blood volume, malnutrition, and a compromised immune system (16), severely affecting post-operative recovery, prolonging the length of stay (LOS), and even increasing mortality (17, 18). Four main clinical treatments are available: medium-chain triglyceride diet (MCT diet) [with or without enteral nutrition (EN)] or low-fat diet, parenteral nutrition (PN), drug therapy (somatostatin such as octreotide), and surgery (4, 19–21). However, there is no consensus on the optimal management of CL (22).

CL also lacks uniformity for a definitive diagnosis (17, 23–25). Generally, drainage fluid triglyceride levels >110 mg/dl may indicate the possibility of CL (26). Long-chain triglycerides (LCTs) are broken down in the intestine into chylomicrons, which enter the circulation through the lymphatics. Lymphatic vessels transporting chylomicrons form an elongated lymphatic structure with saccular dilatation called the cisterna chyli (CC) anterior to the l1–l2 vertebrae (24, 27). All lymphatic vessels together form the thoracic duct (TD), except for the lymphatic vessels in the right upper trunk and right upper extremity (15). Triglycerides from the lymphatic vessels leak into the abdominal cavity to form chylous ascites (CA) (28). Collection in the pleural cavity results in chylothorax (24). Chyluria disease (CD) can be considered when a fistulous communication between the lymphatic trunk or lymphatic vessels and the urinary tract contributes to intermittent or continuous milky white urine (29, 30) because of various causes. CL can occur when the TD, CC, and lymphatic trunk or lymphatic vessels around the intestine are blocked or ruptured (31, 32). CL is distinguished from lymphatic leakage by the pathological leakage of chylomicron rather than pure lymphocytes from broken lymphatic vessels after digestion and absorption through the gastrointestinal tract. Therefore, drainage fluid appears usually milky white or even pink (2, 33). Whereas, short- and medium-chain triglycerides (MCTs) enter the liver directly through the hepatic portal vein (34). A more direct basis for confirmation is that the fluid becomes clear after the cessation of the LCT diet (35).

The intervention of an MCT diet could not only meet patients' nutritional needs and reduce their discomfort but also reduce chylomicron and promote lymphatic vessel healing (36, 37). By observing the outcomes of previous dietary interventions in patients with CL, we found that by severely restricting the intake of LCT, the drainage fluid would immediately become clear. Conversely, it would quickly become a turbid liquid. In the present study, 63 patients who underwent thyroid surgery, cardiac surgery, thoracic surgery, hepatobiliary surgery, gastrointestinal surgery, and surgeries from urology and gynecology and had post-operative CL were evaluated retrospectively. We screened patients who underwent the same surgery during the same period as these CL patients did not develop CL. LOS between CL and non-CL patients was compared to discuss the effect of this nutritional management strategy. We also explore the factors that influence the effectiveness of this management strategy.

2. Methods

2.1. Patient selection and data collection

This study was approved by the ethics committee of our hospital. Certainly, all patients were given informed consent to the oral nutritional intervention they received. After the approval, we retrospectively collected and analyzed the data of patients with CL after surgery between March 2020 and April 2022.

The study retrospectively reviewed patients who were provided nutritional intervention because of the post-operative presence of milky, murky, pinky, whitish, or yellowish drained fluid from March 2020 to April 2022 at the Second Affiliated Hospital of Dalian Medical University, People's Republic of China. Sixty-three CL patients who had undergone cardiac, thyroid, thoracic, hepatobiliary, gastrointestinal, urological, and gynecological surgeries were included (Figure 1). Clinical data were collected retrospectively from a review of electronic medical records. We collected patient data on demography, preoperative BMI, surgical procedure and site, post-operative nutrition-related laboratory results (albumin and hemoglobin), daily volume of CL, LOS, and days of CL. These patients were classified according to the surgical site (medial, left, right, and bilateral sites of the body) and compared statistical differences in the amount of drainage among the four sites of surgery. A logistical regression analysis was used to assess the association between potential risk factors (surgical procedure,

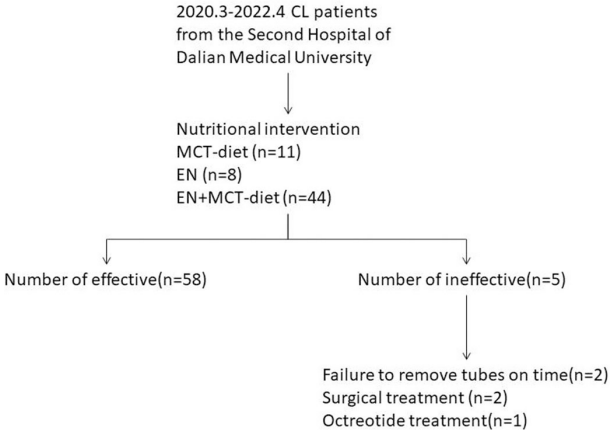


FIGURE 1
Flow diagram.

volume at consultation, post-operative hemoglobin, and post-operative albumin) and efficacy.

2.2. Identification and management of CL

CL was clinically diagnosed after the observation of a milky, murky, pinky, whitish, or yellowish drainage fluid. In cases of suspected CL but unclear clinical features, drainage fluid triglyceride concentration was determined to differentiate between CL and lymphatic leak. A concentration of >1.2 mmol/L confirmed a diagnosis of CL. Not all such cases underwent fluid triglyceride concentration determination, but nutritional interventions were nonetheless performed.

2.3. Oral nutritional intervention program

The nutritional intervention program was provided by nutritionists from the Clinical Nutrition Department in our institution. Patients' energy requirements were calculated using the H–B equation, and protein requirements were set to 1.0–1.5 g/kg body weight according to patients' individual situations. The diet and enteral formula in our nutrition strategy were standardized. Briefly, we provided the MCT diet consisting of rice or steamed bread (containing 200 g of rice or flour), 500 g of vegetables, 6 egg whites, 6 g of salt, 250 ml of skim milk, and 25 g of coconut oil. The diet provides ∼1,200 kcal of energy and ∼45 g of protein. Fruits of the patient's choice (except those with high-fat content, such as durian and avocado) were usually allowed. All other foods were excluded. The taste and texture of this diet are similar to those of a normal Chinese diet. The diet was supplemented with low-fat EN (Yi di su, Hangzhou Nutrition Biotechnology Co., Ltd) and whey protein powder (Nutrasumma, Qingdao Nutrasumma Health Technology Co., Ltd) between meals when the dietary intake of protein and energy was inadequate. The MCT diet was given when the patient was able to eat a regular diet. A low-fat EN (Yi di su) and whey protein powder (Nutrasumma) were provided to meet the patient's energy and protein demands when only a liquid diet was available (Table 1). The drainage tubes were removed at the discretion of the surgeon, and ordinarily, a volume of <30–50 ml/24 h of liquid from the tube was an indication for tube removal. Patients continued the MCT diet for 1–2 weeks after the removal of the drainage tube before transitioning to normal meals. When fluid drained from the drainage tube does not reduce in volume after the oral diet for 3 consecutive days, patients were fasted off water and diet and administered PN or growth inhibitor drugs (octreotide). At the discretion of the surgeons or nutritionists, a second surgery procedure should be performed. If the tube is not removed by the time the patient is discharged, discharge instructions are given by the nutritionists from the Clinical Nutrition Department. Such patients would continue taking the MCT diet, whey protein powder, and fat-soluble vitamin supplements at home. Patients were provided with full diet recommendations on types and quantities of food allowed and foods to be excluded (Table 2).

TABLE 1 Carbohydrates, proteins (amino acids), and fats in the MCT diet and low-fat EN.

	MCT diet	Low-fat formula	Whey Protein
	Provided by dietitian	Yi di su®	Nutrasumma®
Carbohydrates	12.8	18.6	0
Proteins	3.75	4.3	25
Fats	2.08	0.43	0

Each value was expressed in g/100 kcal.

TABLE 2 Dietary instructions for patients with CL.

Types of food	Our suggestion
Staple foods	Use steaming and boiling cooking methods; avoid frying, deep-frying, and foods made with oil
Animal and seafoods	Egg whites are allowed; animal foods, such as egg yolks, fish, shrimp, and meat are not allowed
Dairy products	Skimmed milk and skimmed yogurt can be consumed; avoid whole milk and its products
Bean products	Not allowed to consume
Vegetable category	Allowed to consume
Fruit category	Aside from fruits with high-fat content, such as durian and avocado, all others can be consumed
Oils	Food should be cooked with coconut oil but not with animal or vegetable oils
Whey protein powder	Based on the patient's daily requirement minus the protein content of the MCT diet
Multivitamin tablets	One tablet a day

2.4. Statistical analysis

A normality test was performed for all continuous variables. Albumin levels before and after intervention were normal distribution, presented as mean ± SD. Other data were skewed distribution, presented as median (ranges). Categorical variables were compared using the χ^2 test or Fisher's exact test. In comparing categorical data using Pearson's χ^2 test, Fisher's exact test was used when the number of cells was <5. The Mann–Whitney U-test or variance analysis was used to compare multiple continuous independent samples. The Wilcoxon or Student's *t*-test was used to compare two independent samples. Additionally, binary regression analysis was used to evaluate the potential impact of interested predictors on the efficiency of intervention, and factors with a *p*-value of < 0.05 (including surgery procedure, leakage volume at the consultation, post-operative albumin, and post-operative hemoglobin) were included in logistic regression analysis. Statistical significance was defined as a *p*-value of <0.05. All statistical analyses were performed using the Statistical Package for Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic and baseline characteristics of patients

We collected data on all patients with CL who underwent oral nutritional intervention from March 2020 to April 2022. Of the 63 patients, 26 were men and 37 were women. Their age ranged from 31 to 83 years (median, 61), and their BMI ranged from 15 to 34 kg/m^2 (median, 23.9). Surgical sites were divided into middle, left, right, and bilateral according to the location of the surgical site in the body. Location on the middle side was performed in 11 patients (17.5%), on the left side in 18 patients (28.6%), on the right side in 17 patients (27.0%), and on the bilateral sides in 17 patients (27.0%). Types of surgeries were thyroid surgery in 12 patients (19.0%), cardiovascular surgery in 6 patients (9.5%), thoracic surgery in 2 patients (3.2%), hepatobiliary surgery in 4 patients (6.3%), gastrointestinal surgery in 24 patients (38.1%), urological surgery in 5 patients (7.9%), and gynecological surgery in 10 patients (15.9%). These patients were classified according to surgical sites (medial, left, right, and bilateral sites) and compared with the leakage volume of onset of intervention among the four sites of surgery. The volume of fluid was 110 (67–1,660) (ml) for patients with a middle surgical site, 120 (20–500) (ml) for patients with a left-sided surgical site, 220 (44–510) (ml) for patients with a right-sided surgical site, and 95 (30–535) (ml) for patients with a bilateral site. No statistically significant difference in drainage volume among the four groups was recorded ($P = 0.422$). The leakage volume of onset of intervention was 195 (80–598) (ml) for patients with thyroid surgery, 525 (185–1,020) (ml) for patients with cardiovascular surgery, 1,070 (1,020–1,120) (ml) for patients with thoracic surgery, 625 (250–910) (ml) for patients with hepatobiliary surgery, 137 (34–630) (ml) for patients with gastrointestinal surgery, 610 (360–1,440) (ml) for patients with urological surgery, and 485 (160–1,000) (ml) for patients with gynecological surgery. In this study, among the surgery departments, there was a statistically significant difference in drainage volume among different types of surgeries ($P < 0.05$) (Table 3).

TABLE 3 Patients' demographics.

Parameter		Median/*n*	Range/%
Age (yr)		61	31–83
Sex	Men	26	41.3
	Women	37	58.7
BMI (kg/m^2)		23.9	15–34
Location of surgery* (*n*)	Middle	11	17.5
	Left	18	28.6
	Right	17	27.0
	Bilateral	17	27.0
Types of surgeries (*n*)	Thyroid surgery	12	19.0
	Cardiac surgery	6	9.5
	Thoracic surgery	2	3.2
	Hepatobiliary surgery	4	6.3
	Gastrointestinal surgery	24	38.1
	Urological surgery	5	7.9
	Gynecological surgery	10	15.9
Leakage volume of onset of intervention (ml)			
Location of surgery*	Middle	110	67–1,660
	Left	120	20–500
	Right	220	44–510
	Bilateral	95	30–535
Types of surgeries#	Thyroid surgery	195	80–598
	Cardiac surgery	525	185–1,020
	Thoracic surgery	1,070	1,020–1,120
	Hepatobiliary surgery	625	250–910
	Gastrointestinal surgery	137	34–630
	Urological surgery	610	360–1,440
	Gynecological surgery	485	160–1,000

#The leakage volume of onset of intervention was $P < 0.05$ between different departments.
*It is divided into middle, left, right, and bilateral according to the location of the surgical site in the body.

3.2. Incidence and management of CL

Among all patients, 12 patients were from thyroid patients (CL incidence 3.72%), 6 patients were from cardiovascular surgical patients (CL incidence 5.22%), 4 patients were from hepatobiliary patients (CL incidence 2.25%), 24 patients were from gastrointestinal surgical patients (CL incidence 2.15%), 5 patients were from urological patients (CL incidence 1.28%), and 10 patients were from gynecologic surgical patients (CL incidence 2.77%).

All patients had an initial oral nutritional intervention, 11 patients had an MCT diet, 44 patients had an EN plus MCT diet, and 8 patients had an EN. The chylous leakage volume began to decrease 1 day after starting the MCT and/or EN treatments in most of the seven types of surgeries cases. For most successful cases, the first 3 days of leakage volume tend to reduce rapidly (Figure 2).

One case from thyroid surgery had leakage volume changed from 345 ml to 500 ml after 3 days with the MCT diet plus EN, so a secondary surgery was performed. One case from thoracic surgery had no significant change in leakage volume after 2 days with EN, but had leakage volume changed from 1,125 ml to 1,610 ml

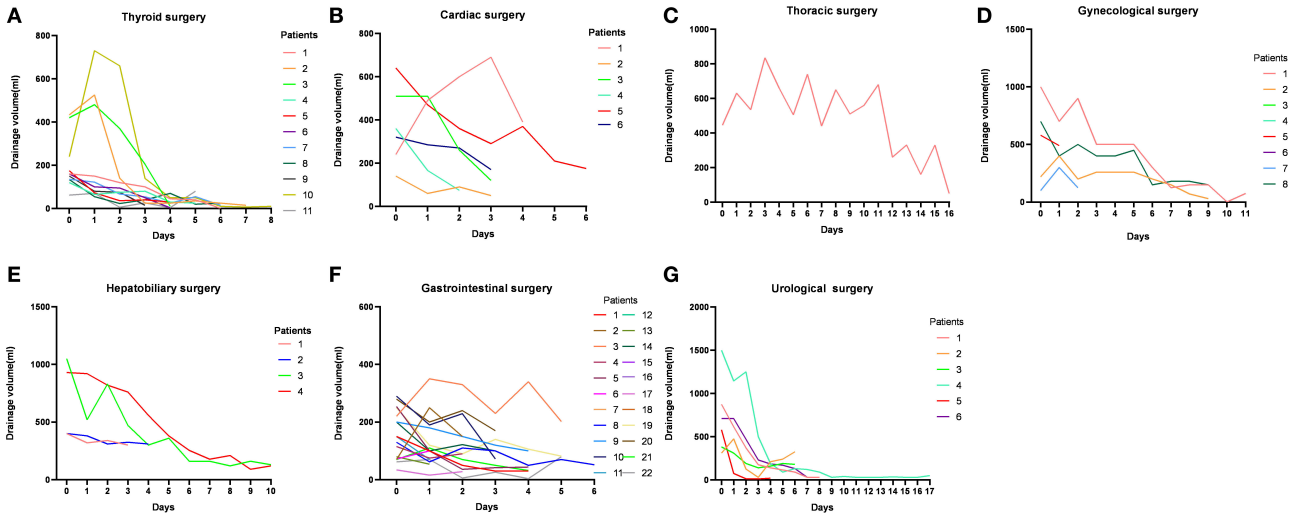


FIGURE 2
Daily changes in the volume of chylous leakage in successful cases in seven types of surgeries.

after fasting 5 days, so a secondary surgery was performed. Two cases from gastrointestinal surgery were discharged with a tube and at the first outpatient return visit still failed to be extubated. One case from gynecological surgery was readmitted for CL within 30 days.

3.3. Effectiveness of nutritional intervention

In this study, an effective oral nutritional intervention was defined as (1) tube removal before discharge; (2) tube was not extubated before discharge but extubated at the first outpatient return visit as scheduled; and (3) no readmission for CL within 30 days. An ineffective oral nutritional intervention was defined as (1) secondary surgery was implemented; (2) PN >50% energy; (3) use of octreotide; (4) discharged without extubation and the tube at the first outpatient return visit still failed to be extubated; and (5) readmission for CL within 30 days.

The number of effective cases after intervention was 11 (91.7%) for thyroid surgery, 6 (100%) for cardiovascular surgery, 1 (50%) for thoracic surgery, 4 (100%) for hepatobiliary surgery, 22 (91.7%) for gastrointestinal surgery, 5 (100%) for urological surgery, and 9 (90%) for gynecological surgery, amounting to 58 (92.1%) cases in total. No statistical differences in effective rates were observed among departments ($X^2 = 4.7$, $P = 0.533$) (Table 4).

We recorded the days of drainage for all patients when they were in the hospital, but those who were discharged with a drainage tube and were extubated at the first outpatient return visit as scheduled would usually be considered a better recovery at discharge and after discharge. Both the days and volume of drainage after discharge could not be followed up. For the other five patients on whom oral nutritional therapy failed to work, they continued to receive other medical treatments due to high drainage volume. Therefore, the drainage volume and days of these patients were recorded in the inpatient medical records. Days of drainage in effective patients were as follows: 6 (4–8) days in thyroid surgery, 4 (3–7) days in cardiac surgery, 17 days in thoracic surgery, 8 (4–11) days in hepatobiliary surgery, 3 (1–7) days in gastrointestinal surgery, 7 (1–18) days in urological surgery, and 3 (1–21) days in gynecological surgery. Days of drainage in non-effective patients were as follows: 6 days in thyroid surgery, 6 days in thoracic surgery, 30 days in gastrointestinal surgery, and 48 days in gynecological surgery (Table 4).

The LOS was 14 (10–21) days in patients with CL from the thyroid surgery department and 11 (7–31) days among patients without CL, with a statistically significant difference in LOS between the two groups ($Z = 2.6$, $P = 0.008$). Patients with CL stayed longer than those without CL in the thyroid surgery department after the nutritional intervention. The LOS was 15 (9–36) days in patients with CL from the gynecology department and 11 (8–27) days in patients without CL, with a statistically significant difference in LOS between both groups ($Z = 2.0$, $P = 0.044$). Patients with CL stayed longer than those without CL in the gynecology department after the nutritional intervention. The LOS of patients with CL after the nutritional intervention in the other departments did not differ from those of patients without CL (Table 4). Five of the included patients had an ineffective intervention; one patient resorted to octreotide use, two patients were not extubated as scheduled, and two patients underwent secondary surgery.

3.4. Factors associated with recovery after intervention in post-operative CL

A logistic regression model was established by including post-operative albumin, post-operative hemoglobin, surgical procedure, and drainage volume at consultation (Table 5). The relationship between post-operative albumin and intervention outcome was not statistically significant ($P = 0.191$). The relationship between surgical procedures and intervention outcomes was not statistically

TABLE 4 Comparison of efficiency after intervention in different types of surgeries.

Types of surgeries	Number of effective cases [*n* (%)]		X^2 test	Days of drainage [Median (ranges)]		K–W test	LOS [Median (ranges)]		Wilcoxon test
	Effective	Non-effective	*P*-value	Effective	Non-effective	*P*-value	CL	Non-CL*	*P*-value
Thyroid surgery	11 (91.7)	1 (8.3)	0.533	6 (4–8)		0.008	14 (10–21)	11 (7–31)	0.008
Cardiac surgery	6 (100)	0 (0)		4 (3–7)	0		15 (11–28)	11 (5–28)	0.321
Thoracic surgery	1 (50)	1 (50)		17	6		6	7 (5–12)	-
Hepatobiliary surgery	4 (100)	0 (0)		8 (4–11)	-		21 (16–23)	14 (1–15)	0.148
Gastrointestinal surgery	22 (91.7)	2 (8.3)		3 (1–7)	30		14 (8–25)	13 (11–31)	0.555
Urological surgery	5 (100)	0 (0)		7 (1–18)	-		14 (9–19)	9 (5–13)	0.148
Gynecological surgery	9 (90)	1 (10)		3 (1–21)	48		15 (9–36)	11 (8–27)	0.004
Total	58 (92.1)	5 (7.9)							

*Non-CL, patients who underwent the same surgery procedure at the same period but did not develop CL.
M, median; MD, median difference; *p*-value<0.05.

significant ($P = 0.837$). Additionally, the volume of consultation on intervention outcomes was not statistically significant ($P = 0.995$). Each unit increase in post-operative hemoglobin would increase the probability of an effective outcome by 8%, which was statistically significant ($P = 0.037$).

3.5. Albumin levels before and after the intervention and variation of leakage volume for different interventions

Consideration of the potential serious influence of CL on patients' nutrition conditions, we observed albumin level changes, too. The analysis of 58 successful patients' albumin levels before and after intervention revealed that the value after the intervention was higher than that before the intervention ($P = 0.007$). Finally, whether different oral nutritional interventions exert differences in CL outcomes aroused our interest. We divided our oral nutritional intervention method into three groups: MCT diet, EN, and MCT diet plus EN, and differences in albumin before and after intervention among the three groups were observed. No significant differences in albumin level were recorded for different interventions ($P = 0.555$) (Table 6). Similarly, variations in drainage volume before and after consultation were analyzed; and no differences in median drainage volume among the three groups were recorded ($P = 0.347$) (Table 6). The intervention strategy did not compromise but improved, the nutritional status. There was also no difference in the impacts of the three different interventions on patient outcomes.

4. Discussion

Post-operative CL is a surgical complication due to damage to the lymphatic system (38). Its occurrence as a surgical complication may induce malnutrition and lead to a state of immune compromise, even affecting the long-term outcome of patients undergoing surgical treatment for malignant disease (10, 39). The use of a dietary program such as the MCT diet in patients with CL can reduce the burden on damaged lymphatic vessels for the reason that MCT is not usually absorbed through the intestinal lymphatics (10). Since short- and medium-chain triglyceride acids are mostly water-soluble and absorbed through the portal circulation rather than gastrointestinal lymph, the MCT diet can bypass the gastrointestinal lymphatic system, allowing reduced chylous flow at the CL site, thus resulting in quicker healing. However, no unanimous consensus on its use has been reached (23, 40, 41). Octreotide can reduce visceral blood flow, lymphatic flow, and the secretion of digestive glands, thus lessening the absorption of LCT which decreases the triglyceride content of lymphatic vessels and supports the healing of the site where CL occurs quickly (42–44). TPN provides nutrients through the veins, thus avoiding the absorption of LCT into the lymphatic vessels through the intestine. However, long-term PN would weaken the intestinal functional and have adverse effect on the patient's management. TPN and/or octreotide are considered in cases where EN/diet is not effective (45, 46). Secondary

TABLE 5 Multivariate analysis of factors associated with recovery after intervention in post-operative CL.

	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI	
							Lower	Upper
Procedure*	−0.237	1.153	0.042	1	0.837	0.789	0.082	7.563
Volume at consultation	0.000	0.002	0.000	1	0.995	1.000	0.995	1.005
Post-operative albumin	−0.220	0.168	1.713	1	0.191	0.803	0.578	1.115
Post-operative hemoglobin	0.077	0.037	4.334	1	0.037	1.080	1.004	1.160
Constant	2.693	5.862	0.211	1	0.646	14.780		

*neck = 1; thorax = 2; abdomen = 3; pelvis = 4.

procedures, such as lymphatic embolization, surgical ligation, and abdominal venous shunts, are mostly used in refractory cases after the failure of conservative treatment (10, 47). The MCT diet is the least invasive and most economical option. However, the scope of MCT diet use for CL is still unclear. This study sought to investigate the effect of the MCT diet and/or EN interventions on the prognosis of patients with post-operative CL by reviewing such interventions in patients with CL across different departments in the hospital from March 2020 to April 2022. Our study found that the MCT diet and EN had a positive effect on CL and were applicable to the vast majority of patients. Additionally, they could alleviate patients' discomfort and fear of fasting or secondary surgery. Therefore, for patients with post-operative CL, we recommend the MCT diet as a first line of intervention.

There was no report on the relationship between the maximum leakage and the necessity to initiate dietary interventions. Thyroid surgery specialists suggested criteria for secondary surgical treatment range from outputs of >500 mL/day to >1,000 mL/day output for 5 days (16). The published report suggests the conclusion. We thus conclude that drainage of more than 11.6 ml/kg of body weight per day predicted failure of conservative therapy and the volume might prove useful in guiding early thoracic duct ligation. For example, a person weighs 70 kg. Then, when his daily drainage volume reaches 812 ml, it indicates the failure of conservative therapy (48). The research about chylothorax suggested: early surgical intervention was indicated if drainage of >500 mL of chylous fluid was observed during the first 24 h. If the drainage was <300 ml/day 3 days after the chylothorax diagnosis, the patients continued the low-fat diet. If the volume remained >300 mL/day after 3 days, surgical intervention was considered (49). We observed the intervention effect in CL patients whose highest leakage volume after intervention onset was higher than 500 ml in this study. There were 10 cases ranging from 500 ml to 999 ml, of which three cases failed (1 case from thyroid surgery, 1 case from gastrointestinal surgery, and 1 case from gynecological surgery) and 7 cases succeeded (2 cases from thyroid surgery, 2 cases from cardiovascular surgery, 1 case from hepatobiliary surgery, 1 case from gastrointestinal surgery, and 1 case from gynecological surgery). There were six cases ranging from 1,000 ml to 1,999 ml, all of which were successful (one case from cardiovascular surgery, one case from thoracic surgery, one case from hepatobiliary surgery, two cases from urological surgery, and one case from gynecological surgery). There was one case of >2,000 ml that failed (from thoracic surgery). We found that the conservative treatment was still effective for chylous drainage of >500 ml/day (13 in 17 cases were successful) in the present study. Based on the results of these retrospective cases, we suggested that oral nutritional intervention should be tried as prior management. More active treatment should be adopted if there is no significant drainage output decrease within 1 to 3 days. The reason we made the suggestion is that in successful cases of this study, we observed an obvious drainage fluid reduction in volume and the fluid turning to clear approximately 3 days after the MCT diet and EN intervention, which was consistent with published data that reported success of fasting and octreotide treatment (49, 50). In our successful cases, the maximum drainage volume was 1,440 ml. Drainage volume should not be the only factor for the determination of the choice of treatment. Treatment effects can often be measured by how much volume changes in response to a particular intervention (16). Therefore, we believe that the MCT diet and EN can still be attempted for at least 3 days even if early drainage is within 1,500 ml.

The clinical efficacy of MCT and/or EN in this study was higher than the published literature. All other departments except thoracic surgery had an over 90% effective rate of intervention, and no statistical difference in effective rate was observed among different departments, suggesting that our nutritional intervention program was not affected by the different surgical procedures. The effective rates of conservative therapy in other studies were lower than in our study. A retrospective study about non-surgery CL reported that 66% of patients failed after conservative treatment (51). A systematic review indicated that the success rates of three non-surgical treatments with MCT diet, low-fat diet, and enteral nutrition were 77.3%, 75.9%, and 63.2%, respectively (36). In a collective review, only 43% of patients resolved CL with conservative treatment with the MCT diet alone (52). In a retrospective observational study of patients with CA following lymph node dissection due to gynecologic tumor, 5 patients (41.7%) had complete symptom relief with the MCT diet alone, while 7 (58.3%) patients underwent paracentesis with drainage of fluid (53). In another retrospective observational study, 71% of gynecological surgery post-operative CL patients responded to conservative

TABLE 6 Comparison of preintervention and postintervention albumin levels for different interventions and variations of leakage volume for different interventions.

Intervention	N*	Albumin (mg/L) (Mean ± SD)		F	P	N	Changes in leakage volume (ml/day) [Median (range)]	H	P
		Before intervention	After intervention						
EN	6	33.09 ± 3.96	30.95 ± 6.70	0.596	0.555	8	50 (−15–590)	2.119	0.347
MCT diet and EN	32	32.27 ± 4.42	34.99 ± 5.17			44	105 (−75–1370)		
MCT diet	9	33.12 ± 2.62	34.29 ± 6.70			11	256 (30–475)		
Total	47	32.54 ± 4.03	35.11 ± 4.95						
t		−2.762							
P		0.07							

*Since albumin levels were not tested in 16 patients in the hospital; these cases were excluded. Hence, the albumin level in 47 patients was analyzed before and after the intervention. The ANOVA and *t*-test were used for statistical analyses.

treatment (28). The phenomenon, the higher efficiency rate in this study than aforementioned published reports, may be contributed that there is no consensus on the standardized diagnosis and therapy procedure of CL and its effective interventions (5). For this reason, here instead of confirming the diagnosis of CL based absolutely on drainage triglyceride level and drainage volume as advised in previous reports, we confirmed the diagnosis immediately upon the observation of cloudy drainage fluid after related surgery (lymph node dissection, especially, and abdominal aortic lymph node dissection) and administered nutritional interventions. Therefore, it is possible to advance the intervention time, which may result in a better outcome than previous studies (54, 55). In addition, the MCT diet in our hospital and dietary guidance at discharge are standardized, which has not been reported in other MCT diet-related studies. Standardized diet preparation and guidance could be more conducive to the accurate implementation of nutrition programs, thus ensuring effectiveness.

Previous studies noted longer LOS in CL patients than non-CL patients after colorectal cancer and pancreaticoduodenectomy (56, 57). In this study, the LOS for patients with CL was longer than that for those without CL in thyroid surgery and gynecology, too. The difference in LOS among patients in the thyroid surgery department [14 (10–21) days vs. 11 (7–13) days, $P = 0.008$] may be because cervical lymph nodes collect most of the lymphatic flow in the extremities and the trunk (58). The MCT diet had a greater effect on the reduction of chylous flow in the digestive tract and did not stop lymphatic flow production. Hence, although CL was better controlled in patients with CL after thyroid surgery, lymph leaks may be less likely to heal relative to other sites of surgery (33). This may explain the longer LOS for patients with CL after thyroid surgery. Additionally, patients with CL after gynecological surgery also had a longer LOS, [15 (9–36) days vs. 11 (8–27) days, $P = 0.044$]. In this study, all CL patients in gynecology had tumor occupation and underwent pelvic lymph node dissection, and most of the patients also underwent abdominal aortic lymph node dissection. We speculate that pelvic tumor resection leads to less compression around the lymphatic vessels, which is detrimental to the healing of the lymphatic vessels. While no statistical difference in LOS was observed between patients with CL and non-CL in other types of surgeries. For this outcome, we believe that the MCT diet standardized protocol allows for better home management, and we also have detailed guidance at discharge, so that patients can be discharged with the drain tube. Generally, the drain tube would be removed in the outpatient return visit 1 or 2 weeks later. Therefore, LOS is not significantly longer in patients with CL. Thus, hospital medical resources are saved and patients' subjective comfort is improved.

Days of drainage after intervention onset were also a significant parameter to evaluate the clinical effect. We compared the intervention effects of EN, MCT, and TPN. The results showed that the days of drainage was similar between the present study and the published study [review (59) and (60)]. For example, a systematic review showed that the median for days of drainage was 5, 7.5, 29, or 19 days in patients with chylous ascites cured by TPN alone after hepatobiliary surgery, gastrointestinal surgery, and urological surgery (59). In the present study, the duration median was 8, 3, or 7 days in hepatobiliary surgery, gastrointestinal surgery, and urological surgery. For gynecological surgery patients

with chylous leakage cured by TPN alone, the median was 15 (7–16) days (60). The median for days of drainage was 3 (1–21) days (3 cases discharged with a drainage tube on day 1 of intervention and 1 on day 2) in the present study under a similar condition.

Additionally, we performed a binary logistic regression analysis of our nutritional intervention outcomes, which showed no statistically significant difference in the effect of post-operative albumin, surgical procedures, and volume of leakage on effective outcomes. What needs to be explained is that the thyroid surgery case was not included in the binary logistic regression analysis as post-operative albumin and hemoglobin levels were not determined among patients who underwent thyroid surgery. Higher hemoglobin levels on the first day after surgery had a promotive effect on the probability of effective intervention. We found no relevant reports on the analysis of factors associated with effective postintervention outcomes. However, it was reported that lower hemoglobin is associated with a higher incidence rate of CL (14), which may predict that lower hemoglobin probably influences the effects of oral nutritional interventions. Our analysis of post-operative hemoglobin on intervention outcomes may inform future studies.

Limitations of this study are as follows: (1) This study was a single-center retrospective analysis, and no comparison could be made with other hospitals. (2) We also did not compare the efficacy of our intervention with other interventions (fasting, octreotide, and secondary surgery), which may make the results less convincing. The reason is that on the one hand, we used oral nutrition intervention in the initial stage of clinical intervention, and it achieved a good effect. Therefore, we adopted this method for all patients. On the other hand, before we regulated oral interventions, this phenomenon was not well-documented in our medical documentation, making it difficult to retrieve these cases from our medical record system as historical controls. (3) Some clinical data (e.g., post-operative albumin and drained triglycerides) were incomplete, as they were not tested in some patients at that time. As a result, it is difficult to draw strong conclusions about the effectiveness of our approach. (4) Although we have compared efficacy with published studies, there is a problem of inconsistent baseline. (5) There may also be some reasons leading to different discharges and extubation indications in different departments, thus affecting the statistical results of discharge time. As for the strength of this study, conservative treatment, such as MCT diet and EN, achieved successful outcomes while alleviating patient discomfort, fear of medication and secondary surgery, and reduced complications without significantly prolonged LOS. Although CL is a relatively rare clinical complication, it can seriously affect patients' prognosis. Prospective clinical intervention trials could be conducted to explore the mechanisms of treatment with MCT diet/EN of CL. In addition, the role of hemoglobin in the MCT treatment of CL can be explored.

5. Conclusion

In conclusion, ∼90% of post-operative CL cases could be cured with our MCT diet/EN management strategy, which is higher than what was reported in many studies. Furthermore, the post-operative hemoglobin level can promote the prognosis of patients with CL. We believe that this management strategy works well, with a minimal patient burden and good nutritional condition. We detail this strategy in the study, hoping to provide useful information to others.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZL designed the research and revised the manuscript. JJ collected the data of all cases. KW developed a treatment plan and wrote the manuscript. JX analyzed the data. LL, XL, and YY performed clinical nutrition therapy. All authors contributed to the manuscript and approved the submitted version.

Acknowledgments

The authors would like to thank ZL for their assistance with designing the research and revising the study. Furthermore, the authors would like to also thank LL, XL, and YY for performing clinical nutrition therapy. The authors would like to also thank JJ for collecting the data and JX for analyzing the data.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Satala CB, Bara TJ, Jung I, Tudorache V, Gurzu S. Chylous ascites, unusual association with ductal pancreatic adenocarcinoma with plasmacytoid morphology: a case report and literature review. *Surgery J.* (2021) 7:e158–e62. doi: 10.1055/s-0041-1728651

2. Adler E, Bloyd C, Wlodarczyk S. Chylous ascites. *J Gen Intern Med.* (2020) 35:1586–7. doi: 10.1007/s11606-019-05532-3

3. Abu Hilal M, Layfield DM, Di Fabio F, Arregui-Fresneda I, Panagiotopoulou IG, Armstrong TH, et al. Postoperative chyle leak after major pancreatic resections in patients who receive enteral feed: risk factors and management options. *World J Surg.* (2013) 37:2918–26. doi: 10.1007/s00268-013-2171-x

4. Tai E, Min A, Rajan DK. A single-center experience with percutaneous interventional management of refractory chylous ascites. *Can Assoc Radiol J l'Association.* (2021) 72:871–5. doi: 10.1177/0846537120929429

5. Strobel O, Brangs S, Hinz U, Pausch T, Hüttner FJ, Diener MK, et al. Incidence, risk factors and clinical implications of chyle leak after pancreatic surgery. *Br J Surg.* (2017) 104:108–17. doi: 10.1002/bjs.10316

6. Feng JL, Zhou QY, Chen J, Wang JD. Analysis of chyle leakage after central lymph node dissection for thyroid carcinoma. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* (2019) 54:597–600. doi: 10.3760/cma.j.issn.1673-0860.2019.08.007

7. Moussa AM, Maybody M, Gonzalez-Aguirre AJ, Buicko JL, Shaha AR, Santos E. Thoracic duct embolization in post-neck dissection chylous leakage: a case series of six patients and review of the literature. *Cardiovasc Intervent Radiol.* (2020) 43:931–7. doi: 10.1007/s00270-020-02475-9

8. Jeon YJ, Cho JH, Hyun D, Shin S, Kim HK, Choi YS, et al. Management of chyle leakage after general thoracic surgery: impact of thoracic duct embolization. *Thoracic cancer.* (2021) 12:1382–6. doi: 10.1111/1759-7714.13914

9. Ohtsuka T, Ninomiya M, Kobayashi J, Kaneko Y, VATS. thoracic-duct division for aortic surgery-related chylous leakage. *Eur J Cardio-Thoracic Surg.* (2005) 27:153–5. doi: 10.1016/j.ejcts.2004.09.019

10. Shyr BU, Shyr BS, Chen SC, Shyr YM, Wang SE. Chyle leakage after robotic and open pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci.* (2020) 27:273–9. doi: 10.1002/jhbp.716

11. van Beek DJ, Nell S, Vorselaars W, Bonsing BA, van Eijck CHJ, van Goor H, et al. Complications after major surgery for duodenopancreatic neuroendocrine tumors in patients with MEN1: results from a nationwide cohort. *Ann Surg Oncol.* (2021) 28:4387–99. doi: 10.1245/s10434-020-09496-1

12. Capocasale E, Iaria M, Vistoli F, Signori S, Mazzoni MP, Dalla Valle R, et al. Incidence, diagnosis, and treatment of chylous leakage after laparoscopic live donor nephrectomy. *Transplantation.* (2012) 93:82–6. doi: 10.1097/TP.0b013e31823b2d8e

13. Kim BS, Yoo ES, Kim TH, Kwon TG. Chylous ascites as a complication of laparoscopic nephrectomy. *J Urol.* (2010) 184:570–4. doi: 10.1016/j.juro.2010.03.128

14. Chen L, Lin L, Li L, Xie Z, He H, Lin C, et al. Lymphatic leakage after pelvic lymphadenectomy for cervical cancer: a retrospective case-control study. *BMC Cancer.* (2021) 21:1242. doi: 10.1186/s12885-021-08984-1

15. Loukas M, Wartmann CT, Louis RG Jr, Tubbs RS, Salter EG, Gupta AA, et al. Cisterna chyli: a detailed anatomic investigation. *Clin Anatomy.* (2007) 20:683–8. doi: 10.1002/ca.20485

16. Delaney SW, Shi H, Shokrani A, Sinha UK. Management of chyle leak after head and neck surgery: review of current treatment strategies. *Int J Otolaryngol.* (2017) 2017:8362874. doi: 10.1155/2017/8362874

17. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition and classification of chyle leak after pancreatic operation: a consensus statement by the international study group on pancreatic surgery. *Surgery.* (2017) 161:365–72. doi: 10.1016/j.surg.2016.06.058

18. Moro K, Koyama Y, Kosugi SI, Ishikawa T, Ichikawa H, Hanyu T, et al. Low fat-containing elemental formula is effective for post-operative recovery and potentially useful for preventing chyle leak during postoperative early enteral nutrition after esophagectomy. *Clin Nutr.* (2016) 35:1423–8. doi: 10.1016/j.clnu.2016.03.018

19. Rocha G, Arnet V, Soares P, Gomes AC, Costa S, Guerra P, et al. Chylothorax in the neonate-A stepwise approach algorithm. *Pediatr Pulmonol.* (2021) 56:3093–105. doi: 10.1002/ppul.25601

20. Cope C. Diagnosis and treatment of postoperative chyle leakage via percutaneous transabdominal catheterization of the cisterna chyli: a preliminary study. *J Vasc Intervent Radiol JVIR.* (1998) 9:727–34. doi: 10.1016/S1051-0443(98)70382-3

21. Chen Z, Zhang Z, Lin B, Feng W, Meng F, Shi X. Relationship between early oral intake post pancreaticoduodenectomy and Chyle leakage: a retrospective cohort study. *J Invest Surg J Academy Surgical Res.* (2021) 34:575–82. doi: 10.1080/08941939.2019.1663378

22. Bibby AC, Maskell NA. Nutritional management in chyle leaks and chylous effusions. *Br J Commun Nurs.* (2014) Suppl Nutrition:S6–8. doi: 10.12968/bjcn.2014.19.Sup11.S6

23. Xiang D, Liu Z, Yang T, Bai B, Zhang J, Wang C, et al. Finger-pressing: a simple and efficient way to stop chyle leak post neck dissection. *Endocrine.* (2020) 67:374–8. doi: 10.1007/s12020-019-02119-0

24. Malik HZ, Crozier J, Murray L, Carter R. Chyle leakage and early enteral feeding following pancreatico-duodenectomy: management options. *Dig Surg.* (2007) 24:418–22. doi: 10.1159/000108324

25. Assumpcao L, Cameron JL, Wolfgang CL, Edil B, Choti MA, Herman JM, et al. Incidence and management of chyle leaks following pancreatic resection: a high volume single-center institutional experience. *J Gastrointest Surg.* (2008) 12:1915–23. doi: 10.1007/s11605-008-0619-3

26. Zhang C, Gong L, Wu W, Zhang M, Zhang H, Zhao C. Association between low-fat enteral nutrition after esophagectomy and a lower incidence of chyle leakage: a call for more and better evidence. *J Int Med Res.* (2020) 48:6370. doi: 10.1177/0300060520926370

27. Dogan NU, Dogan S, Erol M, Uzun BT. Cisterna chyli: an important landmark in laparoscopic paraaortic lymphadenectomy. *Gynecol Oncol.* (2020) 156:511. doi: 10.1016/j.ygyno.2019.12.004

28. Tulunay G, Ureyen I, Turan T, Karalok A, Kavak D, Ozgul N, et al. Chylous ascites: analysis of 24 patients. *Gynecol Oncol.* (2012) 127:191–7. doi: 10.1016/j.ygyno.2012.06.023

29. Stainer V, Jones P, Juliebø S, Beck R, Hawary A. Chyluria: what does the clinician need to know? *Ther Adv Urol.* (2020) 12:1756287220940899. doi: 10.1177/1756287220940899

30. Parthasarathy S, Miller FH, Casalino DD. Chyluria. *J Urol.* (2012) 187:1856–7. doi: 10.1016/j.juro.2012.02.008

31. Donlon NE, Nugent TS, Power R, Butt W, Kamaludin A, Dolan S, et al. Embolization or disruption of thoracic duct and cisterna chyli leaks post oesophageal cancer surgery should be first line management for ECCG-defined type III chyle fistulae. *Irish J Med Sci.* (2021) 190:1111–6. doi: 10.1007/s11845-020-02396-z

32. Bhardwaj R, Vaziri H, Gautam A, Ballesteros E, Karimeddini D, Wu GY. Chylous ascites: a review of pathogenesis, diagnosis and treatment. *J Clin Translat Hepatol.* (2018) 6:105–13. doi: 10.14218/JCTH.2017.00035

33. Athanasiadis DI, Carr RA, Painter R, Selzer D, Lee NK, Banerjee A, et al. Chylous ascites in the setting of internal hernia: a reassuring sign. *Surg Endosc.* (2022) 36:2570–3. doi: 10.1007/s00464-021-08545-4

34. Nguyen TK, Luong TH, Nguyen NC, Nguyen HH, Nguyen NH, Trinh HS. Successful minimal invasive treatment of chylous ascites following pancreaticoduodenectomy: a case report and review of literature. *Annals Med Surg.* (2012). 66:102451. doi: 10.1016/j.amsu.2021.102451

35. Gregor RT. Management of chyle fistulization in association with neck dissection. *Otolaryngol Head Neck Surg J Am Acad Otolaryngol Head Neck Surg.* (2000) 122:434–9. doi: 10.1016/S0194-5998(00)70061-1

36. Steven BR, Carey S. Nutritional management in patients with chyle leakage: a systematic review. *Eur J Clin Nutr.* (2015) 69:776–80. doi: 10.1038/ejcn.2015.48

37. Hillerdal G. Chylothorax and pseudochylothorax. *Eur Resp J.* (1997) 10:1157–62. doi: 10.1183/09031936.97.10051157

38. Inoue M, Nakatsuka S, Yashiro H, Tamura M, Suyama Y, Tsukada J, et al. Lymphatic intervention for various types of lymphorrhea: access and treatment. *Radiographics Rev Publication Radiol Soc North America Inc.* (2016) 36:2199–211. doi: 10.1148/rg.2016160053

39. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the international study group of liver surgery. *Surgery.* (2011) 149:680–8. doi: 10.1016/j.surg.2010.12.002

40. Petrella F, Casiraghi M, Radice D, Bertolaccini L, Spaggiari L. Treatment of chylothorax after lung resection: indications, timing, and outcomes. *Thorac Cardiovasc Surg.* (2020) 68:520–4. doi: 10.1055/s-0040-1710071

41. Miserachs M, Lurz E, Levman A, Ghanekar A, Cattral M, Ng V, et al. Diagnosis, outcome, and management of chylous ascites following pediatric liver transplantation. *Liver Transplant Am Assoc Study Liver Dis Int Liver Transplant Soc.* (2019) 25:1387–96. doi: 10.1002/lt.25604

42. Jiang H, Deng XF, Duan CM, Chen C, Xiang JL, Lu YL, et al. Somatostatin receptors SSTR2 and SSTR5 are expressed in the human thoracic duct. *Lymphology.* (2011) 44:21–8. Available online at: https://journals.librarypublishing.arizona.edu/lymph/article/id/3694/

43. Collard JM, Laterre PF, Boemer F, Reynaert M, Ponlot R. Conservative treatment of postsurgical lymphatic leaks with somatostatin-14. *Chest.* (2000) 117:902–5. doi: 10.1378/chest.117.3.902

44. Rimensberger PC, Müller-Schenker B, Kalangos A, Beghetti M. Treatment of a persistent postoperative chylothorax with somatostatin. *Ann Thoracic Surgery.* (1998) 66:253–4. doi: 10.1016/S0003-4975(98)00361-0

45. Jain A, Singh SN, Singhal P, Sharma MP, Grover M. A prospective study on the role of octreotide in management of chyle fistula neck. *Laryngoscope.* (2015) 125:1624–7. doi: 10.1002/lary.25171

46. Reiterer F, Grossauer K, Morris N, Uhrig S, Resch B. Congenital pulmonary lymphangiectasis. *Paediatr Respir Rev.* (2014) 15:275–80. doi: 10.1016/j.prrv.2014.05.002

47. Weiser AC, Lindgren BW, Ritchey ML, Franco I. Chylous ascites following surgical treatment for wilms tumor. *J Urol.* (2003) 170(4 Pt 2):1667–9. doi: 10.1097/01.ju.0000085655.48806.87

48. Shah RD, Luketich JD, Schuchert MJ, Christie NA, Pennathur A, Landreneau RJ, et al. Post-esophagectomy chylothorax: incidence, risk factors, and outcomes. *Annals Thoracic Surgery.* (2012) 93:897–903. doi: 10.1016/j.athoracsur.2011.10.060

49. Takuwa T, Yoshida J, Ono S, Hishida T, Nishimura M, Aokage K, et al. Low-fat diet management strategy for chylothorax after pulmonary resection and lymph node dissection for primary lung cancer. *J Thorac Cardiovasc Surg.* (2013) 146:571–4. doi: 10.1016/j.jtcvs.2013.04.015

50. Nishigori H, Ito M, Nishizawa Y, Koyama A, Koda T, Nakajima K, et al. Post-operative chylous ascites after colorectal cancer surgery. *Surg Today.* (2012) 42:724–8. doi: 10.1007/s00595-012-0132-x

51. Browse NL, Wilson NM, Russo F, Al-Hassan H, Allen DR. Aetiology and treatment of chylous ascites. *Br J Surgery.* (1992) 79:1145–50. doi: 10.1002/bjs.1800791110

52. Aalami OO, Allen DB, Organ CH Jr. Chylous ascites: a collective review. *Surgery.* (2000) 128:761–78. doi: 10.1067/msy.2000.109502

53. Frey MK, Ward NM, Caputo TA, Taylor J, Worley MJ Jr, Slomovitz BM. *Lymphatic Ascites Foll Pelvic Paraaortic Lymph Proc Gynecol Malignancies Gynecol Oncol.* (2012) 125:48–53. doi: 10.1016/j.ygyno.2011.11.012

54. Kaas R, Rustman LD, Zoetmulder FA. Chylous ascites after oncological abdominal surgery: incidence and treatment. *Eur J Surg Oncol Br Assoc Surg Oncol.* (2001) 27:187–9. doi: 10.1053/ejso.2000.1088

55. Schild HH, Strassburg CP, Welz A, Kalff J. Treatment options in patients with chylothorax. *Dtsch Arztebl Int.* (2013) 110:819–26. doi: 10.3238/arztebl.2013.0819

56. van der Gaag NA, Verhaar AC, Haverkort EB, Busch OR, van Gulik TM, Gouma DJ. Chylous ascites after pancreaticoduodenectomy: introduction of a grading system. *J Am Coll Surg.* (2008) 207:751–7. doi: 10.1016/j.jamcollsurg.2008.07.007

57. Matsuda T, Fujita H, Kunimoto Y, Kimura T, Ogino K. Chylous ascites as a complication of laparoscopic colorectal surgery. *Asian J Endosc Surg.* (2013) 6:279–84. doi: 10.1111/ases.12057

58. Polistena A, Vannucci J, Monacelli M, Lucchini R, Sanguinetti A, Avenia S, et al. Thoracic duct lesions in thyroid surgery: an update on diagnosis, treatment and prevention based on a cohort study. *Int J Surgery.* (2016) 28 Suppl 1:S33–7. doi: 10.1016/j.ijsu.2015.05.058

59. Weniger M, D'Haese JG, Angele MK, Kleespies A, Werner J, Hartwig W. Treatment options for chylous ascites after major abdominal surgery: a systematic review. *Am J Surg.* (2016) 211:206–13. doi: 10.1016/j.amjsurg.2015.04.012

60. Scaletta G, Quagliozzi L, Cianci S, Vargiu V, Mele MC, Scambia G, et al. Management of postoperative chylous ascites after surgery for ovarian cancer: a single-institution experience. *Updates Surg.* (2019) 71:729–34. doi: 10.1007/s13304-019-00656-x

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 14 August 2023
DOI 10.3389/fnut.2023.1218738

OPEN ACCESS

EDITED BY
Silvia Lai,
Sapienza University of Rome, Italy

REVIEWED BY
Hongli Gao,
Capital Medical University, China
Luca Salomone,
Sapienza University of Rome, Italy
Cheng-fu Cao,
Peking University People's Hospital, China

*CORRESPONDENCE
Xiangwen Liang
✉ liangxiangwen315@163.com

†These authors have contributed equally to this work

RECEIVED 08 May 2023
ACCEPTED 21 July 2023
PUBLISHED 14 August 2023

CITATION
Li Y, Wang Z, Sun T, Zhang B and Liang X (2023) Geriatric nutritional risk index was associated with in-hospital mortality among cardiac intensive care unit patients.
Front. Nutr. 10:1218738.
doi: 10.3389/fnut.2023.1218738

Geriatric nutritional risk index was associated with in-hospital mortality among cardiac intensive care unit patients

Yuefeng Li[1†], Zhengdong Wang[1†], Tienan Sun[2], Biyang Zhang[2] and Xiangwen Liang[1*]

[1]The First People's Hospital of Yulin, Yulin, Guangxi, China, [2]Department of Cardiology, Affiliated Anzhen Hospital, Capital Medical University, Beijing, China

Background: Identifying risk factors associated with cardiac intensive care unit (CICU) patients' prognosis can help clinicians intervene earlier and thus improve their prognosis. The correlation between the geriatric nutrition risk index (GNRI), which reflects nutritional status, and in-hospital mortality among CICU patients has yet to be established.

Method: The present study retrospectively enrolled 4,698 CICU patients. Based on the nutritional status, the participants were categorized into four groups. The primary endpoint was in-hospital mortality. The length of hospital stay and length of CICU stay were the secondary endpoints. To explore the correlation between nutritional status and in-hospital mortality, a logistic regression analysis was conducted. The nonlinear associations of GNRI with in-hospital mortality were evaluated using restricted cubic spline (RCS). Furthermore, subgroup analyses were conducted to evaluate the effect of the GNRI on in-hospital mortality across different subgroups, with calculation of the *p* for interaction.

Result: A higher risk of malnutrition was significantly linked to an increased incidence of in-hospital mortality (High risk vs. No risk: 26.2% vs. 4.6%, $p < 0.001$), as well as a longer length of hospital stay (High risk vs. No risk: 15.7, 9.1–25.1 vs. 8.9, 6.9–12.9, $p < 0.001$) and CICU stay (High risk vs. No risk: 6.4, 3.8–11.9 vs. 3.2, 2.3–5.1, $p < 0.001$). An elevated GNRI was significantly associated with an increased risk of in-hospital mortality even after controlling for pertinent confounding factors (High risk vs. No risk: OR, 95% CI: 2.37, 1.67–3.37, $p < 0.001$, *p* for trend <0.001). Additionally, the RCS model showed a linear relationship between GNRI and in-hospital mortality, with the risk of in-hospital mortality significantly decreasing as GNRI increased (non-linear $p = 0.596$). Furthermore, in the subgroups of hypertension, ventricular arrhythmias, cardiac arrest, shock, and chronic kidney disease, there was a significant interaction between nutritional status and in-hospital mortality.

Conclusion: Among CICU patients, a low GNRI was a significant predictor of in-hospital mortality. Furthermore, patients with a higher risk of malnutrition, as indicated by low GNRI values, experienced significantly longer hospital and CICU stays.

KEYWORDS

MIMIC-IV database, cardiac intensive care unit, geriatric nutritional risk index, nutritional status, in-hospital mortality

1. Introduction

Since its establishment in the 1960s with the objective of resuscitating patients with acute myocardial infarction (AMI), the coronary care unit (CCU) has undergone a transformation into a cardiac intensive care unit (CICU) (1–3). With the complexity of the clinical condition of patients, the current indications for CICU cover AMI, advanced heart failure (HF), cardiogenic shock (CS), organ failure, and multi-systemic critical illness (4). Patients admitted to the CICU often have many non-cardiac conditions in addition to cardiac disease, such as sepsis, acute renal failure, and acute respiratory failure (5, 6). These complications were associated not only with the severity of the underlying disease and the need for intensive care, but also with elevated morbidity and mortality rates, leading to greater resource utilization and medical costs (7–11). Therefore, identifying risk factors related to the prognosis of CICU patients is crucial for clinical physicians, which can help clinicians to intervene early in the treatment of patients and thus improve their prognosis.

Malnutrition is widespread in critically ill patients and is related to a worse prognosis (12–14). Calculated from serum albumin, height, and weight, the GNRI is a convenient and accessible indicator to evaluate the nutritional status of patients (15, 16). Patients with lower GNRI scores were considered to have poorer nutritional status and had worse outcomes (17, 18). The GNRI score is now used as a risk index for a variety of diseases, such as uremia, sepsis, and cardiovascular diseases (CVD) (19–21). Previous studies have linked GNRI to a poor outcome in various CVDs, including acute HF, coronary artery disease (CAD), and acute ST-segment elevation myocardial infarction (22–25). Hence, in critically ill patients admitted to the CICU, employing GNRI as a tool to assess nutritional status might enhance risk stratification, and providing timely nutritional support could potentially enhance long-term prognosis. However, no studies have been undertaken to investigate the impact of nutritional status on the prognosis of CICU patients. The aim of this study was to explore an association between GNRI and in-hospital mortality in CICU patients.

2. Methods

2.1. Population selection criteria

This was an observational, retrospective study that included patients from the CICU and CCU, extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV version 2.0). The database provides comprehensive and high-quality data on patients admitted to intensive care units at Beth Israel Deaconess Medical Center between 2008 and 2019 (26). As shown in Figure 1, all patients who were initially admitted to the hospital for a duration of more than two days were included. Patients with the following conditions were excluded: (1) non-cardiac hospitalization; (2) weight, height and albumin data missing; (3) age < 18 years. A total of 4,698 patients were enrolled.

2.2. Data extraction

The data utilized in this study was extracted from the publicly available critical care database known as MIMIC-IV (26). The following information was collected: demographics, vital sign, comorbidities and medical history, laboratory parameter and treatment (Details can be found in Supplementary material).

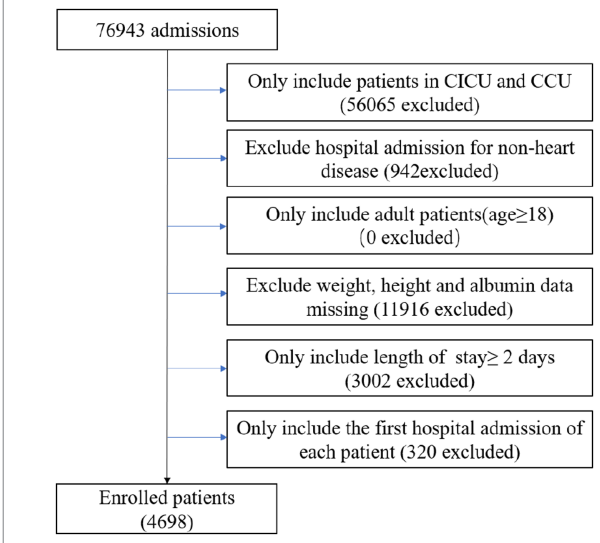


FIGURE 1
Flow chart of study population. CCU, coronary artery care unit; CICU, cardiac intensive care unit.

2.3. Definition of nutritional status and endpoints

According to GNRI, all patients were classified into four groups (15): No nutrition risk: GNRI≥98 ($n = 1,560$), Low nutrition risk: 92 ≤ GNRI <98 ($n = 1,067$), Moderate nutrition risk: 82 ≤ GNRI <92 ($n = 1,214$), High nutrition risk: GNRI<82 ($n = 828$). The GNRI index was calculated as follows: GNRI = [14.89 × serum albumin (g/dL)] + [41.7 × actual BMI/ideal BMI] (27). Ideal BMI was set to 22 kg/m^2 (28). If the patient's BMI exceeded the ideal BMI, the "actual BMI/ideal BMI" ratio was set to 1. The primary endpoint was in-hospital mortality. The secondary endpoints were length of hospital stay and length of CICU stay.

2.4. Statistical analysis

The baseline characteristics were reported as mean ± standard deviation (SD) for normally distributed quantitative data, median [interquartile range (IQR)] for skewed data, and number (%) for categorical data. Analysis of variance, Kruskal-Wallis, and chi-square tests were conducted to compare patient characteristics according to nutritional status. Binary logistic regression analysis was used to determine the association between nutritional status and in-hospital mortality, and the results were presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). To account for relative confounding variables, a multivariate logistic analysis using the stepwise method with removal at $p > 0.05$ was performed on all baseline covariates listed in Table 1 (Details can be found in Supplementary material). Furthermore, we created a restricted cubic

TABLE 1 Characteristics of patients stratified by nutritional status.

Characteristics	Total (n = 4,697)	Nutritional risk stratification				p-value
		No nutrition risk GNRI≥98 (n = 1,560)	Low nutrition risk 92 ≤ GNRI <98 (n = 1,067)	Moderate nutrition risk 82 ≤ GNRI<92 (n = 1,242)	High nutrition risk GNRI<82 (n = 828)	
Age(years)	68.4 ± 13.3	68.5 ± 12.7	69.7 ± 12.9	68.5 ± 13.4	66.2 ± 14.4	<0.001
Gender, *n* (%)						<0.001
Male	2,906 (61.9)	1,032 (66.2)	652 (61.1)	758 (61.0)	464 (56.0)	
Female	1791 (38.1)	528 (33.8)	415 (38.9)	484 (39.0)	364 (44.0)	
Race, *n* (%)						0.027
White	3,237 (68.9)	1,065 (68.3)	749 (70.2)	864 (69.6)	559 (67.5)	
Black	306 (6.5)	79 (5.1)	70 (6.6)	92 (7.4)	65 (7.9)	
Other	1,154 (24.6)	416 (26.7)	248 (23.2)	286 (23.0)	204 (24.6)	
Body mass index (kg/m^2)	28.8 ± 6.8	29.4 ± 6.1	29.41 ± 6.93	28.48 ± 6.81	27.56 ± 7.52	<0.001
Systolic blood pressure (mmHg)	115.5 ± 21.8	115.0 ± 20.9	115.29 ± 21.36	116.11 ± 22.89	116.06 ± 22.34	0.487
Diastolic blood pressure (mmHg)	60.8 ± 15.0	60.2 ± 14.3	61.21 ± 15.32	61.30 ± 15.85	60.56 ± 14.80	0.201
Heart rate (beats/min)	84.7 ± 17.6	82.1 ± 14.9	84.00 ± 17.21	85.80 ± 18.11	88.47 ± 20.75	<0.001
Comorbidities and medical history, n (%)						
Congestive heart failure	2,609 (55.5)	726 (46.5)	671 (62.9)	772 (62.2)	440 (53.1)	<0.001
Coronary artery disease	3,296 (70.2)	1,168 (74.9)	782 (73.3)	872 (70.2)	474 (57.2)	<0.001
Acute myocardial infarction	1745 (37.2)	519 (33.3)	441 (41.3)	502 (40.4)	283 (34.2)	<0.001
Cardiomyopathy	411 (8.8)	111 (7.1)	109 (10.2)	132 (10.6)	59 (7.1)	0.001
Atrial fibrillation	2,830 (60.3)	895 (57.4)	650 (60.9)	791 (63.7)	494 (59.7)	0.008
Ventricular arrhythmias	701 (14.9)	170 (10.9)	161 (15.1)	222 (17.9)	148 (17.9)	<0.001
Atrioventricular block	453 (9.6)	157 (10.1)	106 (9.9)	120 (9.7)	70 (8.5)	0.623
Cardiac arrest	410 (8.7)	91 (5.8)	68 (6.4)	134 (10.8)	117 (14.1)	<0.001
Valve disease	2,162 (46.0)	833 (53.4)	514 (48.2)	539 (43.4)	276 (33.3)	<0.001
Shock	1,380 (29.4)	232 (14.9)	279 (26.1)	439 (35.3)	430 (51.9)	<0.001
Pulmonary embolism	191 (4.1)	36 (2.3)	34 (3.2)	58 (4.7)	63 (7.6)	<0.001
Endocarditis	152 (3.2)	9 (0.6)	22 (2.1)	50 (4.0)	71 (8.6)	<0.001
Dyslipidemia	2,778 (59.1)	1,059 (67.9)	659 (61.8)	701 (56.4)	359 (43.4)	<0.001
Hypertension	1924 (41.0)	779 (49.9)	435 (40.8)	422 (34.0)	288 (34.8)	<0.001
Diabetes	1810 (38.5)	572 (36.7)	429 (40.2)	495 (39.9)	314 (37.9)	0.203
Acute kidney injury	4,254 (90.6)	1,369 (87.8)	966 (90.5)	1,144 (92.1)	775 (93.6)	<0.001
Chronic kidney disease	1,500 (31.9)	392 (25.1)	363 (34.0)	487 (39.2)	258 (31.2)	<0.001
Malignancy	226 (4.8)	39 (2.5)	52 (4.9)	65 (5.2)	70 (8.5)	<0.001
Laboratory parameters						
White blood cell (10^9/L)	10.64 ± 5.55	9.14 ± 4.37	10.01 ± 4.66	11.40 ± 5.63	13.13 ± 7.16	<0.001
Hemoglobin (g/dL)	11.01 ± 2.27	12.06 ± 2.17	11.15 ± 2.10	10.31 ± 2.03	9.92 ± 2.12	<0.001
Platelet (10^9/L)	210.35 ± 96.79	207.80 ± 75.62	212.84 ± 90.18	209.94 ± 106.76	212.52 ± 121.66	0.526
ALT (U/L)	24 [16, 47]	23 [16, 36]	23 [15, 44]	26 [15, 64]	28 [16, 70]	<0.001
AST (U/L)	32 [21, 66]	26 [20, 40]	31 [21, 61]	40 [23, 93]	45 [25, 125]	<0.001
Creatinine (mg/dL)	1.58 ± 1.50	1.33 ± 1.02	1.56 ± 1.44	1.79 ± 1.84	1.77 ± 1.67	<0.001
Glucose (mg/dL)	142.40 ± 69.30	134.13 ± 54.98	142.38 ± 69.15	149.17 ± 80.63	147.85 ± 73.65	<0.001
Albumin (g/L)	3.43 ± 0.65	4.11 ± 0.26	3.57 ± 0.14	3.10 ± 0.20	2.43 ± 0.35	<0.001
Sodium (mmol/L)	138.21 ± 4.59	138.47 ± 3.65	138.12 ± 4.47	137.88 ± 5.06	138.31 ± 5.47	0.007

(Continued)

TABLE 1 (Continued)

Characteristics	Total (n = 4,697)	Nutritional risk stratification				p-value
		No nutrition risk GNRI≥98 (n = 1,560)	Low nutrition risk 92 ≤ GNRI <98 (n = 1,067)	Moderate nutrition risk 82 ≤ GNRI<92 (n = 1,242)	High nutrition risk GNRI<82 (n = 828)	
Potassium (mmol/L)	4.25 ± 0.65	4.22 ± 0.54	4.24 ± 0.67	4.30 ± 0.67	4.23 ± 0.76	0.012
Treatment, n (%)						
Oral anticoagulants	2,111 (44.9)	711 (45.6)	506 (47.4)	579 (46.6)	315 (38.0)	<0.001
Antiplatelet	4,213 (89.7)	1,504 (96.4)	969 (90.8)	1,096 (88.2)	644 (77.8)	<0.001
Beta-blockers	4,183 (89.1)	1,459 (93.5)	968 (90.7)	1,082 (87.1)	674 (81.4)	<0.001
ACEI/ARB	2,168 (46.2)	820 (52.6)	561 (52.6)	536 (43.2)	251 (30.3)	<0.001
Corticosteroids	1,412 (30.1)	393 (25.2)	337 (31.6)	390 (31.4)	292 (35.3)	<0.001
Vasoactive agent	3,613 (76.9)	1,228 (78.7)	823 (77.1)	920 (74.1)	642 (77.5)	0.033
Mechanical vent	3,241 (69.0)	1,065 (68.3)	700 (65.6)	832 (67.0)	644 (77.8)	<0.001
ECMO	69 (1.5)	10 (0.6)	11 (1.0)	17 (1.4)	31 (3.7)	<0.001

GNRI, geriatric nutrition risk index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECMO, extracorporeal membrane oxygenation.

TABLE 2 Outcomes of patients stratified by nutritional status.

Outcomes	Total	Nutritional risk stratification				p value
		No nutrition risk GNRI≥98	Low nutrition risk 92 ≤ GNRI <98	Moderate nutrition risk 82 ≤ GNRI<92	High nutrition risk GNRI<82	
In-hospital mortality, n (%)	572 (12.2)	71 (4.6)	105 (9.8)	179 (14.4)	217 (26.2)	<0.001
Length of hospital stay (days)	10.9 [7.3, 17.0]	8.9 [6.9, 12.9]	10.8 [7.3, 15.6]	12.7 [8.3, 19.6]	15.7 [9.1, 25.1]	<0.001
Length of CICU stay (days)	4.1 [2.8, 7.1]	3.2 [2.3, 5.1]	4.0 [2.7, 6.2]	4.7 [3.1, 8.1]	6.4 [3.8, 11.9]	<0.001

Non-normally distributed continuous variables were presented as median (IQR). Categorical variables were presented as number (percentage). GNRI, geriatric nutrition risk index; CICU, cardiac intensive care unit.

spline curve (RCS) based on the multivariate logistic regression model to investigate the relationship between GNRI and in-hospital mortality. Three knots were chosen for examination. In subgroup analysis, univariate binary logistic regression was used to assess the correlation between nutritional status and in-hospital mortality in various comorbidity subgroups. The results were expressed as OR and 95% CI, with p for interaction computed.

All tests were two-sided, and statistical significance was defined as $p < 0.05$. R software was used to perform all data analysis.

3. Results

3.1. Patient characteristics

The patients were classified into four groups based on their nutritional status: No nutrition risk (n = 1,560), Low nutrition risk (n = 1,067), Moderate nutrition risk (n = 1,214), High nutrition risk (n = 828). Table 1 summarized the characteristics of the different nutritional states. Patients with high nutrition risk were younger, female sex, less often white, had a lower BMI but a higher heartrate, and were more likely to have a history of congestive HF, cardiomyopathy, atrial fibrillation, ventricular arrhythmias, acute myocardial infarction, cardiac arrest, pulmonary embolism, endocarditis, acute kidney injury, chronic kidney disease, shock and malignancy, but less often had coronary artery disease, valve disease, hypertension, and diabetes. Furthermore, patients with a high nutritional risk had higher levels of white blood cells, ALT, AST, creatinine, glucose, and potassium, while having lower levels of hemoglobin, sodium, and albumin. In addition, they received more corticosteroids, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO), while receiving less oral anticoagulant, antiplatelet, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and vasoactive agent therapy.

3.2. Association between nutritional status and adverse outcomes

Overall, in-hospital mortality rate was 12.2%. As nutrition risk groups increased, in-hospital mortality increased significantly (High risk vs. No risk: 26.2% vs. 4.6%, $p < 0.001$) (Table 2). Higher nutrition risk was significantly associated with the increased length of hospital stay (High risk vs. No risk: 15.7, 9.1–25.1 vs. 8.9, 6.9–12.9, $p < 0.001$) and CICU stay (High risk vs. No risk: 6.4, 3.8–11.9 vs. 3.2, 2.3–5.1, $p < 0.001$) respectively (Table 2). As shown in Table 3, in model 1, higher nutrition risk was associated with the increased risk of in-hospital mortality (High risk vs. No risk: OR, 95% CI: 7.45,

TABLE 3 The association between nutritional status and in-hospital mortality.

Model	Logistic regression analysis		
	OR (95% CI)	*p* value	*p* for trend
Model 1			<0.001
No nutrition risk: GNRI≥98	Ref		
Low nutrition risk: 92 ≤ GNRI <98	2.29 [1.68, 3.14]	<0.001	
Moderate nutrition risk: 82 ≤ GNRI<92	3.53 [2.67, 4.73]	<0.001	
High nutrition risk: GNRI<82	7.45 [5.64, 9.95]	<0.001	
GNRI	0.93 [0.92, 0.94]	<0.001	
Model 2			<0.001
No nutrition risk: GNRI≥98	Ref		
Low nutrition risk: 92 ≤ GNRI <98	1.57 [1.09, 2.27]	0.016	
Moderate nutrition risk: 82 ≤ GNRI<92	1.65 [1.18, 2.33]	0.004	
High nutrition risk: GNRI<82	2.37 [1.67, 3.37]	<0.001	
GNRI	0.96 [0.97, 0.98]	<0.001	

Model 1: unadjusted. Model 2: adjusted for age, sex, race, white blood cell, sodium, congestive heart failure, coronary artery disease, atrial fibrillation, ventricular arrhythmias, cardiac arrest, shock, pulmonary embolism, dyslipidemia, diabetes, acute kidney injury, chronic kidney disease, oral anticoagulants, antiplatelet, beta-blockers, ACEI/ARB, corticosteroids, mechanical vent, ECMO. GNRI, geriatric nutrition risk index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; CI, confidence interval.

5.64–9.95, $p < 0.001$, p for trend <0.001). In Model 2, we adjusted for relevant confounding variables and found that a higher nutrition risk was significantly associated with an increased risk of in-hospital mortality (High risk vs. No risk: OR, 95% CI: 2.37, 1.67–3.37, $p < 0.001$, p for trend <0.001). When analyzing GNRI as a continuous variable, we found that an increase of one unit in GNRI was associated with a reduction in the risk of in-hospital mortality by approximately 0.07-fold in Model 1 and 0.04-fold in Model 2, respectively.

Figure 2 displayed the use of restricted cubic splines (RCS) to visually represent the relationship between MACE and GNRI, as well as fit the model. After potential confounders were considered, a linear association between GNRI and in-hospital mortality was confirmed (non-linear $p = 0.596$). As GNRI increased, the risk of in-hospital mortality decreased significantly.

3.3. Subgroup analysis

In all subgroup analyses (Table 4), we found that patients with hypertension (p for interaction<0.001) had increased risks of in-hospital mortality for higher nutrition risk. But patients with ventricular arrhythmias (p for interaction = 0.046), cardiac arrest (p for interaction = 0.029), shock (p for interaction<0.001), and chronic kidney disease (p for interaction<0.001) had lower risks of in-hospital mortality. In the remaining subgroups, no significant interactions were found.

4. Discussion

Our findings revealed that GNRI was an independent predictor of in-hospital mortality among CICU patients. The RCS analysis further confirmed a linear relationship between GNRI and in-hospital mortality. Furthermore, we found that higher nutrition risk was significantly related to the increased length of hospital stay and CICU stay. Significant interactions were observed in the relationship between GNRI and in-hospital mortality in hypertension, ventricular arrhythmias, cardiac arrest, shock, and chronic kidney disease subgroups.

Malnutrition, a condition characterized by an imbalance between the body's energy intake and demands, has been unequivocally linked to cardiovascular disease (29). However, the underlying mechanism responsible for this association was multifaceted, with inflammation, metabolism, and aging all implicated in this pathological relationship (30, 31). Indeed, previous investigations have demonstrated that malnutrition was intricately linked to inflammation (30, 32). The inflammatory reaction, in turn, could antagonize albumin synthesis, a key protein involved in maintaining optimal nutritional status, and further aggravate malnutrition, engendering a self-perpetuating cycle of deleterious consequences (33). Furthermore, emerging evidence has suggested that malnutrition could precipitate the onset of various pathologies, such as free radical damage, impaired insulin secretion, lipolysis, and lipid oxidation. These adverse events, in turn, could incite tissue damage, diabetes, and fatty liver disease, thus perpetuating the vicious cycle of malnutrition (34–36). Importantly, previous research has also highlighted the unfavorable prognostic implications of malnutrition, manifesting as an adverse prognosis in various diseases, such as HF, CAD, and peripheral arterial disease (37–40).

Various systems are commonly employed in clinical practice to assess nutritional status, including subjective global assessment (SGA) (41) and mini-nutritional assessment (MNA) (42, 43). Nonetheless, many of these indicators have been discarded due to their complexity and vulnerability to subjective influences (41–43). Meanwhile, laboratory indices such as albumin (44) and hemoglobin (45) have been utilized to assess nutritional status and their association with patient prognosis has been established. However, these indicators are limited in that they only reflect a singular aspect and their predictive ability can be influenced by external factors. In recent years, GNRI has gained popularity as a commonly used tool in clinical nutrition assessment, primarily due to its convenience and accessibility (46). Moreover, it has been clinically established that a correlation between

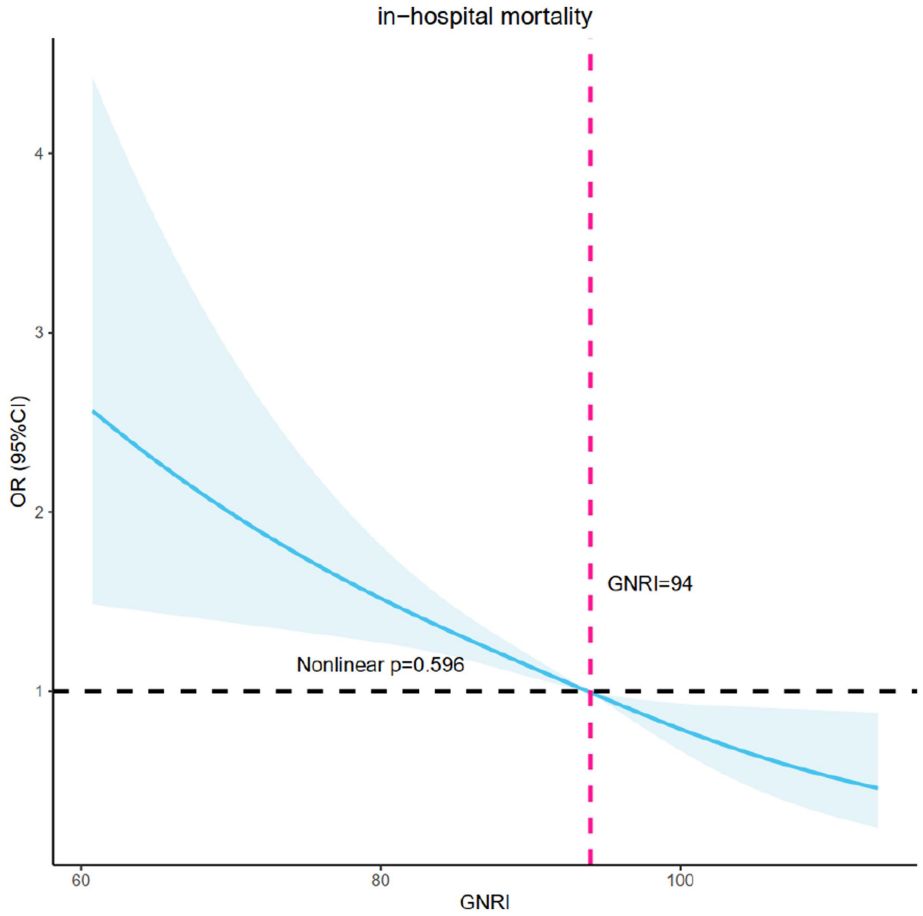


FIGURE 2
RCS model showing the association between the nutritional status and in-hospital mortality. RCS, restricted cubic spline curve.

GNRI and the development and prognosis of several cardiovascular diseases, including HF, CAD, and stroke (47–49). A study that enrolled 2,299 patients with non-ST-segment elevation acute coronary syndrome found that a lower GNRI was significantly related to poor prognosis (50). An observational study showed that patients undergoing coronary artery bypass grafting with decreased GNRI had an increased incidence of MACE and a lower survival rate during long-term follow-up (51). According to a meta-analysis, low baseline GNRI was identified as a reliable predictor of cardiovascular events in CAD patients. In addition, another study conducted on elderly patients with HF demonstrated that a lower GNRI could independently predict MACE, thereby affirming the risk stratification ability of GNRI (22).

In the realm of scoring systems, GNRI exerts its preeminence by virtue of its remarkable faculty for risk stratification. The singularity of GNRI lies not only in its robustness, but also in its simplicity, which sets it apart from more intricate scoring mechanisms (52). As far as we knew, this study was the first to examine the correlation between GNRI and in-hospital mortality among CICU patients. As with prior research, the GNRI has been shown to be a reliable predictor of in-hospital mortality among CICU patients. This discovery reinforced the use of GNRI as a prognostic indicator in clinical settings and enhanced risk assessment and stratification based on traditional risk factors. Notably, among patients without ventricular arrhythmias, shock, chronic kidney disease or cardiac arrest, the effect of nutritional status on in-hospital mortality was enhanced, implying that clinicians should not ignore CICU patients without diseases that had a high case fatality rate, as paying attention to nutritional status and intervening accordingly could benefit patients more.

The RCS curve revealed a linear negative relationship between GNRI and in-hospital mortality: as nutritional status improved as measured by GNRI, the in-hospital mortality risk decreased, suggesting that clinicians might be able to improve poor outcomes by increasing GNRI with more aggressive treatment and better care. Furthermore, as the level of nutrition risk increased, the length of hospitalization and CICU stay rose significantly, compounding the emotional, physical, and financial stress experienced by patients. The potential explanation for this phenomenon was that patients with optimal nutritional status exhibited a more rapid convalescence from the ailment, thereby resulting in expedited hospital discharge and diminished expenses associated with hospitalization. As a result, indicators like the GNRI, which is more cost-effective and accessible, should receive more attention. When a full assessment of a patient's health status is not possible in an emergency, the use of GNRI could quickly identify high-risk patients and provide clinicians with new treatment suggestions. This is especially true in medical settings that are deprived of adequate resources and infrastructure, such as those in geographically isolated regions or areas with poor healthcare

TABLE 4 Subgroup analysis of associations between in-hospital mortality and nutritional status.

Subgroups	*N*	No nutrition risk	Low nutrition risk	Moderate nutrition risk	High nutrition risk	*p* for interaction
Congestive heart failure						0.122
Yes	2,609	Reference	1.79 (1.23–2.61)	2.52 (1.77–3.57)	6.12 (4.29–8.71)	
No	2088	Reference	2.81 (1.59–4.97)	5.40 (3.27–8.93)	9.89 (6.07–16.12)	
Coronary artery disease						0.447
Yes	3,296	Reference	2.25 (1.57–3.23)	3.52 (2.52–4.90)	8.13 (5.80–11.41)	
No	1,401	Reference	2.40 (1.29–4.48)	3.61 (2.04–6.36)	6.76 (3.92–11.65)	
Acute myocardial infarction						0.625
Yes	1745	Reference	1.61 (1.02–2.55)	2.70 (1.78–4.10)	6.34(4.15–9.70)	
No	2,952	Reference	2.90 (1.90–4.45)	4.21 (2.84–6.25)	8.57(5.82–12.62)	
Cardiomyopathy						0.132
Yes	411	Reference	1.12 (0.47–2.67)	1.34 (0.60–3.00)	3.99 (1.73–9.19)	
No	4,286	Reference	2.49 (1.78–3.48)	3.96 (2.91–5.38)	8.08 (5.96–10.96)	
Atrial fibrillation						0.146
Yes	2,830	Reference	2.73 (1.87–3.98)	3.55(2.48–5.06)	7.10(4.96–10.17)	
No	1867	Reference	1.43 (0.81–2.55)	3.34(2.06–5.43)	8.00(5.03–12.72)	
Ventricular arrhythmias						0.046
Yes	701	Reference	1.40 (0.77–2.55)	2.37(1.39–4.02)	4.00(2.31–6.94)	
No	3,996	Reference	2.56 (1.77–3.71)	3.69 (2.61–5.22)	8.60 (6.13–12.06)	
Atrioventricular block						0.408
Yes	453	Reference	0.99 (0.39–2.50)	2.27 (1.06–4.89)	4.50 (2.04–9.92)	
No	4,244	Reference	2.56 (1.83–3.57)	3.79 (2.78–5.16)	8.05 (5.93–10.95)	
Cardiac arrest						0.029
Yes	410	Reference	1.36 (0.65–2.86)	2.48 (1.34–4.58)	3.25 (1.74–6.05)	
No	4,287	Reference	2.60 (1.83–3.70)	3.50 (2.51–4.88)	8.11 (5.84–11.24)	
Valve disease						0.532
Yes	2,162	Reference	2.25 (1.46–3.49)	3.02 (2.00–4.56)	6.84 (4.47–10.46)	
No	2,535	Reference	2.32 (1.49–3.63)	3.94 (2.63–5.90)	7.78 (5.23–11.56)	
Shock						<0.001
Yes	1,380	Reference	0.99 (0.66–1.48)	1.29(0.90–1.86)	1.86(1.30–2.65)	
No	3,317	Reference	4.62 (2.48–8.61)	6.10(3.35–11.12)	15.05(8.27–27.39)	
Pulmonary embolism						0.787
Yes	191	Reference	7.50 (0.85–65.99)	8.19 (1.01–66.45)	17.50 (2.24–136.71)	
No	4,506	Reference	2.20(1.60–3.02)	3.43(2.57–4.59)	7.16 (5.36–9.56)	
Endocarditis						0.468
Yes	152	Reference	1.26 (0.11–14.05)	0.89 (0.09–8.65)	2.52 (0.29–21.60)	
No	4,545	Reference	2.29 (1.67–3.14)	3.62 (2.71–4.83)	7.60 (5.69–10.14)	
Dyslipidemia						0.966
Yes	2,778	Reference	2.44 (1.62–3.68)	3.89 (2.66–5.69)	6.89 (4.62–10.29)	
No	1919	Reference	2.00 (1.23–3.22)	2.89 (1.87–4.46)	6.61 (4.35–10.05)	
Hypertension						<0.001
Yes	1924	Reference	3.33 (1.71–6.48)	10.68 (5.93–19.23)	16.89 (9.32–30.60)	
No	2,773	Reference	1.84 (1.29–2.63)	1.97 (1.41–2.75)	4.84 (3.48–6.73)	
Diabetes						0.308

(Continued)

TABLE 4 (Continued)

Subgroups	*N*	No nutrition risk	Low nutrition risk	Moderate nutrition risk	High nutrition risk	*p* for interaction
Yes	1810	Reference	2.01 (1.26–3.20)	2.92 (1.90–4.48)	6.26 (4.07–9.62)	
No	2,887	Reference	2.50 (1.64–3.81)	4.04 (2.75–5.94)	8.46 (5.79–12.38)	
Acute kidney injury						0.305
Yes	4,254	Reference	2.19 (1.60–3.01)	3.40 (2.54–4.53)	6.94 (5.21–9.26)	
No	443	Reference	5.82 (0.60–56.65)	3.96 (0.35–44.20)	24.26 (2.85–206.35)	
Chronic kidney disease						<0.001
Yes	1,500	Reference	1.75 (1.12–2.72)	1.53 (1.00–2.34)	3.86 (2.50–5.95)	
No	3,197	Reference	2.50 (1.59–3.90)	5.81 (3.91–8.63)	11.17 (7.56–16.50)	
Malignancy						0.381
Yes	226	Reference	1.14 (0.30–4.36)	1.23 (034–4.38)	3.50 (1.10–11.13)	
No	4,471	Reference	2.35 (1.70–3.23)	3.69 (2.75–4.95)	7.62 (5.68–10.22)	

Binary logistic regression analysis was used and results were presented as OR (odds ratio) and 95% CI (confidence interval). *p* for interaction was calculated using binary logistic analysis to determine whether there is interaction between different subgroups and nutritional status.

facilities. Taken together, we believe that for patients with comorbid malnutrition in the CICU, the earlier their nutritional status is improved, the better their prognosis is likely to be.

While this study had some limitations. (1) This study only assessed the initial GNRI of CICU patients and did not record and analyze the dynamic changes in GNRI. (2) The use of public databases limited the collection of relevant information that could have influenced the model, such as detailed causes of death, left ventricular ejection fraction, specific coronary artery lesions, revascularization, types of myocardial infarction, and precise clinical symptoms. (3) Due to the retrospective nature of our study, we were unable to determine a specific cause for hospitalization. (4) Since it was a single-center retrospective study, it was susceptible to certain biases that might compromise the accuracy of the findings, thereby reducing their strength and rendering them incapable of establishing causality. Multi-central research is needed to further verify the current discovery among a wider range of people.

5. Conclusion

GNRI, being a simple and easily measurable tool in clinical practice, contributed significantly to the prognosis of in-hospital mortality among patients admitted to the CICU. Moreover, we found that higher nutrition risk, as indicated by low GNRI values, was significantly associated with prolonged hospital and CICU stays. Prospective, randomized studies are needed to establish whether interventions aimed at improving nutritional status could improve clinical outcomes. Moreover, we observed that higher nutrition risk, as indicated by low GNRI values, was significantly associated with prolonged hospital and CICU stays.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://doi.org/10.13026/6mm1-ek67.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YL and ZW: conceptualization. TS and BZ: methodology. YL and ZW: writing – original draft. XL: writing – review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1218738/full#supplementary-material

References

1. Leong DP, Joseph PG, McKee M, Anand SS, Teo KK, Schwalm JD, et al. Reducing the global burden of cardiovascular disease, Part 2: prevention and treatment of cardiovascular disease. *Circ Res*. (2017) 121:695–0. doi: 10.1161/CIRCRESAHA.117.311849

2. Morrow DA, Fang JC, Fintel DJ, Granger CB, Katz JN, Kushner FG, et al. Evolution of critical care cardiology: transformation of the cardiovascular intensive care unit and the emerging need for new medical staffing and training models: a scientific statement from the American Heart Association. *Circulation*. (2012) 126:1408–28. doi: 10.1161/CIR.0b013e31826890b0

3. Katz JN, Shah BR, Volz EM, Horton JR, Shaw LK, Newby LK, et al. Evolution of the coronary care unit: clinical characteristics and temporal trends in healthcare delivery and outcomes. *Crit Care Med*. (2010) 38:375–1. doi: 10.1097/CCM.0b013e3181cb0a63

4. Jentzer JC, van Diepen S, Barsness GW, Katz JN, Wiley BM, Bennett CE, et al. Changes in comorbidities, diagnoses, therapies and outcomes in a contemporary cardiac intensive care unit population. *Am Heart J*. (2019) 215:12–9. doi: 10.1016/j.ahj.2019.05.012

5. Morrow DA. Trends in cardiac critical care: reshaping the cardiac intensive care unit. *Circ Cardiovasc Qual Outcomes*. (2017) 10:e004010. doi: 10.1161/CIRCOUTCOMES.117.004010

6. Sinha SS, Sjoding MW, Sukul D, Prescott HC, Iwashyna TJ, Gurm HS, et al. Changes in primary noncardiac diagnoses over time among elderly cardiac intensive care unit patients in the United States. *Circ Cardiovasc Qual Outcomes*. (2017) 10:e003616. doi: 10.1161/CIRCOUTCOMES.117.003616

7. Stevens V, Geiger K, Concannon C, Nelson RE, Brown J, Dumyati G. Inpatient costs, mortality and 30-day re-admission in patients with central-line-associated bloodstream infections. *Clin Microbiol Infect*. (2014) 20:O318–24. doi: 10.1111/1469-0691.12407

8. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med*. (2007) 33:66–73. doi: 10.1007/s00134-006-0399-8

9. Hein OV, Birnbaum J, Wernecke K, England M, Konertz W, Spies C. Prolonged intensive care unit stay in cardiac surgery: risk factors and long-term-survival. *Ann Thorac Surg*. (2006) 81:880–5. doi: 10.1016/j.athoracsur.2005.09.077

10. Cook DJ, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care*. (2001) 5:368–5. doi: 10.1186/cc1071

11. Garrouste-Orgeas M, Timsit JF, Vesin A, Schwebel C, Arnodo P, Lefrant JY, et al. Selected medical errors in the intensive care unit: results of the IATROREF study: parts I and II. *Am J Respir Crit Care Med*. (2010) 181:134–2. doi: 10.1164/rccm.200812-1820OC

12. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. *Crit Care*. (2019) 23:368. doi: 10.1186/s13054-019-2657-5

13. Singer P. Preserving the quality of life: nutrition in the ICU. *Crit Care*. (2019) 23:139. doi: 10.1186/s13054-019-2415-8

14. Wischmeyer PE. Nutrition therapy in sepsis. *Crit Care Clin*. (2018) 34:107–5. doi: 10.1016/j.ccc.2017.08.008

15. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr*. (2005) 82:777–3. doi: 10.1093/ajcn/82.4.777

16. Cereda E, Pedrolli C. The geriatric nutritional risk index. *Curr Opin Clin Nutr Metab Care*. (2009) 12:1–7. doi: 10.1097/MCO.0b013e3283186f59

17. Gärtner S, Kraft M, Krüger J, Vogt LJ, Fiene M, Mayerle J, et al. Geriatric nutritional risk index correlates with length of hospital stay and inflammatory markers in older inpatients. *Clin Nutr*. (2017) 36:1048–53. doi: 10.1016/j.clnu.2016.06.019

18. Rus VA, Chitu M, Cernea S, Benedek I, Hodas R, Zavate R, et al. Altered nutritional status, inflammation and systemic vulnerability in patients with acute myocardial infarction undergoing percutaneous coronary revascularisation: A prospective study in a level 3 cardiac critical care unit. *Nutr Diet*. (2020) 77:212–2. doi: 10.1111/1747-0080.12536

19. Matsukuma Y, Tanaka S, Taniguchi M, Nakano T, Masutani K, Hirakata H, et al. Association of geriatric nutritional risk index with infection-related mortality in patients undergoing hemodialysis: the Q-Cohort Study. *Clin Nutr*. (2019) 38:279–7. doi: 10.1016/j.clnu.2018.01.019

20. Takahashi H, Ito Y, Ishii H, Aoyama T, Kamoi D, Kasuga H, et al. Geriatric nutritional risk index accurately predicts cardiovascular mortality in incident hemodialysis patients. *J Cardiol*. (2014) 64:32–6. doi: 10.1016/j.jjcc.2013.10.018

21. Lee JS, Choi HS, Ko YG, Yun DH. Performance of the geriatric nutritional risk index in predicting 28-day hospital mortality in older adult patients with sepsis. *Clin Nutr*. (2013) 32:843–8. doi: 10.1016/j.clnu.2013.01.007

22. Li H, Cen K, Sun W, Feng B. Prognostic value of geriatric nutritional risk index in elderly patients with heart failure: a meta-analysis. *Aging Clin Exp Res*. (2021) 33:1477–86. doi: 10.1007/s40520-020-01656-3

23. Wada H, Dohi T, Miyauchi K, Doi S, Naito R, Konishi H, et al. Prognostic impact of the geriatric nutritional risk index on long-term outcomes in patients who underwent percutaneous coronary intervention. *Am J Cardiol*. (2017) 119:1740–5. doi: 10.1016/j.amjcard.2017.02.051

24. Honda Y, Nagai T, Iwakami N, Sugano Y, Honda S, Okada A, et al. Usefulness of geriatric nutritional risk index for assessing nutritional status and its prognostic impact in patients aged ≥65 years with acute heart failure. *Am J Cardiol*. (2016) 118:550–5. doi: 10.1016/j.amjcard.2016.05.045

25. Jia Y, Gao Y, Li D, Cao Y, Cheng Y, Li F, et al. Geriatric nutritional risk index score predicts clinical outcome in patients with acute st-segment elevation myocardial infarction. *J Cardiovasc Nurs*. (2020) 35:E44–e52. doi: 10.1097/JCN.0000000000000674

26. Johnson A, Bulgarelli L., Pollard T., Horng S., Celi L. A., Mark R MIMIC-IV (version 2.0). PhysioNet (2022).

27. Yamada K, Furuya R, Takita T, Maruyama Y, Yamaguchi Y, Ohkawa S, et al. Simplified nutritional screening tools for patients on maintenance hemodialysis. *Am J Clin Nutr*. (2008) 87:106–3. doi: 10.1093/ajcn/87.1.106

28. Shah B, Sucher K, Hollenbeck CB. Comparison of ideal body weight equations and published height-weight tables with body mass index tables for healthy adults in the United States. *Nutr Clin Pract*. (2006) 21:312–9. doi: 10.1177/0115426506021003312

29. Bellanti F, Lo Buglio A, Quiete S, Vendemiale G. Malnutrition in hospitalized old patients: screening and diagnosis. *Clin Outcomes Manag Nutr*. (2022) 14:910. doi: 10.3390/nu14040910

30. Nakagomi A, Kohashi K, Morisawa T, Kosugi M, Endoh I, Kusama Y, et al. Nutritional status is associated with inflammation and predicts a poor outcome in patients with chronic heart failure. *J Atheroscler Thromb*. (2016) 23:713–7. doi: 10.5551/jat.31526

31. Wells JL, Dumbrell AC. Nutrition and aging: assessment and treatment of compromised nutritional status in frail elderly patients. *Clin Interv Aging*. (2006) 1:67–79. doi: 10.2147/ciia.2006.1.1.67

32. Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. *Eur Heart J*. (1998) 19:761–5. doi: 10.1053/euhj.1997.0858

33. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. *J Am Geriatr Soc*. (2006) 54:1674–81. doi: 10.1111/j.1532-5415.2006

34. Thompson DS, Bourdon C, Massara P, Boyne MS, Forrester TE, Gonzales GB, et al. Childhood severe acute malnutrition is associated with metabolic changes in adulthood. *JCI Insight*. (2020) 5:e141316. doi: 10.1172/jci.insight.141316

35. Spoelstra MN, Mari A, Mendel M, Senga E, van Rheenen P, van Dijk TH, et al. Kwashiorkor and marasmus are both associated with impaired glucose clearance related to pancreatic β-cell dysfunction. *Metabolism*. (2012) 61:1224–30. doi: 10.1016/j.metabol.2012.01.019

36. Badaloo AV, Forrester T, Reid M, Jahoor F. Lipid kinetic differences between children with kwashiorkor and those with marasmus. *Am J Clin Nutr*. (2006) 83:1283–8. doi: 10.1093/ajcn/83.6.1283

37. Nakamura T, Matsumoto M, Haraguchi Y, Ishida T, Momomura SI. Prognostic impact of malnutrition assessed using geriatric nutritional risk index in patients aged ⩾80 years with heart failure. *Eur J Cardiovasc Nurs*. (2020) 19:172–7. doi: 10.1177/1474515119864970

38. Matsuo Y, Kumakura H, Kanai H, Iwasaki T, Ichikawa S. The geriatric nutritional risk index predicts long-term survival and cardiovascular or limb events in peripheral arterial disease. *J Atheroscler Thromb*. (2020) 27:134–3. doi: 10.5551/jat.49767

39. Kunimura A, Ishii H, Uetani T, Aoki T, Harada K, Hirayama K, et al. Impact of geriatric nutritional risk index on cardiovascular outcomes in patients with stable coronary artery disease. *J Cardiol*. (2017) 69:383–8. doi: 10.1016/j.jjcc.2016.09.004

40. Arikawa R, Kanda D, Ikeda Y, Tokushige A, Sonoda T, Anzaki K, et al. Prognostic impact of malnutrition on cardiovascular events in coronary artery disease patients with myocardial damage. *BMC Cardiovasc Disord*. (2021) 21:479. doi: 10.1186/s12872-021-02296-9

41. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr*. (1987) 11:8–13.

42. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev*. (1996) 54:S59–65. doi: 10.1111/j.1753-4887.1996.tb03793.x

43. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. (1999) 15:116–2. doi: 10.1016/S0899-9007(98)00171-3

44. Nelson JJ, Liao D, Sharrett AR, Folsom AR, Chambless LE, Shahar E, et al. Serum albumin level as a predictor of incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. (2000) 151:468–7. doi: 10.1093/oxfordjournals.aje.a010232

45. Pei J, Wang X, Chen P, Zheng K, Hu X. Hb Levels and sex differences in relation to short-term outcomes in patients with acute myocardial infarction. *Front Cardiovasc Med* (2021). 16:653351. doi: et al10.3389/fcvm.2021.653351

46. Narumi T, Arimoto T, Funayama A, Kadowaki S, Otaki Y, Nishiyama S, et al. Prognostic importance of objective nutritional indexes in patients with chronic heart failure. *J Cardiol*. (2013) 62:307–3. doi: 10.1016/j.jjcc.2013.05.007

47. Cheng YL, Sung SH, Cheng HM, Hsu PF, Guo CY, Yu WC, et al. Prognostic nutritional index and the risk of mortality in patients with acute heart failure. *J Am Heart Assoc*. (2017) 6:e004876. doi: 10.1161/JAHA.116.004876

48. Lee M, Lim JS, Kim Y, Lee JH, Kim CH, Lee SH, et al. Association between geriatric nutritional risk index and post-stroke cognitive outcomes. *Nutrients*. (2021) 13:1776. doi: 10.3390/nu13061776

49. Fan Y, He L, Zhou Y, Man C. Predictive value of geriatric nutritional risk index in patients with coronary artery disease: a meta-analysis. *Front Nutr*. (2021) 8:736884. doi: 10.3389/fnut.2021.736884

50. Zhao Q, Zhang TY, Cheng YJ, Ma Y, Xu YK, Yang JQ, et al. Impacts of geriatric nutritional risk index on prognosis of patients with non-ST-segment elevation acute coronary syndrome: results from an observational cohort study in China. *Nutr Metab Cardiovasc Dis*. (2020) 30:1685–96. doi: 10.1016/j.numecd.2020.05.016

51. Tasbulak O, Guler A, Duran M, Sahin A, Bulut U, Avci Y, et al. Association between nutritional indices and long-term outcomes in patients undergoing isolated coronary artery bypass grafting. *Cureus*. (2021) 13:e16567. doi: 10.7759/cureus.16567

52. Duerksen DR, Laporte M, Jeejeebhoy K. Evaluation of nutrition status using the subjective globalassessment: malnutrition, cachexia, and sarcopenia. *Nutr Clin Pract*. (2021) 36:942–6. doi: 10.1002/ncp.10613

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 16 August 2023
DOI 10.3389/fnut.2023.1228826

OPEN ACCESS

EDITED BY
Barbara Troesch,
Nutricia/Danone, Switzerland

REVIEWED BY
Khalid Zaman,
The University of Haripur, Pakistan
Carlo Pedrolli,
Azienda Provinciale per i Servizi Sanitari (APSS), Italy

*CORRESPONDENCE
Nina Kaegi-Braun
✉ nina@kaegi-braun.ch

RECEIVED 25 May 2023
ACCEPTED 31 July 2023
PUBLISHED 16 August 2023

CITATION
Rigling M, Schuetz P and Kaegi-Braun N (2023) Is food insecurity contributing to malnutrition in older adults in Switzerland? – A cross-sectional study.
Front. Nutr. 10:1228826.
doi: 10.3389/fnut.2023.1228826

Is food insecurity contributing to malnutrition in older adults in Switzerland? – A cross-sectional study

Maurus Rigling[1,2], Philipp Schuetz[1,2] and Nina Kaegi-Braun[1]*

[1]Division of General Internal and Emergency Medicine, Medical University Department, Kantonsspital Aarau, Aarau, Switzerland, [2]Medical Faculty, University of Basel, Basel, Switzerland

Background: Food insecurity has been defined as "*limited access to food, at the level of individuals or households, due to lack of money or other resources*" and may increase the nutritional risk, which in turn leads to poor health, development of chronic diseases, poor psychological and cognitive functioning, and substandard academic achievements. There is limited data on the importance of food insecurity in a rich country such as Switzerland.

Methods: This is a cross-sectional analysis of data from a structured survey in an elderly population of Switzerland. The data was assessed between June and August 2021 in the course of a 7-year phone call follow-up from the EFFORT trial, which included medical inpatients at nutritional risk from 2014 to 2018. A validated questionnaire (Six-Item Short Form 2012 of the U.S: Household Food Security Survey Module) was used to assess food security status.

Results: Of the 433 included patients, 30 (6.9%) were food insecure. A significant association between food insecurity and age, governmental financial support and self-reported loneliness was found. When compared with the food secure group, there was a significant lower quality of life measured by the EQ-5D VAS.

Conclusion: In an older Swiss population of patients at nutritional risk, food insecurity was named as a contributing factor for malnutrition in about 7% of patients, particularly younger individuals with financial support, and self-reported loneliness. In the assessment of malnutrition, physician and dieticians should ask for food insecurity and if detect take appropriate actions.

KEYWORDS

food security, malnutrition, health, quality of life, older adults, food insecurity, nutritional risk, risk factors

1. Introduction

Since 2014 the global prevalence of moderate or severe food insecurity has been slowly on the rise (1). Food insecurity has been defined as "*limited access to food, at the level of individuals or households, due to lack of money or other resources*" and has been associated with poor dietary intake and nutritional status, poor health, increased risk for the development of chronic diseases, poor psychological and cognitive functioning, and substandard academic achievement (2).

In 2020 it was estimated that the increase of food insecurity was equal to that of the previous 5 years combined (1). Worldwide around 2.4 billion people suffer from some form of food

insecurity in Africa and Asia (1). On a much smaller scale, food insecurity is also a problem in high-income countries (3–6). In Europe and Northern America, studies found that in 2020 around 9 % of the population were moderately or severely food insecure (1). In these countries, food insecurity can coexist with food waste, overproduction and abundant food availability (7). In recent years, this was especially the case in countries, that suffered a financial crisis (8, 9), while currently the COVID-19 pandemic globally further increased the risk for food insecurity (10, 11). The consequences of food insecurity are most visible in low-income countries, where hunger-related malnutrition is a serious problem. In high-income countries, undernutrition is more commonly seen in ill patients (disease-related malnutrition, DRM) resulting from anorexia, catabolic metabolism and immobility. According to a recent meta-analysis of Kantilafti et al., there is a reverse relationship between food insecurity and multimorbidity (12). They found a 1.5-fold increased probability of multimorbidity among people with food insecurity. Conversely, people with multimorbidity had more than two times higher odds to present with food insecurity. Food security, morbidity and malnutrition are therefore supposed to have a complex interplay. Despite the rising prevalence of food insecurity and its burden on health, there is a lack of evidence in many European countries, including Switzerland (4). While in the United States and Canada food security is routinely monitored, there is no such monitoring in Switzerland and consequently data on food insecurity are missing (13, 14).

Even though Switzerland has a high standard of living, a low poverty rate and strong welfare programs, the question about the existence of food insecurity should still be raised. We hypothesize that there is a relevant amount of food insecure people living in Switzerland, especially in the time of the COVID-19 pandemic. The goal of this study was to estimate the prevalence of food insecurity in an elderly Swiss population at nutritional risk. Furthermore, the identification of risk factors and the investigation of the consequences are crucial to increase the awareness of health care workers and to take further actions. Therefore, in a second step, we aimed to find predictive factors for food insecurity and we study the influence of food insecurity regarding clinical outcomes, quality of life and health. This study may help to better identify people at risk and guide future interventions and policies.

2. Materials and methods

2.1. Study design and setting

This is a cross-sectional analysis of data from a systemic survey of participants included in the EFFORT Trial (The Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial), a multicenter Swiss randomized controlled trial. The survey was conducted between June and August 2021 in the course of a 7-year phone call follow-up of the trial. This study included medical patients at nutritional risk hospitalized between 2014 and 2018. Nutritional risk during the initial hospital stay was defined by the Nutritional Risk Screening 2002 (NRS 2002) tool and all patients with a score ≥ 3 points (15) and with an expected length of hospital stay of more than 4 days were included. These participants were randomly assigned to receive either protocol-guided individualized nutritional support to reach protein and caloric goals (intervention group) or standard hospital food (control group). 30 days, 180 days, 3–5 years and 5–7 years after hospital discharge participants were contacted by blinded study nurses or doctoral students for structured telephone interviews. Food security was assessed in the final follow-up call 7 years after study inclusion. Detailed information about the trial have been published previously (16).

2.2. Assessment of food security status

We used the validated Six-Item Short Form 2012 of the U.S: Household Food Security Survey Module (17). The six-item short form of the survey module was developed by researchers at the National Center for Health Statistics of the U.S in collaboration with Abt Associates Inc. and first published in 1999 (18). The questions in the six-item module are essentially unchanged from those in the original module from 1995. There were three minor revisions in 2006, 2008, and 2012. The sum of affirmative responses to the six questions is the raw score. The food security status is assigned as follows: 0–1 points = high or marginal food security, 2–4 = low food security and 5–6 = very low food security. Further the participants can be classified into "food secure" (0–1 points) and "food insecure" ($\geq$ 2 points). We translated the Six-Item Short Form from English to German.

2.3. Predictive variables

Sociodemographic characteristics (age, sex and region) were reported at study inclusion and age was extrapolated to the current date. Nutritional data (BMI, height, weight) and Barthel Index (19), living situation, education, the need of financial support and COVID-associated factors (i.e., self-reported loneliness) were assessed during the phone interview.

2.4. Outcome variables

Health outcomes (defined as need for rehospitalization in the last 2 years, number of hospitalizations during the last 2 years, number of falls) and quality of life [measured by EQ-5D (20)] were also structurally assessed during the telephone interview. Weight loss was calculated using the last weight from the 5-year follow-up and the current patient-reported weight. We used current BMI and weight loss data to retrospectively calculate "Malnutrition Universal Screening Tool (MUST) score (21), without considering additional scoring for acute illness, because patients were in an outpatient setting.

2.5. Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) and compared using student's *t*-test, while categorical variables are shown in numbers and percentages and were analyzed by Pearson's χ^2 test. Uni- and multivariate logistic regression analyses were used to investigate possible predictive factors for food insecurity. For the analysis of associated adverse health outcomes, we used linear and logistic regression and adjusting for age. All statistical analyses

were performed using Stata version 15.1 (StataCorp). $p < 0.05$ was considered statistically significant, and all tests were 2-tailed.

3. Results

From April 2014 to February 2018, 5,015 patients were screened and 2028 included in the initial EFFORT trial. During the 7-year follow-up 1,137 patients died and 279 were lost to follow-up. 152 patients withdrew informed consent and 27 had a missing food security questionnaire. The final analysis cohort thus consisted of 434 patients (Figure 1). Baseline characteristics for the overall population and those stratified according to food security are shown in Table 1. Of the 434 included patients, 30 (6.9%) met the definition of food insecurity. Food insecure participants were significantly younger and more independent in activities of daily living (Barthel Index). Two thirds of food insecure participants were younger than 65 years. There were no differences between male and female. Of all the food insecure participants, 50% received financial support, while only 15.8% were financially supported in the food secure group. The category food insecurity contains low (5.8%) and very low food security (1.2%), as illustrated in Figure 2. Figure 3 shows the distribution of the affirmative answers to the U.S. Household Food Security Survey Module (Six-Item Short Form).

3.1. Predictors for food insecurity

In the univariate logistic regression analysis, we found significant associations between food insecurity and age (OR 0.95, 95% CI

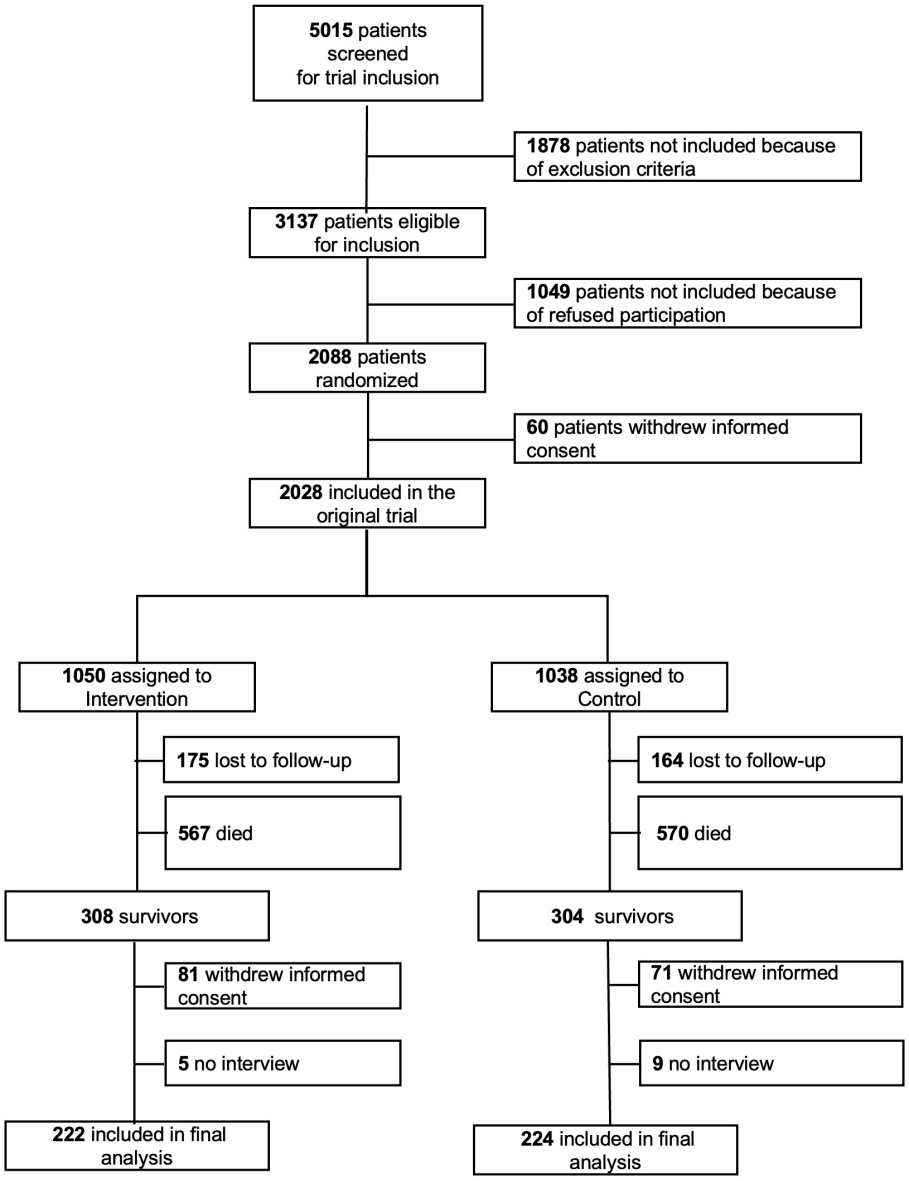


FIGURE 1
Study flow chart.

10.3389/fnut.2023.1228826

TABLE 1 Baseline characteristics.

	Overall	Food secure	Food insecure	*p* value
N	434	404	30	
Sociodemographics				
Age, mean (SD)	74.18 (15.46)	75.27 (14.72)	59.60 (18.01)	<0.001
Male sex	213 (49.1%)	198 (49.0%)	15 (50.0%)	0.92
Nutritional assessment				
BMI, mean (SD)	25.65 (4.91)	25.65 (4.79)	25.63 (6.38)	0.98
Weight, mean (SD)	72.80 (16.90)	72.61 (16.29)	75.28 (23.81)	0.41
Height, mean (SD)	167.91 (9.05)	167.76 (8.94)	170.03 (10.39)	0.18
Activity of daily living				
Barthel, median (IQR)	85.91 (16.12)	85.50 (16.34)	91.50 (11.68)	0.049
Living situation				
Home without help	282 (68.8%)	263 (69.0%)	19 (65.5%)	0.75
Home with professional help	106 (25.9%)	97 (25.5%)	9 (31.0%)	
Institutionalized	22 (5.4%)	21 (5.5%)	1 (3.4%)	
Education				
Middle school	28 (6.5%)	26 (6.5%)	2 (6.7%)	0.15
High school	29 (6.7%)	24 (6.0%)	5 (16.7%)	
Apprenticeship	301 (69.8%)	280 (69.8%)	21 (70.0%)	
University	72 (16.7%)	70 (17.5%)	2 (6.7%)	
No education	1 (0.2%)	1 (0.2%)	0 (0.0%)	
Financial support	78 (18.0%)	63 (15.8%)	15 (50.0%)	<0.001
Region				
Eastern part	116 (26.7%)	108 (26.7%)	8 (26.7%)	0.94
Western part	169 (38.9%)	156 (38.6%)	13 (43.3%)	
Midlands	93 (21.4%)	87 (21.5%)	6 (20.0%)	
Central part	56 (12.9%)	53 (13.1%)	3 (10.0%)	
Loneliness				
Never	329 (76.0%)	314 (77.9%)	15 (50.0%)	<0.001
Rarely	25 (5.8%)	22 (5.5%)	3 (10.0%)	
Sometimes	43 (9.9%)	34 (8.4%)	9 (30.0%)	
Often	25 (5.8%)	24 (6.0%)	1 (3.3%)	
Always	11 (2.5%)	9 (2.2%)	2 (6.7%)	

BMI, body-mass index.

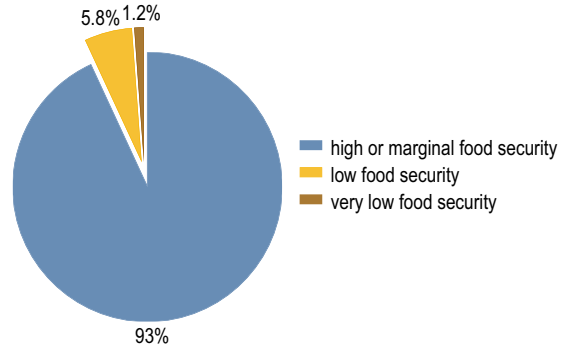


FIGURE 2
Distribution of the level of food security of all participants.

0.93–0.97), governmental financial support (OR 5.35, 95% CI 2.49–11.49) and self-reported loneliness (OR 3.34 95%CI 1.54–7.26). These results remained robust in the multivariate analysis. There was no significant association between food insecurity and sex, education, housing situation, or region (Table 2).

3.2. Predictive score for food insecurity

We constructed a simple predictive score for food insecurity containing three items: age < 65, financial support and self-reported loneliness. We assigned one point to each of these parameters. As shown in Figure 4, the probability for food insecurity showed a stepwise increase with a low probability <5% for 0 or 1 point, to 15.8% for 2 points up to 61.5% for patients with 3 points.

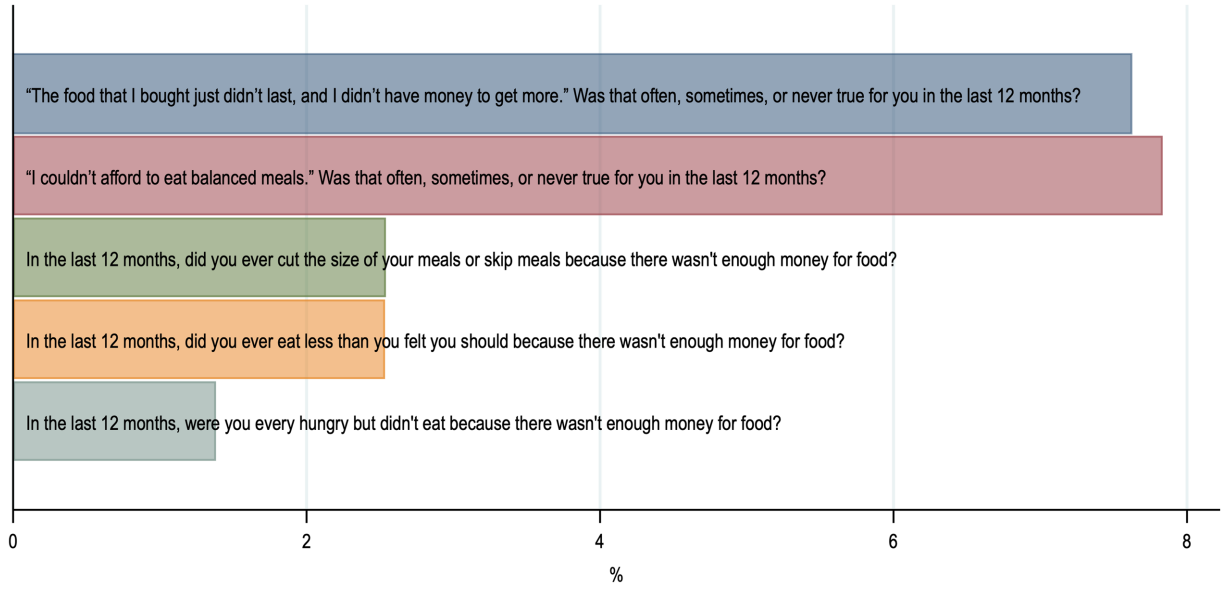


FIGURE 3
Distribution of positive answers to the questions of U.S. Household Food Security Survey Module (Six-Item Short Form).

3.3. Association of food insecurity and health, nutrition and quality of life

After adjustment for age, we found a trend toward higher risk for hospitalization in the food insecure group (OR 1.98, 95% CI 0.91–4.34), while there was no significant difference in the number of hospitalizations per person. Additionally, the odds for falls were 2.5-fold higher in the food insecure group (Table 3).

Regarding the nutritional status, there were no difference in the prevalence of malnutrition defined by the MUST score (OR 1.08, 95% CI 0.43–2.72). Total weight change did not differ between food secure and food insecure individuals. However, individually, food insecure participants showed significant higher weight loss among participants who reported weight loss (−4.62 vs. −9.81 kg, Coeff −5.2, 95% CI 8.61−1.79).

When compared to the food secure group, there was a significant lower quality of life measured by the EQ-5D index and the EQ-5D VAS when adjusted for age. There was no difference in activities of daily living and functional decline, measured by the Barthel Index and change of the Barthel Index.

4. Discussion

In this cross-sectional study with an elderly, multimorbid population, we found a prevalence of 6.9% for food insecurity. Significant predictors for food insecurity included lower age, need for financial support and self-reported loneliness. Food security tended to have a significant impact on health care use, falls and quality of life without directly influencing the severity of nutritional status.

In 2020, a survey done in the general Swiss population estimated the prevalence of moderate to severe food insecurity to be around 2.2% (22). That is considerably lower than the moderate to severe food insecurity in Europe and Northern America (8.8% in 2020) (1). The contrast between the prevalence of food insecurity in our study population (6.9%) and the Swiss population (2.2% in 2020) shows that our study population is an important at-risk subpopulation for food insecurity in Switzerland. Additionally, the survey was conducted in the middle of the COVID-19 pandemic. The COVID-19 pandemic triggered a global economic recession starting in 2020 and extending into 2021. The results were record levels of unemployment, lost livelihoods and rising poverty levels in many countries around the world (22) leading to rising food insecurity (10, 11).

Younger age was one of the risk factors for food insecurity, which we were able to identify. Similarly, in Canada, the prevalence of food insecurity was shown to be lower in households with seniors' incomes as their primary income (13). This in part was interpreted in the context of Canada's pension program, which provides some financial protection. In our population food insecurity was significant lower in the age group 65 and older (3% vs. 19.4%). We assume that similar protection mechanisms like in Canada could be in place in Switzerland through the pension program. In contrast, in Portugal and Greece data shows a trend of higher food insecurity in the elderly population (8, 23). In Greece it was estimated that 69% of older adults (≥60 years) living in the community were affected by some form of food insecurity (8). One would expect elderly residents living in an institution to be protected from food insecurity. But in our population, there were no differences in food insecurity between participants living in an institution and participants living at home.

Another significant predictor for food insecurity in our analysis was need for financial support. Of all food insecure participants, 50% received financial support and most food insecure participant, who received financial support were in working age. Similar results were found in the report "Household Food Insecurity in Canada 2021" with 63% of households relying on social assistance were food insecure (13). This raises the question, whether financial support is insufficient to prevent food insecurity. Due to the cross-sectional nature of the study, no further conclusions can be drawn. However, financial support might rather be a consequence than a cause of food insecurity. Beside age and financial support, a third predictive factor for food insecurity was self-reported loneliness. Social isolation may thus be a

10.3389/fnut.2023.1228826

TABLE 2 Predictors for food insecurity.

	OR univariate (95% CI)	*P* Value	OR multivariate (95% CI)	*P* Value
Sociodemographics				
Age	0.95 (0.93–0.97)	0.000	0.95 (0.92–0.98)	0.000
Male sex	1.04 (0.50–2.18)	0.917	1.67 (0.66–4.25)	0.278
Nutritional assessment				
BMI	1.00 (0.93–1.08)	0.985	0.94 (0.86–1.01)	0.104
Weight	1.01 (0.99–1.03)	0.405	–	–
Height	1.03 (0.99–1.07)	0.185	–	–
Activity of daily living				
Barthel-Index	1.03 (1.00–1.07)	0.052	1.05 (1.00–1.10)	0.072
Living situation				
Home without help	Ref		Ref	
Home with professional help	1.28 (0.56–2.94)	0.553	2.12 (0.65–6.92)	0.215
Institutionalized	0.66 (0.08–5.17)	0.692	Omitted	–
Institutionalized (y/n)	0.61 (0.08–4.72)	0.638	4.75 (0.34–65.75)	0.245
Education				
Higher education	0.51 (0.21–1.24)	0.136	0.55 (0.28–1.10)	0.093
Financial support	5.35 (2.49–11.49)	0.000	5.61 (2.11–14.86)	0.001
Region				
Ostschweiz	Ref		Ref	
Nordwestschweiz	1.13 (0.45–2.81)	0.801	1.77 (0.59–5.27)	0.305
Mittelland	0.93 (0.31–2.78)	0.898	1.04 (0.29–3.82)	0.947
Zentralschweiz	0.76 (0.19–3.00)	0.700	0.80 (0.13–4.95)	0.811
Zentralschweiz	0.76 (0.19–3.00)	0.700	0.80 (0.13–4.95)	0.811
Loneliness				
Self-reported loneliness (y/n)	3.34 (1.54–7.26)	0.002	2.71 (1.04–7.11)	0.042

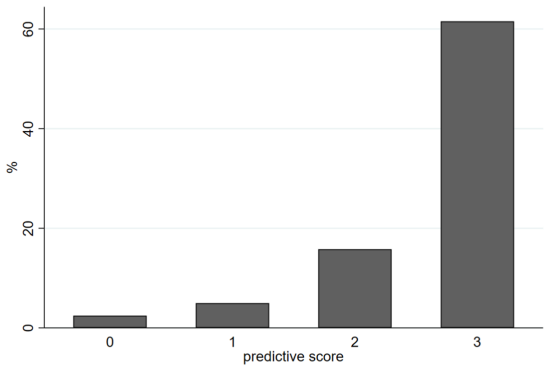


FIGURE 4
Predictive score for food insecurity containing three items: age<65, financial support and self-reported loneliness. Each item gets one point.

risk factor for food insecurity. Other studies have shown a relationship between food insecurity and poor mental health (13).

The second important question is, how does food insecurity influence clinical outcomes. In our regression analysis, there was a trend toward lower hospitalization rates and less falls in food secure patients. Previous studies showed that food insecure people are more vulnerable to chronic disease (8, 23). Chronic disease leads to higher health related expenses. And higher expenses could lead to worsening or the beginning of food insecurity. In Canada, food insecurity is associated with higher healthcare expenses (13). Scarcity in financial resources could lead to suboptimal treatment adherence, which could lead to worsening of chronic conditions, more complications and more hospitalizations. This vicious cycle could be a potential intervention point for reducing food insecurity.

Using the Malnutrition Universal Screening Tool (MUST) under the assumption that there is no acute illness present, we found no difference in the prevalence of malnutrition between food secure and food insecure participants. Other studies, which investigated the impact of food insecurity on malnutrition risk, could find an increased risk for malnutrition in food insecure participants (8, 24, 25). A study in the US showed a significant lower mean intake for 12 nutrients including energy, protein, iron, zinc, vitamins, riboflavin, niacin, B-6 and B-12 (24). An interesting finding was, that the mean weight change in the last 2 years did not differ according to food security status, but weight loss was more extreme in the food insecure individuals. In the U.S., studies have shown an association between

Table 3 Assoiciation between food insecurity and outcomes in nutrition, quality of life and health.

Outcomes	Food secure *N* or *n* (% or SD)	Food insecure *N* or *n* (% or SD)	OR or coefficient (95% CI)	value of *p*	adjusted OR or coefficient* (95% CI)	value of *p*
Health						
Hospitalization (y/n)	159 (39.4%)	15 (50.0%)	1.54 (0.73–3.24)	0.254	1.98 (0.91–4.34)	0.086
Hospitalization (n)	0.85 (1.29)	1.24 (2.01)	0.39 (−0.13–0.9)	0.138	0.43 (−0.1–0.96)*	0.110
Elective	123 (30.4%)	12 (40.0%)	1.14 (0.33–3.93)	0.841	1.28 (0.35–4.64)	0.709
Emergency	36 (8.9%)	3 (10.0%)	1.52 (0.71–3.26)	0.278	1.93 (0.86–4.29)	0.109
Falls	115 (28.7%)	10 (33.3%)	1.24 (0.56–2.74)	0.588	2.5 (1.03–6.06)	0.042
Nutrition						
Malnutrition (MUST score)	70 (17.7%)	7 (23.3%)	1.42 (0.59–3.43)	0.44	1.08 (0.43–2.72)	0.874
Weight loss last 3 months (y/n)	96 (23.9%)	9 (30.0%)	1.36 (0.6–3.07)	0.457	1.43 (0.61–3.34)	0.405
Weight change in the last 2 years in kg	−0.750 (5.52)	−0.026 (8.00)	0.72 (−1.51–2.96)	0.525	0.23 (−2.07–2.53)*	0.844
Weight loss in the last 2 years (y/n)	184 (45.5%)	7 (23.3%)	0.36 (0.15–0.87)	0.023	0.47 (0.19–1.14)	0.093
Weight loss in kg	−4.61 (4.35)	−9.81 (7.62)	−5.2 (−8.61—1.79)	0.003	−5.08 (−8.5--1.65)*	0.004
Weight gain in the last 2 years (y/n)	168 (41.6%)	19 (63.3%)	2.43 (1.13–5.23)	0.024	1.75 (0.79–3.91)	0.169
Weight gain in kg	3.95 (3.87)	4.25 (4.85)	0.3 (−1.77–2.37)	0.774	0.29 (−1.92–2.5)*	0.797
Quality of life						
Eq5d Score	0.736 (0.28)	0.68 (0.32)	−0.05 (−0.16–0.05)	0.338	−0.13 (−0.23--0.03)*	0.014
Eq5d VAS	69.45 (20.01)	61.83 (22.07)	−7.62 (−15.12--0.11)	0.047	−11.12 (−18.78--3.47)*	0.005
Barthel-Index	85.50 (16.34)	91.5 (11.68)	6 (0.03–11.98)	0.049	−1.75 (−7.24–3.75)*	0.532

BMI, body-mass index. MUST, malnutrition universal screening tool. Eq5d Score, European quality of life 5 dimensions index (EQ-5D; values range from −0·205 to 1, with higher scores indicating better quality of life). Eq5d VA, Visual-analogue scale (EQ-5D VAS; scores range from 0 to 100, with higher scores indicating better health status).

food insecurity and risk for obesity (26), which was not found in our data.

When compared with the food secure group, there was a significant lower quality of life measured by the EQ-5D VAS and EQ-5D Score. This is congruent with what another study has shown: food insecurity having a significant impact on quality of life (23).

In previous studies, food security was associated with impaired mobility and lower activities of daily living (27). In our study activity of daily living measured by Barthel-Index was not significantly different between the two groups when adjusting for age.

4.1. Strengths and limitations

This is one of the first studies to report food security in a Swiss at-risk population using a standardized and validated screening tool. Additionally, the survey was conducted during a time of rising food insecurity and is therefore highly relevant. We are aware of several limitations. First, in this cross-sectional study design, outcomes happened before food security was recorded and therefore there is no proof of causality. Due to the study design, the results should be seen as hypothesis-generating and used as basis for further larger investigations in this field. Second, the population is very selected because it includes only survivors of the EFFORT study population. With our data, we can only make limited conclusions for the entire Swiss population. Because we do not have data from all regions of Switzerland, some regional differences should be expected, especially between different language regions. And it is expected that we will miss certain important subpopulations with food insecurity in our study population. For example, healthy single mothers. In the US, food insecurity is highest for single mother households and households with income below the poverty line (14). Third, we had no data on possible confounders for outcome calculation such as the presence of chronic conditions, income, household structure, smoking, alcohol consumption and health care expenses. Fourth, the approach to determine the nutrition status of participants with the MUST Score is limited. For example, protein or micronutrient deficiencies would not have shown up. And finally, we did not perform a systematic literature review and may have missed some important previous studies on the topic. As such, it is important to be able to consider all studies from different journals without delisting of specific journals (28).

4.2. Conclusion

In an elderly Swiss population, food insecurity was present in about 7% of the participants, particularly younger individuals with financial support, and self-reported loneliness. As food insecure

individuals tended to have a higher health care use and an impaired quality of life, further scientific attention should be paid to the association between food insecurity, disease and health outcomes including strategies to improve food security status. In the assessment of malnutrition, physician and dieticians should ask for food insecurity and if detect take appropriate actions. Large, population-based assessment would be helpful to assess the prevalence and burden of food insecurity in Switzerland to understand the true magnitude of the problem.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Our analyzed data will be available to others with the publication of this manuscript on receipt of a letter of intention detailing the study hypothesis and statistical analysis plan, as already outlined in the primary EFFORT publication. Signing a data access agreement is asked from all applicants. Requests to access these datasets should be directed to schuetzph@gmail.com.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Northwest and Central Switzerland (EKNZ). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MR and NK-B contributed to the conception and design of the study and performed the statistical analysis. NK-B organized the database. MR wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

The Swiss National Science Foundation (SNSF professorship, PP00P3_150531 and PP00P3_176972) and the Research Council of the Kantonsspital Aarau, Switzerland (1410.000.058 and 1410.000.044) provided funding for the original trial.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. FAO, IFAD, UNICEF, WFP and WHO. (2021). *The State of Food Security and Nutrition in the World 2021. Transforming food systems for food security, improved nutrition and affordable healthy diets for all*. Rome: FAO.

2. Position of the American Dietetic Association. Food insecurity and hunger in the United States. *J Am Diet Assoc*. (2006) 106:446–58. doi: 10.1016/j.jada.2006.01.016

3. Hossain MB, Long MA, Stretesky PB. Welfare state spending, income inequality and food insecurity in Affluent nations: a cross-national examination of OECD countries. *Sustainability*. (2020) 13:324. doi: 10.3390/su13010324

4. Zaçe D, di Pietro ML, Reali L, de Waure C, Ricciardi W. Prevalence, socio-economic predictors and health correlates of food insecurity among Italian children-findings from a cross-sectional study. *Food Secur*. (2021) 13:13–24. doi: 10.1007/s12571-020-01111-1

5. Beacom E, Furey S, Hollywood L, Humphreys P. Investigating food insecurity measurement globally to inform practice locally: a rapid evidence review. *Crit Rev Food Sci Nutr*. (2021) 61:3319–39. doi: 10.1080/10408398.2020.1798347

6. Penne T, Goedemé T. Can low-income households afford a healthy diet? Insufficient income as a driver of food insecurity in Europe. *Food Policy*. (2021) 99:101978. doi: 10.1016/j.foodpol.2020.101978

7. Secondi L, Principato L, Laureti T. Household food waste behaviour in EU-27 countries: a multilevel analysis. *Food Policy*. (2015) 56:25–40. doi: 10.1016/j.foodpol.2015.07.007

8. Grammatikopoulou MG, Gkiouras K, Theodoridis X, Tsisimiri M, Markaki AG, Chourdakis M, et al. Food insecurity increases the risk of malnutrition among community-dwelling older adults. *Maturitas*. (2019) 119:8–13. doi: 10.1016/j.maturitas.2018.10.009

9. Chatzivagia E, Pepa A, Vlassopoulos A, Malisova O, Filippou K, Kapsokefalou M. Nutrition transition in the post-economic crisis of Greece: assessing the nutritional gap of food-insecure individuals. A cross-sectional study. *Nutrients*. (2019) 11:2914. doi: 10.3390/nu11122914

10. Laborde D, Martin W, Swinnen J, Vos R. COVID-19 risks to global food security. *Science*. (2020) 369:500–2. doi: 10.1126/science.abc4765

11. Fang D, Thomsen MR, Nayga RM, Yang W. Food insecurity during the COVID-19 pandemic: evidence from a survey of low-income Americans. *Food Secur*. (2022) 14:165–83. doi: 10.1007/s12571-021-01189-1

12. Kantilafti M, Giannakou K, Chrysostomou S. Multimorbidity and food insecurity in adults: a systematic review and meta-analysis. *PLoS One*. (2023) 18:e0288063. doi: 10.1371/journal.pone.0288063

13. Tarasuk V, Li T, Fafard St-Germain AA. *Household food insecurity in Canada, 2021*. Toronto: Research to identify policy options to reduce food insecurity (PROOF) (2022).

14. Coleman-Jensen A, Rabbitt MP, Gregory CA, Singh A. (2022). Household food security in the United States in 2021. Available at: www.ers.usda.gov

15. Kondrup J. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. (2003) 22:321–36. doi: 10.1016/S0261-5614(02)00214-5

16. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet*. (2019) 393:2312–21. doi: 10.1016/S0140-6736(18)32776-4

17. U.S. Household Food Security Survey Module: Six-Item Short Form Economic Research Service. ed: USDA; September 2012. [cited 2023 May 25]. Available from: https://www.ers.usda.gov/media/8282/short2012.pdf

18. Blumberg SJ, Bialostosky K, Hamilton WL, Briefel RR. The effectiveness of a short form of the household food security scale. *Am J Public Health*. (1999) 89:1231–4. doi: 10.2105/AJPH.89.8.1231

19. Fi M, Dw B. Functional evaluation: the BARTHEL index. *Md State Med J*. (1965) 14:61–5.

20. Balestroni G, Bertolotti G. EuroQol-5D (EQ-5D): an instrument for measuring quality of life. *Monaldi Arch Chest Dis* 9. (2012) 78:155–9. doi: 10.4081/monaldi.2012.121

21. Stratton RJ, King CL, Stroud MA, Jackson AA, Elia M. Malnutrition universal screening tool predicts mortality and length of hospital stay in acutely ill elderly. *Br J Nutr*. (2006) 95:325–30. doi: 10.1079/bjn20051622

22. FAO. (2020). *The State of Food and Agriculture 2020. Overcoming water challenges in agriculture*. Rome.

23. Fernandes SG, Rodrigues AM, Nunes C, Santos O, Gregório MJ, de Sousa RD, et al. Food insecurity in older adults: Results from the epidemiology of chronic diseases cohort study 3. *Front Med (Lausanne)*. (2018) 5.

24. Lee JS, Frongillo EA. Nutritional and health consequences are associated with food insecurity among U.S. elderly persons. *J Nutr*. (2001) 131:1503–9.

25. Gkiouras K, Cheristanidis S, Papailia TD, Grammatikopoulou MG, Karamitsios N, Goulis DG, et al. Malnutrition and food insecurity might pose a double burden for older adults. *Nutrients*. (2020) 12:1–11.

26. Larson NI, Story MT. Food insecurity and weight status among U.S. children and families. *Am J Prev Med*. (2011) 40:166–73.

27. Schwartz N, Tarasuk V, Buliung R, Wilson K. Mobility impairments and geographic variation in vulnerability to household food insecurity. *Soc Sci Med*. (2019) 243:112636.

28. Zaman K. *The Clarivate Controversy: How CiteScore Rank Provides a Response to Arbitrary Delisting*. (2023). doi: 10.5281/ZENODO.7784725

frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 03 November 2023
DOI 10.3389/fnut.2023.1173106

OPEN ACCESS

EDITED BY
Matthias Pirlich,
Imperial Oak Outpatient Clinic, Germany

REVIEWED BY
Victoria J. Kain,
Griffith University, Australia
Jiahua Lyu,
Sichuan Cancer Hospital, China

*CORRESPONDENCE
Elisabeth L. Zeilinger
✉ elisabeth.zeilinger@univie.ac.at

†These authors have contributed equally to this work and share first authorship

RECEIVED 24 February 2023
ACCEPTED 19 October 2023
PUBLISHED 03 November 2023

CITATION
Kum L, Zeilinger EL, Vohla D, Kitta A, Brunevskaya N, Adamidis F, Ecker F, Masel EK, Mayr-Pirker B, Meyer AL, Sturtzel B, Kreye G and Unseld M (2023) Routine laboratory parameters to support decision on parenteral nutrition in palliative care. *Front. Nutr.* 10:1173106. doi: 10.3389/fnut.2023.1173106

Routine laboratory parameters to support decision on parenteral nutrition in palliative care

Lea Kum[1†], Elisabeth L. Zeilinger[1,2,3*†], Dagmar Vohla[1], Anna Kitta[1], Nadine Brunevskaya[1,2], Feroniki Adamidis[1], Franziska Ecker[1], Eva K. Masel[1], Brigitte Mayr-Pirker[4], Alexa L. Meyer[3], Bärbel Sturtzel[3], Gudrun Kreye[5] and Matthias Unseld[1,3]

[1]Division of Palliative Medicine, Department of Medicine I, Medical University of Vienna, Vienna, Austria, [2]Department of Clinical and Health Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria, [3]Academy for Ageing Research, Haus der Barmherzigkeit, Vienna, Austria, [4]Department of Geriatric Medicine, Christian Doppler University Hospital, Paracelsus Medical University, Salzburg, Austria, [5]Division of Palliative Care, Department of Internal Medicine II, University Hospital Krems, Karl Landsteiner University of Health Sciences, Krems, Austria

Introduction: Parenteral nutrition (PN) is widely used in palliative care (PC), but there is limited evidence to support its use at the end of life (EOL). This aim of this was to investigate the relationship between routine laboratory parameters and survival in patients receiving PN, and to develop a decision tree model to support clinicians decide whether to start or forgo PN.

Methods: The laboratory parameters of 113 patients with advanced diseases who were admitted to a specialized palliative care unit (PCU) were analyzed at two points in time: T0 = before PN, T1 = two weeks after initiation of PN. Univariate Mann-Whitney U-tests and multivariate linear regression models, as well as a decision tree analysis were computed; all in relation to survival time.

Results: The final regression model was significant with p = 0.001 (adjusted R2 = 0.15) and included two predictors for survival time after PN initiation: the CRP/albumin ratio and urea at T1 (ps = 0.019). Decision tree analysis revealed three important predictors for classification of survival time after PN initiation: CRP, urea, and LDH (all at T0).

Discussion: The decision tree model may help to identify patients likely to benefit from PN, thus supporting the clinical decision whether or not to start PN.

KEYWORDS

decision tree, parenteral nutrition, routine laboratory parameters, prognostic score, biomarkers, palliative care, cancer, cachexia

1. Introduction

In the palliative medical field, parenteral nutrition (PN) is a controversially discussed topic. Especially when it comes to end of life (EOL) care there is little evidence on the benefit of PN and termination of PN was described to be one of the ethically most challenging decisions for health care professionals (1). The latest European Society of Medical Oncology (ESMO) guidelines on cancer cachexia in adult patients suggest that the closer to the end of life patients are, the less invasive nutrition should be (2). The guidelines recommend that PN should not be administered when the expected prognosis is less than three to six months (2, 3). The definitions for EOL vary. Depending on the literature, the EOL time span may refer to the last

year or six months or even days and hours of life (4, 5). Hereinafter EOL will concern the last six months of life.

PN is a medical intervention with risk factors that need to be understood and considered to ensure beneficial use. Therefore the three principals [1] indication, [2] therapeutic goal, and [3] patient consent need to be fulfilled before the initiation of PN (6). Next to pleurocentesis and ascites drainage, PN is a commonly used medical application at the EOL (7, 8) which requires an initially invasive procedure for administration. A structured framework was suggested to decide the necessity of an invasive intervention for a patient receiving palliative care (PC), also including PN (9). In particular for decision making at the EOL there are several approaches to define the requirements. All of them have in common that quality of life (QoL), the indication or benefit of the intervention and the patient's will should be taken into account (6, 9). A very strong indication for continuance of PN is to satisfy hunger. If there is no clear medical indication for ongoing PN treatment, this must be discussed with the patient or the legal representative. The use of PN without a clear therapy goal may be considered futile medical care and should be stopped. At this point, the patient needs to be carefully informed of clinician's decision, as nutrition can be an emotionally charged subject (6, 9). Prognosis can also be an important factor to consider when it comes to deciding whether to start or forgo PN. On the one hand, communication and empathic skills are essential for delivering the decision to the patients and their families (10), which can be challenging for both medical and nursing staff (11). On the other hand, more data is needed to support the decision in terms of indication, benefit, and prognosis in regard to PN.

In PC, especially at the EOL, the indication for PN might also differ from other medical fields. Patients who present with weight loss and loss of appetite, but are still able to partially eat orally, are often started on PN treatment at the end of life (12). Negative effects of this invasive procedure must be considered. The risk of infections (13–15) next to a minimal chance of improvement of the nutritional status should be considered. Also, a lack of improvement in QoL has been observed as well as no gain in overall survival (OS) (3,16). Furthermore, an increase in inflammatory activity in patients under PN was even associated with decreased OS. Therefore, several biochemical markers such as albumin, liver function parameters, or C-reactive protein (CRP) have been described to evaluate their prognostic potential. With regard to inflammatory activity, higher levels of CRP were shown to be significantly associated with a negative outcome in terms of OS in different patients receiving PN (17). However, there is a lack of predictive markers that might help in the decision of suspending PN in the palliative setting (17–19).

As prognosis is a commonly used marker in decision-making, the ambition of predicting survival with an objective score is of significant value. One existing score is the objective palliative prognostic score (OPPS) for patients with advanced cancer. It includes heart rate > 120/min, white blood cells >11,000/mm^3, platelets <130,000/mm^3, serum creatinine level > 1.3 mg/dL, serum potassium level > 5 mg/dL, and no history of chemotherapy. By using this score Chen et al. could predict in an accurate way that a patient would die in 7 days (20). However, this was not specific for patients receiving PN.

Other scores such as the Palliative Prognostic Index (21), the Palliative Prognostic (PaP) Score (22) and the Prognosis in Palliative Care Study Score (PiPS) (23) often rely on subjective variables. These include patients' symptoms or condition and physicians' experience. However, routine laboratory blood parameters are commonly available for each patient and are objective diagnostic tools in the daily decision making process of physicians (24, 25). Therefore, an objective prognostic model including routine laboratory parameters might help to aid in the decision whether to start or forgo PN in PC patients at the EOL. However, for PC patients, such a prediction model has not been established, yet.

The main objectives of our study were [1] to investigate the relationship between routine laboratory parameters and patient survival under PN and [2] to build a decision tree model based on routine laboratory parameters to support decision-making related to the initiation of PN. The predictive model is intended to help clinicians make the difficult decision of whether or not to start PN. Having an objective score to contribute to this fundamental care decision may improve person-centered PC and EOL.

2. Materials and methods

2.1. Study design

In this retrospective data analysis, the laboratory parameters of patients admitted to the Division of Palliative Medicine of the Medical University of Vienna between January 2016 and January 2019 have been analyzed.

2.2. PN regimens

The decision regarding whether to administer PN was made by the dietician of the PCU in consultation with the medical staff according to the individual needs of each patient. The PN administered was NuTRIflex® Omega special (625 mL bag with 740 calories, 35 g of proteins, 90 g of carbohydrates and 25 g of fat; B. Braun Melsungen AG, Germany, 2014), with added supplements of Soluvit (vitamins: b1, b6, b12, c, nicotinamide, pantothenic acid, biotin and folic acid; Fresenius Kabi Austria GmbH, Austria, 2013), Vitalipid (contains vitamins: a, d2, e and k1; Baxter Deutschland GmbH, Germany, 2015) and Trace (contains trace elements: Fluorine (F), Iodine (I), Molybdenum (Mo), Iron (Fe), Copper (Cu), Manganese (Mn), Selenium (Se) and Zinc (Zn) as well as electrolytes; Fresenius Kabi Austria GmbH, Austria, 2018). The administration of PN usually takes place overnight. The targeted number of calories was calculated by the dietician based on the individual needs of the patients, with a mean of 1,475 kcal/d.

2.3. Study participants and data collection

All patients admitted to the palliative care unit (PCU) who were started on PN were included in the analysis. The final sample comprised $N = 113$ patients. We collected baseline data as age, sex and body mass index (BMI) and laboratory parameters from the electronic database of the Medical University of Vienna. After exporting data from the electronic system, we performed a random data check to assure correctness of the automated export. To identify the dynamics of the laboratory parameters under PN administration, two time points were set retrospectively: First, on the day of admission (T0), i.e., before PN initiation, and second, two weeks after the initiation of PN (T1). To ensure data protection, personalized files were only stored on

password-protected computers. A pseudonymized file was used for analysis.

2.4. Statistical analysis

For sample description, median, interquartile range (IQR), and total range were used. Table 1 lists all predictor variables included in analysis. Rational for inclusion was based on availability of data. If available, laboratory parameters at two points in time, T0 and T1, as well as the difference between these two points in time were included, to capture changes over time. Based on a recent study (17), we also included the CRP/albumin ratio as predictor. Further aspects included were BMI and sex. Survival time after initiation of PN was specified as primary outcome. As the recommendation for initiation of PN is a survival time of at least three months (2, 3), this cut-off was applied to split the sample into two subsamples containing patients living shorter and longer than three months after initiation of PN, respectively.

In a first step, to compare patients who lived shorter vs. longer than three months, Mann–Whitney U-tests were applied. For these initial explanatory tests, we did not rely on significance values but rather on effect sizes, and calculated the effect size r for each test. Effect sizes are more informative than value of ps, because they are independent of sample size and represent scale-free indices (26, 27). Interpretation followed Cohen's guidelines, with $r = 0.1$ resembling a small effect, $r = 0.3$ a medium effect, and $r = 0.5$ a large effect (28). In a second step, predictors with an effect of $r > 0.2$ in univariate analysis were entered in a stepwise regression analysis to examine their multivariate association with survival time. Variance Inflation Factors (VIFs) were examined and indicated no multicollinearity between predictors in the regression model. Due to high skewness, survival time was $\log(x + 1)$ transformed, which has been shown to be a robust method for skewed data (29). Significance level for determining relevant indicators in regression analysis was set to 5%.

In a final step, a decision tree analysis was conducted as complementary method to establish a classification model for predicting survival time. The goal of a decision tree model is to make predictions or decisions by recursively partitioning a dataset into subsets based on available data, aiming for accurate and interpretable results. Decision trees are a popular machine learning algorithm for classification tasks. They are particularly useful because of their simplicity and interpretability (30). In decision tree analysis, patients are divided into subgroups that differ maximally from each other with respect to the outcome variable based on the values of predictor variables. The present outcome variable was survival time after initial assessment (when PE was initiated). In contrast to other analysis, the results of a decision tree model are robust even when predictors are highly intercorrelated. As growing method, CART (Classification And Regression Trees) was applied. All analysis were performed in IBM SPSS Statistics, v.27. The procedure for CART in SPSS is based on Breiman and colleagues (31).

3. Results

The total sample comprised $N = 113$ patients (55% female) who received PN. Mean age was 60.1 years (SD = 13.1). The most frequent diagnosis was gastrointestinal cancer, followed by cancer of the reproductive organs, ear nose throat cancer, and lung cancer (see Table 2).

All patients analyzed in this study were already deceased at the time of data analysis, therefore survival time was available for the total sample. A total of $n = 93$ patients lived less than three months after initial assessment, and $n = 20$ patients lived three months or longer. The characteristics of these two samples are depicted in Table 1. Mann–Whitney U tests revealed a significant difference between these two groups in three parameters: Albumin at T1 with an effect of $r = 0.27$, urea at T0 with an effect of $r = 0.23$, and the difference in albumin from T0 to T1 with an effect of $r = 0.24$. However, although not statistically significant due to the small sample size, the following two parameters also showed an effect size of $r > 0.2$: Leukocytes at T1 with $r = 0.22$, and CRP/albumin difference from T0 to T1, with $r = 0.21$. Results of all univariate analysis are given in Table 1.

In a next step, a multivariate stepwise regression analysis was computed. The five parameters with $r > 0.2$ were entered as predictors (albumin at T1, urea at T0, albumin difference T0 to T1, leukocytes at T1, and CRP/albumin difference from T0 to T1) and log-transformed survival time was used as dependent variable. The final multivariate regression model was significant with $p = 0.001$ (adjusted $R2 = 0.15$). Results indicate that only the CRP/albumin difference and urea at T0 were significant predictors for survival time in a multivariate linear model. Results of the regression analysis are detailed in Table 3.

In a final step, the decision tree method was applied to establish a model for supporting decision-making on whether or not to initiate PN. Results revealed three important predictors for classification of survival time after PN initiation (see Figure 1): CRP, urea, and LDH (all at T0). Patients with CRP ≤ 1.12 had a mean survival of 5.5 months. Patients with CRP > 1.12 were further split into groups by urea, with a cut-off value of 13.8. Patients below this value, had a mean survival of 2.9 months; patients above were further split according to their LDH level with a cut-off of 138.5. Patients below this cut-off had a mean survival time of 1.8 months, and patients above the cut-off had a mean survival time of 0.9 months.

Based on this model, we could establish three clinically meaningful groups of patients: The first group is characterized by a CRP level ≤ 1.12; the second group is characterized by a CRP level > 1.12 and a urea level ≤ 13.8; and the third group is characterized by CRP level > 1.12 and an urea level > 13.8. The first two groups have an estimated survival about or above three months, whereas the third group has an estimated survival time below three months.

4. Discussion

Considering the relatively frequent use of PN combined with nearly no evident tool that supports the clinician in the decision-making process, we consider our findings of great interest. The literature on decision tools for starting PN in patients with advanced cancer is sparse (2). The findings of this study add the insight that a combination of routine laboratory parameters, including CRP, urea and LDH, should be considered as prognostically relevant when considering the initiation of PN. Despite the fact that QoL and alleviating symptoms are the primary goals in EOL care (5) our findings can be a useful information for clinicians since the decision to initiate or stop nutritional treatment is considered one of the most challenging tasks (1). Therefore, our decision tree model might

TABLE 1 Characteristics and predictors for analysis in both subsamples.

	Less than three months (n = 93)		More than three months (n = 20)		*p value*	Effect size (r)
	Median (IQR)	Range (Min-Max)	Median (IQR)	Range (Min-Max)		
Age [*years*]	60 (52–69.5)	20–85	61.5 (54–70)	29–78	0.596	0.05
BMI [kg/m^2]	20.3 (17.4–22.7)	12.5–29.3	18.7 (17.2–21.1)	14.4–28	0.266	0.11
Bili T0 [*mg/dl*]	0.4 (0.3–0.8)	0.1–11.5	0.4 (0.3–0.8)	0.1–2.9	0.699	0.04
Bili T1 [*mg/dl*]	0.4 (0.3–1)	0.1–16.9	0.4 (0.3–0.5)	0.2–5.1	0.522	0.07
Albumin T0 [*g/L*]	29.1 (25–34.2)	17.8–44	29.7 (25–34.6)	0.4–40	0.728	0.03
Albumin T1 [*g/L*]	25.6 (21.7–30.4)	16–38.7	30.5 (26.9–32.5)	23–37	**0.014**	**0.27**
LDH T0 [*U/L*]	194.5 (154–290.8)	114–1878	205 (141–266)	70–761	0.91	0.01
LDH T1 [*U/L*]	205 (159–311)	41–630	206 (157–286.3)	106–578	0.867	0.02
GOT T0 [*U/L*]	24.5 (18–42.5)	6–332	25 (16–40)	12–332	0.746	0.03
GOT T1 [*U/L*]	28 (19–44.8)	11–324	26 (18.8–48.3)	13–151	0.86	0.02
GPT T0 [*U/L*]	18 (11–33)	5–289	14 (9.8–31.5)	5–374	0.589	0.05
GPT T1 [*U/L*]	21.5 (14.3–41)	8–251	33 (16.3–49.8)	8–139	0.371	0.10
gGT T0 [*U/L*]	88.5 (41.5–236)	10–2,884	66 (37–300)	15–706	0.879	0.01
gGT T1 [*U/L*]	158.5 (75–385)	13–2,190	155.5 (53.5–395)	21–925	0.95	0.01
AlkP T0 [*U/L*]	111.5 (78.3–211.8)	38–1,690	89 (71–309)	58–826	0.734	0.03
AlkP T1 [*U/L*]	164 (103–338)	41–2,496	164 (107.3–339)	47–920	0.8	0.03
CRP T0 [*mg/dl*]	6.3 (2.9–13.2)	0–46.4	5.1 (2.3–13.5)	1–23	0.541	0.06
CRP T1 [*mg/dl*]	8.9 (4–18.9)	0.4–41.3	7.2 (5.1–10.3)	0.5–18.5	0.218	0.13
Leukocytes T0 [*G/L*]	8.1 (6.2–13.6)	1.9–65.4	7.5 (4.6–10.2)	1.4–18.8	0.192	0.12
Leukocytes T1 [*G/L*]	10.6 (7.2–13.8)	2–99.6	7.3 (5.3–11.4)	1.2–12.5	**0.053**	**0.22**
Sodium T0 [*mmol/L*]	136.5 (133–140)	122–149	137 (134–138)	131–145	0.903	0.01
Sodium T1 [*mmol/L*]	138 (132.5–141.5)	126–154	137 (134–139.8)	124–143	0.648	0.05
Creatinine T0 [*mg/dl*]	0.7 (0.6–1.1)	0.3–4	0.6 (0.5–0.8)	0.3–1.5	0.141	0.14
Creatinine T1 [*mg/dl*]	0.7 (0.5–1.4)	0.2–6	0.7 (0.5–0.8)	0.3–1.7	0.247	0.13
Magnesium T0 [*mmol/L*]	0.7 (0.7–0.9)	0.4–1.3	0.7 (0.7–0.8)	0.4–0.9	0.771	0.03
Calcium T0 [*mmol/L*]	2.1 (2–2.2)	1.1–3.4	2.2 (2–2.3)	1.9–2.8	0.282	0.10
Potassium T0 [*mmol/L*]	3.8 (3.4–4.1)	2.6–6	3.9 (3.2–4.1)	2.8–4.9	0.823	0.02
Potassium T1 [*mmol/L*]	4 (3.5–4.3)	0.5–5.8	4.1 (3.8–4.4)	3.2–6.4	0.301	0.11
Urea T0 [*mg/dl*]	19 (11.7–29.3)	2–76	11 (9.3–20.5)	3.9–34.3	**0.016**	**0.23**
Uric Acid T0 [*mg/dl*]	4.9 (3.4–8.3)	1.2–26.4	4.1 (3.1–6.4)	2–9	0.193	0.13
CRP/albumin ratio T0	0.2 (0.1–0.5)	0–1.9	0.2 (0.1–0.5)	0–5.3	0.969	0.00
CRP/albumin ratio T1	0.3 (0.1–0.8)	0–1.9	0.3 (0.1–0.4)	0–0.8	0.092	0.18
Bili diff	0 (− 0.2 - 0.3)	−10.6 - 14.4	0 (− 0.2–0.1)	−1.1 - 3.3	0.499	0.08
Albumin diff	−4.4 (− 8.2 - 1.2)	−18.7 - 11	−0.1 (− 4.1–4.1)	−8.1 - 28.6	**0.037**	**0.24**
LDH diff	6.5 (− 28–52.8)	−285 - 245	−9.5 (− 41.5–29.8)	−85 - 176	0.383	0.10
GOT diff	3 (− 4–13.3)	−238 - 247	2.5 (− 5.8–12.3)	−181 - 28	0.57	0.06
GPT diff	3 (− 6–18)	−175 - 193	3 (− 6–23)	−235 - 37	0.882	0.02
gGT diff	54.5 (− 14.3–174.3)	−1,386 - 1341	77 (− 4–215)	−188 - 307	0.797	0.03
AlkP diff	37 (1–92)	−233 - 1085	29 (− 14–113.3)	−65 - 354	0.639	0.05
CRP diff	2.6 (− 2.4–7.4)	−30.8 - 35.2	2 (− 2.8–4.2)	−12.6 - 6.9	0.165	0.15
Leukocytes diff	1.5 (− 3.5–5.9)	−41.5 - 34.3	1.3 (− 2.2–2.9)	−10.1 - 3.7	0.434	0.09
Sodium diff	0.5 (− 3–4.8)	−11 - 15	0 (− 2–3)	−12 - 8	0.656	0.05

(Continued)

TABLE 1 (Continued)

	Less than three months (n = 93)		More than three months (n = 20)		*p value*	Effect size (r)
	Median (IQR)	Range (Min-Max)	Median (IQR)	Range (Min-Max)		
Creatinine diff	−0.1 (− 0.2–0.1)	−1.7 - 4.3	0 (− 0.2–0.2)	−0.4 - 0.7	0.745	0.04
Potassium diff	0.1 (− 0.3–0.6)	−2.9 - 2	0.2 (− 0.2–0.6)	−0.7 - 3.4	0.439	0.09
CRP/albumin ratio diff	0.1 (0–0.4)	−1.25 - 1.86	0.1 (− 0.2–0.1)	−5.1 - 0.3	**0.059**	**0.21**

Parameters with an effect size $r > 0.2$ are highlighted in bold. Diff = difference in the respective parameter from T0 to T1. BMI, body mass index. Bili, bilirubin. LDH, lactate dehydrogenase. GOT, serum glutamic oxaloacetic transaminase. GPT, serum glutamic pyruvic transaminase. gGT, gamma-glutamyl transferase. AlkP, alkaline phosphatase. CRP, C-reactive protein.

TABLE 2 Diagnosis in the total sample and subsamples.

	Total sample (N = 113)		Less than 3 months (n = 93)		More than 3 months (n = 20)	
Tumor origin	*n*	%	*n*	%	*n*	%
Gastrointestinal	49	43.4	41	44.1	8	40
Reproductive organs	12	10.6	11	11.8	1	5
ENT	11	9.7	7	7.5	4	20
Lung	11	9.7	10	10.8	1	5
Blood	6	5.3	5	5.4	1	5
Breast	5	4.4	4	4.3	1	5
Sarcoma	4	3.5	3	3.2	1	5
NET	3	2.7	1	1.1	2	10
CUP	3	2.7	2	2.2	1	5
Brain	3	2.7	3	3.2	0	0
RCC/Urothelial	2	1.8	2	2.2	0	0
Thyroid	1	0.9	1	1.1	0	0
Mesothelioma	1	0.9	1	1.1	0	0
Nonmalignant						
Cystic fibrosis	1	0.9	1	1.1	0	0
Chronic kidney disease	1	0.9	1	1.1	0	0

ENT, ear nose throat tumor. NET, neuroendocrine tumor. CUP, cancer of unknown primary. RCC, renal cell carcinoma.

TABLE 3 Results of stepwise regression analysis.

	Estimate	*SE*	95% *CI*		*p*
			LL	UL	
Intercept	0.066	0.008	0.05	0.081	<0.001
CRP/albumin ratio	−0.014	0.006	−0.025	−0.002	0.019
Urea T0	−0.001	0	−0.001	0	0.019

The dependent variable, survival time after initial assessment, was log (x + 1) transformed due to high skewness. For the total model, R2 and R2 adjusted was.17 and 0.15, respectively, with $p = 0.001$.

support healthcare professionals when it comes to these ethical decisions at the EOL. For clinically relevant decisions, the decision tree model and cut-offs as outlined in Figure 1 can be applied.

A Japanese study showed that beliefs and perceptions about PN and hydration were important not only for the patients but also for family members (10). Food and nutrition are of eminent importance for patients with advanced cancer because lack of sufficient nutrition is related to fear of death for many patients and their relatives. Since baseline anxiety and stress levels are usually elevated in cancer patients (32, 33) any potential additional stressor should be managed carefully. Previous studies in PC settings suggest that many patients and family members wish to receive nutritional support when patients become unable to take sufficient nourishment orally. At this time period, the negative impact of cachexia, such as anorexia, reduced food intake, muscle loss and body weight loss, become apparent (34–37). Moreover, most patients wished to receive PN and hydration, whereas many hesitated to receive enteral tube feeding under the same conditions (36). Furthermore, an unmet need for nutritional support, or PN and hydration, may be a source of eating-related distress, not only for patients but also for their family members, which needs to be alleviated by integrated palliative, supportive, and nutritional care (38).

Recent guidelines suggest to use life expectancy as decision tool, indicating that if estimated life expectancy is less than three months, PN should not be started (2, 3). In clinical practice, estimation of prognosis can be difficult. Therefore, the use of a prognostic model to estimate patients survival is of great interest for patients with advanced cancer in a PC setting (17, 20–23, 39, 40). Only a few of these models are designed especially for patients on PN for example the objective prognostic score by Llop-Talaveron and colleagues (17) that retrospectively looked at the data of 460 patients who received PN. As prognostic markers, they identified CRP, prealbumin, albumin, CRP/prealbumin and CRP/albumin. They found CRP/albumin to be statistically significant for exitus, infection, sepsis and liver failure. Based on their findings, they suggested a systematic use of the CRP/albumin score before initiating PN (17). Other studies have also shown that for patients receiving PN, an increase in CRP, as well as white blood cell count and worsening of renal function parameters, are linked to a worse outcome (18, 19).

Notably, the present methods of analysis, the regression model and the decision tree model, yielded slightly different results regarding prognostic markers. In the regression model, CRP/albumin difference and urea at T0 were significantly associated with survival time after PN initiation. In the decision tree, the clinically relevant markers for deciding whether to start PN were CRP and urea. It is common for these two analyses, which are inherently different, to yield different results. The regression model investigates a linear relationship between the prognostic markers and the dependent variable, survival time, independent of the length of survival. The decision tree aims to discriminate between two groups of patients, those who live longer than three months and those who live shorter than three months, without assuming linearity, yielding clinically meaningful results. The present study differs from former findings since our cohort solely consists of patients in a palliative setting.

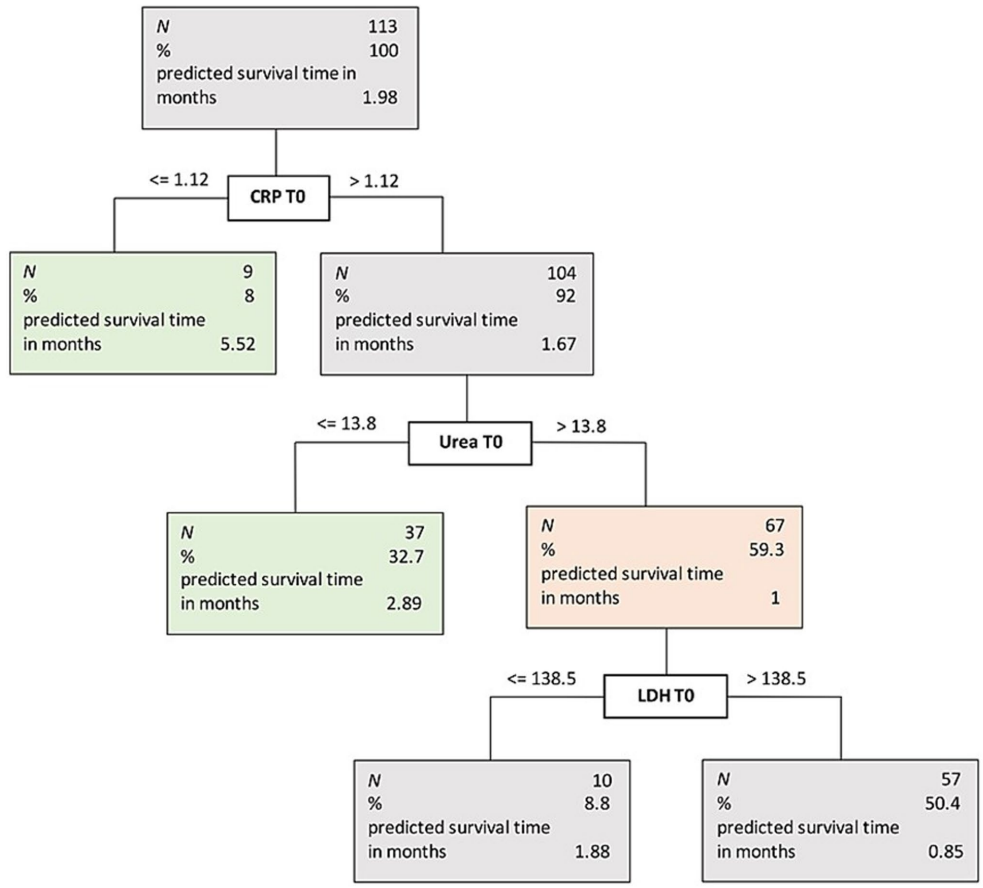


FIGURE 1
Decision tree.

The comparable study from Llop-Talaveron et al. did include all inpatients who did receive PN (17). In our study, we only included patients with advanced diseases who were admitted to a PCU. Since the PCU, is a tertiary center for PC, most patients showed complex symptoms and often were admitted in a very advanced stage of their disease, explaining why OS in general was not longer than six months. In their randomized controlled trial Bouleuc et al. found a life expectancy shorter than three months to be the cut-off for initiating PN (3).

The latest ESMO guidelines from 2022 suggest not to start with PN when survival is considered less than three to six months (2). From a retrospective view, the majority of our cohort was not fit for the initiation of PN, since 93 of 113 patients died in less than three months after initial assessment. This could lead to the conclusion that clinicians were unaware that PN was not indicated at the time of initiating treatment. On the one hand this could be due to negative effects of PN on OS like infections (17, 18). On the other hand, prognosis of the patients might have been estimated to be better. It is commonly known that clinicians tend to overestimate the predicted survival time (41). Thus the need for an objective easy-to-use tool led to the development of a variety of scores such as the 'Objective Palliative Prognostic Score' (OPPS) (20) or the laboratory prognostic score for respiratory malignancy (R-LPS) (39). These scores were designed to predict short term survival. The OPPS predicts survival over the next seven days while the R-LPS predicts death within 14 days (20, 39). As already mentioned, for the decision whether to start or forgo PN a survival time of more than three months is of interest (2).

The R-LPS was designed by analyzing nineteen blood parameters of 649 terminally ill patients. Among other laboratory parameters, CRP was described as an independent factor for survival (39), whereas the OPPS uses the white blood cell count as an inflammatory prognostic marker (20). Our findings support CRP as a prognostic marker. In the group of patients with the longest survival (5.52 months), CRP was below 1.12 mg/dL (see Figure 1). Our findings show that prognosis of patients with advanced diseases was better when blood urea was lower. This is also supported by the R-LPS, where blood urea is described as an independent factor for 14-day survival (39). The CRP/albumin ratio was linearly related to survival time, as shown by regression analysis, but was not part of the final decision tree model. Therefore, in our analysis, CRP was the more relevant factor in deciding on PN than the CRP/albumin ratio.

Lactate dehydrogenase (LDH) was found to be a predictive factor in the 'Objective Prognostic Score' (OPS), a score designed to predict the three-week survival for advanced cancer inpatients in South Korea and prospectively validated (42, 43). In the present decision tree analysis, LDH was found to be a relevant marker, but was not clinically relevant for the decision to start PN treatment. As Figure 1 indicates, LDH only divided the subsample with a median survival time of one month into two groups of 1.88 months and 0.85 months, respectively. Since both groups are far below three month, LDH was not considered clinically relevant in our analysis. However, it might be an interesting predictive marker for patients with a longer mean survival time as the OPS and our findings suggest (42, 43).

One limitation of the present study is the sole use of retrospective data. Planning a prospective trial evaluating prognostic and predictive factors to screen for patients who will benefit from PN could lead to ethical difficulties. The wish for PN can be very prominent in patients with advanced cancer, even if the life expectancy is less than three months and although the wish might be futile. Another limitation is the short period of survival of patients enrolled in the analysis. Further studies need to be conducted to assess the period of survival where patients still benefit from PN treatment and also to validate our findings.

Another major limitation of the present study, related to its retrospective nature, is the lack of detailed information on the indication for PN in the patient collective. Furthermore our study lacks to assess improvement of QoL and alleviation of symptoms. There is no documentation available concerning the nutritional status, the degree of cachexia or an indication like gastrointestinal obstruction or hunger. In the palliative medical field indication for starting PN might differ since the primary goal is improvement of QoL (6, 9, 44). Therefore, PN might also be initiated in patients with no sings for malnutrition but with symptoms like hunger or functional impairment. A large retrospective cohort study that included patients with advanced cancer who died in French hospitals did investigate factors that are associated with PN treatment within the last seven days of life. They identified malnutrition to be significantly associated with the use of PN in PC patients (45).

It is also worth mentioning the lack of data to differentiate whether patients received PN only or had oral food intake alongside. The unavailability of data on how much of the prescribed PN amount was actually administered to the individual patient, can also be considered a limiting factor. In general the heterogeneity of the patient collective is mentioned as a limiting factor in earlier studies an can be applied to the current study as well (46). Due to this heterogeneity individual nutritional interventions did prove to be beneficial before (47, 48).

Furthermore, the study population includes PC patients with different tumor origins. When attempting to predict survival using only laboratory parameters, tumor origin should be considered as a confounding variable. Some comparable previous studies focused on only one tumor entity (39, 40, 49). Others had an even broader subject sample, including non-cancer patients (17). For individual decision making, it might be helpful if future studies could differentiate according to tumor origin. However, it should be noted that PC cohorts will always be heterogeneous and physicians should always focus on improving QoL as the main goal of care. Our findings, as well as previous prognostic scores (21–23) should only help in decision making.

Since this was a retrospective study also the possible PN associated complications could only be analyzed in retrospect. One of the most important complications are infection which we retrospectively identified as clinically relevant when patients were started on antibiotic treatment. This was the case for six patients during the time period of interest. Discussing futile PN with patients and their families is one of the most difficult tasks for oncologists, often more difficult than offering PN. This factor also underlines the importance of PC skills among physicians, which should ideally be taught early in professional training using teaching methods that encourages self-reflection (50). Discussing with patients that they are not feasible to receive PN because they have adverse prognostic factors and will likely not benefit from PN requires more than one sensitive and empathic EOL conversation with these patients. Guidelines for such discussions should also be included in prospective study protocols investigating prognostic and predictive factors for providing PN to patients with advanced cancer.

5. Conclusion

Our findings suggest that CRP, the CRP/albumin ratio and urea are the most important baseline markers for predicting survival after PN initiation. Based on the results of this study, clinical decision making could be informed by the established decision tree model, which could support the identification of patients likely to benefit from PN based on CRP and urea prior to PN initiation. These findings may help clinicians in daily practice to decide when to initiate or forgo PN treatment in terminally ill patients. If used systematically, the decision tree model developed in this study could reduce overtreatment at the end of life.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Medical University of Vienna, Austria. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because it was a retrospective study on routinely collected data.

Author contributions

LK, MU, and EZ: conceptualization. NB and EZ: methodology. EZ: software. FA, FE, AK, GK, LK, EM, BM-P, and DV: validation. FA, AK, LK, EM, MU, AM, BS, and DV: investigation. FA, FE, AK, LK, EM, MU, and DV: resources. NB, LK, EZ, and MU: data curation. GK, LK, DV, MU, and EZ: writing—original draft preparation. FA, NB, FE, AK, GK, LK, EM, BM-P, AM, BS, and DV: writing—review and editing. MU and EZ: supervision. LK and EZ: project administration. All authors contributed to the article and approved the submitted version.

Funding

This research was partly funded by the "City of Vienna Fund for Innovative Interdisciplinary Cancer Research" provided by the Government of Vienna, Austria (Grant number: 21157). The APC was funded by University of Vienna.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Balstad TR, Løhre ET, Thoresen L, Thronæs M, Skjelvan LS, Helgås RG, et al. Parenteral nutrition in advanced Cancer: the healthcare providers' perspective. *Oncol Ther*. (2022) 10:211–23. doi: 10.1007/s40487-022-00189-1

2. Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO clinical practice guidelines☆. *ESMO Open*. (2021) 6:100092. doi: 10.1016/j.esmoop.2021.100092

3. Bouleuc C, Anota A, Cornet C, Grodard G, Thiery-Vuillemin A, Dubroeucq O, et al. Impact on health-related quality of life of parenteral nutrition for patients with advanced Cancer Cachexia: results from a randomized controlled trial. *Oncologist*. (2020) 25:e843–51. doi: 10.1634/theoncologist.2019-0856

4. Huffman JL, Harmer B. End-of-life care In: *StatPearls [internet]*. Treasure Island (FL): StatPearls Publishing (2023) Available at: http://www.ncbi.nlm.nih.gov/books/NBK544276/

5. Hui D, De La Cruz M, Mori M, Parsons HA, Kwon JH, Torres-Vigil I, et al. Concepts and definitions for "supportive care," "best supportive care," "palliative care," and "hospice care" in the published literature, dictionaries, and textbooks. *Support Care Cancer*. (2013) 21:659–85. doi: 10.1007/s00520-012-1564-y

6. Druml C, Ballmer PE, Druml W, Oehmichen F, Shenkin A, Singer P, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. *Clin Nutr*. (2016) 35:545–56. doi: 10.1016/j.clnu.2016.02.006

7. Bozzetti F, Santarpia L, Pironi L, Thul P, Klek S, Gavazzi C, et al. The prognosis of incurable cachectic cancer patients on home parenteral nutrition: a multi-Centre observational study with prospective follow-up of 414 patients. *Ann Oncol*. (2014) 25:487–93. doi: 10.1093/annonc/mdt549

8. Raijmakers NJH, van Zuylen L, Costantini M, Caraceni A, Clark J, Lundquist G, et al. Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects. *Ann Oncol*. (2011) 22:1478–86. doi: 10.1093/annonc/mdq620

9. Strasser F, Blum D, Bueche D. Invasive palliative interventions: when are they worth it and when are they not? *Cancer J*. (2010) 16:483–7. doi: 10.1097/PPO.0b013e3181f842b3

10. Amano K, Maeda I, Morita T, Masukawa K, Kizawa Y, Tsuneto S, et al. Beliefs and perceptions about parenteral nutrition and hydration by family members of patients with advanced Cancer admitted to palliative care units: a Nationwide survey of bereaved family members in Japan. *J Pain Symptom Manag*. (2020) 60:355–61. doi: 10.1016/j.jpainsymman.2020.03.006

11. Zeilinger EL, Gabal A, Adamidis F, Popov P, Jaeger K, Hufgard-Leitner M, et al. Challenges in palliative care nursing at a university hospital: a qualitative interview study. *J Hosp Palliat Nurs*. (2022) 24:E219–25. doi: 10.1097/NJH.0000000000000886

12. Orrevall Y, Tishelman C, Permert J, Lundström S. A national observational study of the prevalence and use of enteral tube feeding, parenteral nutrition and intravenous glucose in cancer patients enrolled in specialized palliative care. *Nutrients*. (2013) 5:267–82. doi: 10.3390/nu5010267

13. Arends J. Struggling with nutrition in patients with advanced cancer: nutrition and nourishment—focusing on metabolism and supportive care. *Ann Oncol*. (2018) 29:ii27–34. doi: 10.1093/annonc/mdy093

14. Virizuela JA, Camblor-Álvarez M, Luengo-Pérez LM, Grande E, Álvarez-Hernández J, Sendrós-Madroño MJ, et al. Nutritional support and parenteral nutrition in cancer patients: an expert consensus report. *Clin Transl Oncol*. (2018) 20:619–29. doi: 10.1007/s12094-017-1757-4

15. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr*. (2017) 36:1187–96. doi: 10.1016/j.clnu.2017.06.017

16. Tobberup R, Thoresen L, Falkmer UG, Yilmaz MK, Solheim TS, Balstad TR. Effects of current parenteral nutrition treatment on health-related quality of life, physical function, nutritional status, survival and adverse events exclusively in patients with advanced cancer: a systematic literature review. *Crit Rev Oncol Hematol*. (2019) 139:96–107. doi: 10.1016/j.critrevonc.2019.04.014

17. Llop-Talaveron J, Badia-Tahull MB, Leiva-Badosa E. An inflammation-based prognostic score, the C-reactive protein/albumin ratio predicts the morbidity and mortality of patients on parenteral nutrition. *Clin Nutr*. (2018) 37:1575–83. doi: 10.1016/j.clnu.2017.08.013

18. Kieler M, Kössler P, Milovic M, Meyer E, Križanová K, Kum L, et al. C-reactive protein and white blood cell count are adverse prognostic markers for patients with advanced cancer on parenteral nutrition in a palliative care unit setting: a retrospective cohort study. *Palliat Med*. (2022) 36:540–8. doi: 10.1177/02692163211073939

19. Kum L, Friedrich A, Kieler M, Meyer E, Popov P, Kössler P, et al. Kidney function worsening is linked to parenteral-nutrition-dependent survival in palliative care patients. *Nutrients*. (2022) 14:769. doi: 10.3390/nu14040769

20. Chen YT, Ho CT, Hsu HS, Huang PT, Lin CY, Liu CS, et al. Objective palliative prognostic score among patients with advanced Cancer. *J Pain Symptom Manag*. (2015) 49:690–6. doi: 10.1016/j.jpainsymman.2014.08.017

21. Morita T, Tsunoda J, Inoue S, Chihara S. The palliative prognostic index: a scoring system for survival prediction of terminally ill cancer patients. *Support Care Cancer*. (1999) 7:128–33. doi: 10.1007/s005200050242

22. Maltoni M, Nanni O, Pirovano M, Scarpi E, Indelli M, Martini C, et al. Successful validation of the palliative prognostic score in terminally ill Cancer patients. *J Pain Symptom Manag*. (1999) 17:240–7. doi: 10.1016/S0885-3924(98)00146-8

23. Gwilliam B, Keeley V, Todd C, Gittins M, Roberts C, Kelly L, et al. Development of prognosis in palliative care study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. *BMJ*. (2011) 343:d4920. doi: 10.1136/bmj.d4920

24. Cotogni P, Stragliotto S, Ossola M, Collo A, Riso S. On behalf of the intersociety Italian working Group for Nutritional Support in Cancer. The role of nutritional support for Cancer patients in palliative care. *Nutrients*. (2021) 13:13020306. doi: 10.3390/nu13020306

25. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. (2017) 36:11–48. doi: 10.1016/j.clnu.2016.07.015

26. Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. *J Grad Med Educ*. (2012) 4:279–82. doi: 10.4300/JGME-D-12-00156.1

27. Hojat M, Xu G. A Visitor's guide to effect sizes – statistical significance versus practical (clinical) importance of research findings. *Adv Health Sci Educ Theory Pract*. (2004) 9:241–9. doi: 10.1023/B:AHSE.0000038173.00909.f6

28. Cohen J. *Statistical power analysis for the behavioral sciences. 2nd* ed. New York: Routledge (1988). 567 p.

29. Hammouri HM, Sabo RT, Alsaadawi R, Kheirallah KA. Handling skewed data: a comparison of two popular methods. *Appl Sci*. (2020) 10:6247. doi: 10.3390/app10186247

30. Müller A, Guido S. *Introduction to machine learning with Python: A guide for data scientists. 1st* ed. Beijing Boston Farnham Sebastopol Tokyo: O'Reilly Media (2016). 398 p.

31. Breiman L. *Classification and regression trees [internet]* Routledge (1984) Available at: https://www.taylorfrancis.com/books/mono/10.1201/9781315139470/classification-regression-trees-leo-breiman.

32. Zeilinger EL, Oppenauer C, Knefel M, Kantor V, Schneckenreiter C, Lubowitzki S, et al. Prevalence of anxiety and depression in people with different types of cancer or haematologic malignancies: a cross-sectional study. *Epidemiol Psychiatr Sci*. (2022) 31:e74. doi: 10.1017/S2045796022000592

33. Unseld M, Zeilinger EL, Fellinger M, Lubowitzki S, Krammer K, Nader IW, et al. Prevalence of pain and its association with symptoms of post-traumatic stress disorder, depression, anxiety and distress in 846 cancer patients: a cross sectional study. *Psycho-Oncology*. (2021) 30:504–10. doi: 10.1002/pon.5595

34. Amano K, Maeda I, Morita T, Tatara R, Katayama H, Uno T, et al. Need for nutritional support, eating-related distress and experience of terminally ill patients with cancer: a survey in an inpatient hospice. *BMJ Support Palliat Care*. (2016) 6:373–6. doi: 10.1136/bmjspcare-2014-000783

35. Amano K, Maeda I, Morita T, Okajima Y, Hama T, Aoyama M, et al. Eating-related distress and need for nutritional support of families of advanced cancer patients: a nationwide survey of bereaved family members. *J Cachexia Sarcopenia Muscle*. (2016) 7:527–34. doi: 10.1002/jcsm.12102

36. Amano K, Morita T, Miyamoto J, Uno T, Katayama H, Tatara R. Perception of need for nutritional support in advanced cancer patients with cachexia: a survey in palliative care settings. *Support Care Cancer*. (2018) 26:2793–9. doi: 10.1007/s00520-018-4104-6

37. Amano K, Morita T, Koshimoto S, Uno T, Katayama H, Tatara R. Eating-related distress in advanced cancer patients with cachexia and family members: a survey in palliative and supportive care settings. *Support Care Cancer*. (2019) 27:2869–76. doi: 10.1007/s00520-018-4590-6

38. Amano K, Baracos VE, Hopkinson JB. Integration of palliative, supportive, and nutritional care to alleviate eating-related distress among advanced cancer patients with cachexia and their family members. *Crit Rev Oncol Hematol*. (2019) 143:117–23. doi: 10.1016/j.critrevonc.2019.08.006

39. Tanaka M, Kawai N, Yuasa N. Prognostic laboratory score to predict 14-day mortality in terminally ill patients with respiratory malignancy. *Int J Clin Oncol*. (2022) 27:655–64. doi: 10.1007/s10147-021-02105-5

40. Yılmaz A, Tekin SB, Bilici M, Yılmaz H. The significance of controlling nutritional status (CONUT) score as a novel prognostic parameter in small cell lung Cancer. *Lung*. (2020) 198:695–704. doi: 10.1007/s00408-020-00361-2

41. Glare P, Virik K, Jones M, Hudson M, Eychmuller S, Simes J, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ*. (2003) 327:195–0. doi: 10.1136/bmj.327.7408.195

42. Suh SY, Choi YS, Shim JY, Kim YS, Yeom CH, Kim D, et al. Construction of a new, objective prognostic score for terminally ill cancer patients: a multicenter study. *Support Care Cancer*. (2009) 18:151–7. doi: 10.1007/s00520-009-0639-x

43. Yoon SJ, Suh SY, Lee YJ, Park J, Hwang S, Lee SS, et al. Prospective validation of objective prognostic score for advanced Cancer inpatients in South Korea: a multicenter study. *J Palliat Med*. (2017) 20:65–8. doi: 10.1089/jpm.2016.0044

44. Pralong A. *S3-Leitlinie Palliativmedizin*. Berlin, Germany: AWMF online, (2020). 551 p.

45. Baumstarck K, Boyer L, Pauly V, Orleans V, Marin A, Fond G, et al. Use of artificial nutrition near the end of life: results from a French national population-based study of hospitalized cancer patients. *Cancer Med*. (2019) 9:530–40. doi: 10.1002/cam4.2731

46. Drinkwater B, Clarke BK, Jones J, Ratcliffe J, Deel-Smith P, Cooper SC. Palliative home parenteral nutrition: clinical service evaluation and identifying potential prognostic factors to assist with patient selection. *Clin Nutr ESPEN*. (2017) 22:81–4. doi: 10.1016/j.clnesp.2017.08.004

47. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. *Am J Clin Nutr*. (2012) 96:1346–53. doi: 10.3945/ajcn.111.018838

48. Langius JAE, Zandbergen MC, Eerenstein SEJ, van Tulder MW, Leemans CR, Kramer MHH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clin Nutr*. (2013) 32:671–8. doi: 10.1016/j.clnu.2013.06.012

49. Feng C, Yu H, Lei H, Cao H, Chen M, Liu S. A prognostic model using the neutrophil-albumin ratio and PG-SGA to predict overall survival in advanced palliative lung cancer. *BMC Palliat Care*. (2022) 21:81. doi: 10.1186/s12904-022-00972-x

50. Adamidis F, Kum L, Kitta A, Unseld M, Praschinger A, Koblizek R, et al. The potential of medical comics to teach palliative care skills: a cross-sectional study of 668 medical students. *Ann Palliat Med*. (2022) 11:3436–43. doi: 10.21037/apm-22-637

frontiers | Frontiers in Nutrition

TYPE Review
PUBLISHED 06 February 2024
DOI 10.3389/fnut.2024.1169538

OPEN ACCESS

EDITED BY
Barbara Troesch,
Nutricia/Danone, Switzerland

REVIEWED BY
Hanping Shi,
Capital Medical University, China
Manfred Eggersdorfer,
University Medical Center Groningen, Netherlands

*CORRESPONDENCE
Refaat Hegazi
✉ refaat.hegazi@abbott.com

RECEIVED 19 February 2023
ACCEPTED 19 January 2024
PUBLISHED 06 February 2024

CITATION
Hegazi R, Miller A and Sauer A (2024) Evolution of the diagnosis of malnutrition in adults: a primer for clinicians.
Front. Nutr. 11:1169538.
doi: 10.3389/fnut.2024.1169538

Evolution of the diagnosis of malnutrition in adults: a primer for clinicians

Refaat Hegazi[1]*, Anthony Miller[2] and Abby Sauer[1]

[1]Department of Scientific and Medical Affairs, Abbott Nutrition, Columbus, OH, United States, [2]Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, Champaign, IL, United States

During the last two decades, the definition, diagnosis, and management of malnutrition have significantly evolved. Malnutrition is generally defined as deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. While malnutrition is associated with a significantly increased risk of morbidity, mortality, and healthcare cost, it is often underdiagnosed both in healthcare and community settings. One contributing factor is the lack of a consensus on its definition and appropriate diagnostic indicators. In the current article, we review the evolution of frameworks for the diagnosis of malnutrition. Recently published consensuses by prominent clinical nutrition societies have established a trajectory for the uniform global diagnosis of malnutrition. Limiting the use of body mass index (BMI) as a diagnostic criterion while emphasizing the use of muscle mass enables a more consistent and accurate diagnosis of malnutrition in the clinical setting. Guidance for the unified methodology and terminology for diagnosing malnutrition, such as the one proposed in the current article will enable policy makers to systematically address the two faces of malnutrition, starvation- and disease-related malnutrition applicable to both pediatric and adult populations. Policies and programs that could address issues of food insecurity and scarcity as well as early diagnosis and management of disease-related malnutrition will empower better care of community nutrition.

KEYWORDS

Malnutrition, diagnosis, definition, GLIM, muscle

1 Introduction

Malnutrition due to illness, poverty, famine, conflict, or natural disasters affects nearly two billion people worldwide (1, 2). Throughout history, hunger and famine have been the most prevalent causes of malnutrition. However, as public health services, food production, and living standards have improved, the definition of malnutrition has become less clear as conditions such as obesity, cachexia, sarcopenia, and micronutrient imbalances have become more prevalent (3–5).

Broadly defined, malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients in relation to their dietary requirements. Undernutrition, the most classical form of malnutrition, denotes insufficient intake of energy and nutrients to meet an individual's needs to maintain good health (6). However, undernutrition among adults can develop due to either starvation and/or disease-related inflammation, often due to acute injury or chronic disease (7, 8). Obesity and micronutrient imbalances are also recognized by World Health Organization (WHO) as subsets of malnutrition. Obesity is a paradoxical condition of

malnutrition often associated with pathological fat deposition, low muscle mass and a lack of micronutrients, such as copper, zinc, and iodine, despite increased energy intake (9, 10). Deficiency or lack of homeostasis of important micronutrients is another form of malnutrition that has major impacts on everyday performance, intellectual and emotional condition, as well as physical health (11, 12).

The lack of widely accepted global diagnostic criteria to detect patients at nutritional risk who might benefit from nutritional support has been a major concern. The varying terminology and criteria used to define malnutrition make interpreting and comparing prevalence rates and study results difficult. Despite global attempts to define malnutrition, such as consensus statements issued by the American Society for Parenteral and Enteral Nutrition (ASPEN)/The Academy of Nutrition and Dietetics (AND) (13), the European Society of Clinical Nutrition and Metabolism (ESPEN) (14), we still lack a single unambiguous, objective, universally acknowledged consensus definition. However, recently, the Global Leadership Initiative on Malnutrition (GLIM) has provided the basis for a set of globally applicable criteria to diagnose adult undernutrition (15).

The current article details how malnutrition diagnosis has evolved from energy and protein energy malnutrition to etiology-based (starvation-and disease-related malnutrition), over time. The main aims are to provide clarity to both clinicians and community nutrition leaders to combine efforts and enable improved evaluation and monitoring of nutritional status to achieve optimal outcomes.

To guide this review, a virtual meeting of coauthors was held in May 2022 to establish the scope and intent of the publication. The population of interest was established to be adult patients with or at risk of malnutrition in various healthcare settings. Global literature was searched for relevant articles involving the stated population using several tradition engines (PubMed, Google, Cochrane, Embase, and Science Direct) without language or geographic restrictions. The following terms, alone and in combinations, directed the searches: malnutrition, malnutrition risk, diagnosis, adult, hospital, community, guidelines, consensus, outcomes. Applicable publications (61 references) among the hundreds that were identified in multiple literature searches report data regarding the change in malnutrition diagnosis in adult patients over time. Information was assessed to best summarize the evolution of malnutrition diagnosis in the adult population over the past decades, which was the aim of this review.

2 Evolution of diagnostic frameworks for diagnosing malnutrition

2.1 Marasmus, kwashiorkor, and unspecified protein-calorie malnutrition

For millennia, people have recognized the link between diet and health. In 200 B.C., Hippocrates established the role of nutrition in health when he observed that "the same diet does not suit men in sickness as in health" (16). This simple observation, by today's standards, was profound in an age when food consumption was thought to provide only a single nutrient to replenish the "innate heat" within each person. Galen, a prominent Greek physician in the post-Hippocrates period, produced the first fundamental work on malnutrition (16). In his book De Marasmo written around 176 A.D., he coined the term "marasmus," which meant to whither, dry up, waste, or decay (17). Previously thought of as "aging resulting from sickness," Galen was the first to describe malnutrition, which he split into three types: "due to starvation," "associated with cold specific to aging," or "associated with heat specific to fevers" (17). Galen's seminal work also detailed several physical symptoms associated with malnutrition, which are still diagnostically used today. For example, physical withering is still a key component of several criteria to diagnose malnutrition (13), and the loss of both muscle and adipose tissue mass has recently been identified in diagnostic criteria (18). Importantly, Galen saw that physicians who diagnosed marasmus of old age were able to cure thinness but not wasting with nutritional intervention, reflecting his rudimentary understanding that body fatness is not completely reflective of nutritional status.

Although nutrition played a prominent role in the ancient understanding of health and disease, a comprehensive work on malnutrition would not be completed until the French physician Bernard of Gordon published De Marasmode Secundum Sententiam Galieni in the early 14th century. Gordon devoted much of his work to interpreting the work of Galen from various translations, with an emphasis on defining "**marasmus**," for which he preferred the definition that implied "drying out" (19). As was common during that time, Gordon relied heavily on analogies to describe the phenomenon he observed. Gordon put forth that marasmus associated with fevers could be compared to an oil lamp and its wick, whereas incineration of the wick reflected the wasting and loss of body mass (19).

Though scientific progress during the next several centuries led to a greater understanding of the chemical basis of nutrition and metabolism, little was written about malnutrition until the late 19th and early 20th centuries, when scientists began to view it as a potentially preventable disease. During this time, meaningful connections were made between nutritional status and disease. For example, it was discovered that an inadequate food supply played a significant role in diphtheria outbreaks (20). The discovery of the link between stored chemical energy and the maintenance of cellular function and structure during the time gave rise to the first diagnoses of malnutrition, which occurred in Europe as early as 1905 (21). As malnutrition became a public health crisis in the United States during the early 19th century, physicians struggled to derive objective measures for its diagnosis. Measurements of height and weight gave way to standardized measurement techniques and criteria meant to make malnutrition diagnosis more consistent (22, 23). However, little progress was made in establishing criteria for diagnosing malnutrition throughout the mid-20th century, although several important studies on the physiology of underlying malnutrition were published (24, 25).

During the 1960s famine crises in Africa, the WHO brought attention to the medical consequences of starvation (26). They characterized a protein-deficient condition characterized by hypo-albuminemic peripheral edema and ascites, which they termed **kwashiorkor**, and an energy-deficient state characterized by severe weight loss due to fat store depletion, termed marasmus. However, this classification did not turn out to be relevant for recognizing and diagnosing malnutrition in hospitals in Western countries in the late 20th century. The concept of clinical malnutrition, according to our current understanding, was first meaningfully introduced in the 1960s (Figure 1). Malnutrition work during this time often referred to a landmark study by Leevy et al. (27), which found that a substantial percentage of hospitalized patients were micronutrient deficient. Importantly, Leevy's work foreshadowed increased interest in the clinical diagnosis of malnutrition.

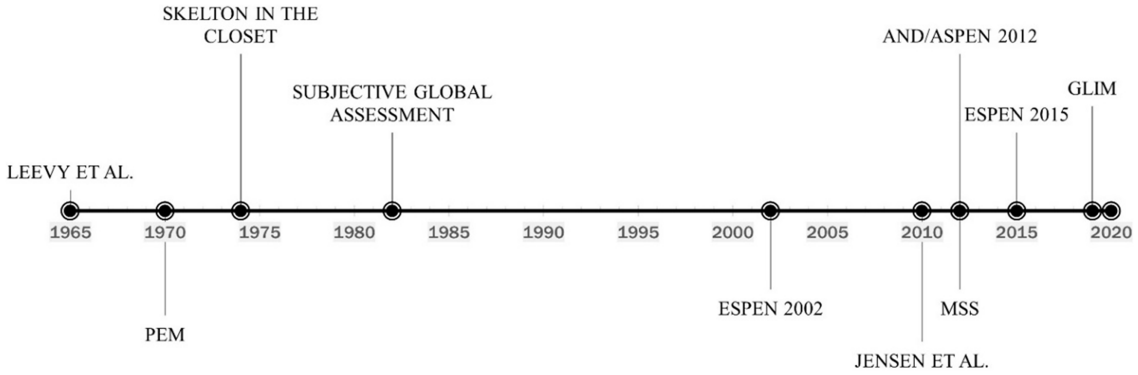


FIGURE 1
Timeline of the evolution of malnutrition definition and diagnosis. PEM, Protein-energy malnutrition; ESPEN, European society for clinical nutrition and metabolism; AND/ASPEN, the academy of nutrition and dietetics/american society for parenteral and enteral nutrition; MSS, malnutrition-sarcopenia syndrome; GLIM, global leadership initiative on malnutrition.

Considering depletion is frequently a combination of protein and energy shortage, the term protein-energy malnutrition (PEM) became widely recognized (28). The clinical parameters used to characterize PEM have evolved, but diagnostic criteria have never been standardized. A variety of biochemical, anthropometric, immunological, and clinical measurements were employed (29). In 1974 (Figure 1), the well-known paper "The Skeleton in the Hospital Closet" by Butterworth (30) along with several other works demonstrated a high prevalence of malnutrition in hospitalized patients (31, 32). The diagnosis of malnutrition began to shift towards the measurement of anthropometric and biochemical markers. Proposed anthropometric markers included body weight (static and change over time), mid-arm muscle circumference (MAMC), and triceps skinfold thickness (TSF) measured in the context of reference standards (33). The use of biochemical markers to diagnose malnutrition was also first described in the 1970s. In 1977, Blackburn et al. (34) proposed the use of serum albumin, transferrin, or total-iron binding capacity as components of nutritional assessment. The concept was reinforced in 1979 when Seltzer et al. (35) recommended that serum albumin be 1 of 2, the other being total lymphocyte count, biochemical parameters for an "instant nutrition assessment". Subsequently, serum albumin and transferrin became highly utilized markers of malnutrition for hospitalized patients (36, 37). However, clinicians at this time simply considered inflammation to be an identifying symptom of malnutrition and not a causative agent, as would be discovered later.

Although the utilization of biochemical markers of nutrition status continued for decades, their use was challenged as early as 1982, and several authors advocated for focus to shift to the use of patient history and physical examination for malnutrition diagnosis. The Subjective Global Assessment (SGA) was developed in 1982 (Figure 1) to assess patients for malnutrition in the clinical setting. The assessment included a physical exam to identify loss of lean mass and adipose tissue, reflecting an increased appreciation for body composition as it relates to nutritional status. Several clinically-available technologies for measuring body composition also began to emerge and were proposed as alternatives to anthropometric measures (38). The primary body compartment of interest was skeletal muscle (39–41). The term "sarcopenia," used to describe the age-related loss of muscle, was coined in 1989 (42). In addition to volume changes in skeletal muscle, investigators also became interested in the association between reduced muscle function and nutritional status, with some suggesting that changes in the functional capability of muscle was the most sensitive indicator of malnutrition (43, 44).

In the 1990s, conversation started to shift towards identifying, documenting, and treating malnutrition using a multidisciplinary approach, which spurred the creation of a wide variety of nutrition screening and assessment tools (45) and diagnostic criteria. Renewed focus on the use of suitable biochemical markers of malnutrition resulted in the recommendation of serum transthyretin, otherwise known as prealbumin, as a more sensitive nutrition marker than albumin and transferrin due to its shorter half-life (46).

In 2002 (Figure 1), the European Society for Clinical Nutrition and Metabolism (ESPEN) developed a set of guidelines for nutrition risk screening applicable to a wide range of settings, including community, clinical, and elderly (47). ESPEN recommended the use of the Malnutrition Universal Screening Tool (MUST) in community settings (48), the Nutritional Risk Screening tool (NRS-2002) in clinical settings (49), and the Mini Nutritional Assessment (MNA) for the elderly (50). While these tools shared several diagnostic criteria for malnutrition including body mass index (BMI), weight loss, and disease severity, none of them (screening not diagnostic tools) appreciate criteria such as muscle mass, muscle function, and the presence of inflammation. Furthermore, clinicians relying on the International Classification of Diseases Volume 9 (ICD-9), which was the standard medical coding manual before 2009, were slow to adopt the new screening tools and most often diagnosed malnutrition with code 262 – Other Severe Protein-Calorie Malnutrition, or code 260 – Kwashiorkor (Table 1) utilizing low serum albumin as a primary diagnostic criterion. This oversimplification of malnutrition diagnosis has led to generalized confusion among clinicians, and often misdiagnosis in the countries where ICD codes are heavily relied upon, such as Australia, Canada, China, Germany, South Africa, the United Kingdom, and the United States, among others.

2.2 Etiology-based diagnosis 2010

As methods for clinical analysis of inflammation advanced at the turn of the 21st century, so did the understanding of its role in malnutrition, as both a symptom and causative factor. Clinicians moved away from the use of the combination of kwashiorkor or

TABLE 1 ICD adult malnutrition codes.

ICD-9	ICD-10
• 260: kwashiorkor	• E40: kwashiorkor
• 261: nutritional marasmus	• E41: nutritional marasmus
• 262: Other severe protein-calorie malnutrition	• E42: Marasmic kwashiorkor
• 263.0: malnutrition of moderate degree	• E43: unspecified severe protein-calorie malnutrition
• 263.1: malnutrition of mild degree	• E44.0: moderate protein-energy malnutrition
• 263.2: arrested development following protein-calorie malnutrition	• E44.1: mild protein-energy malnutrition
• 263.8: other protein-calorie malnutrition	• E45: retarded development following protein-calorie malnutrition
• 263.9: unspecified protein-calorie malnutrition	• E46: unspecified protein-calorie malnutrition

marasmus and depleted serum albumin to etiology-based diagnosis. In 2010 (Figure 1), Jensen et al. (7) suggested that inflammation-associated catabolism of skeletal muscle is a differentiating factor in the diagnosis of malnutrition and proposed an approach based upon etiology that incorporated the impact of the inflammatory response. Patients with malnutrition and without inflammation could be classified as having "Starvation-Related Malnutrition." If inflammation is present at a mild to a moderate degree, the patient could be classified as having "Chronic Disease-Related Malnutrition." If inflammation is present to a severe degree, the patient could be categorized as having "Acute Disease or Injury-Related Malnutrition."

2.3 Malnutrition sarcopenia syndrome 2012

Sarcopenia, defined as loss of muscle mass, strength, and function, can be either primary (age-associated) or secondary (disease, disuse, or undernutrition). Akin to malnutrition, the clinical impact of sarcopenia includes prolonged hospital stay, increased risk of infectious complications, poor wound healing, and mortality. In 2012 (Figure 1), we coined the concept of Malnutrition-Sarcopenia Syndrome (MSS) to highlight the clinical presentation of malnutrition and sarcopenia together in older adults and advocate for the screening, assessment, and treatment of the two conditions concurrently (51). The MSS framework proposes the use of a validated nutrition screening tool, such as MUST, MNA, or NRS-2002 together with the sarcopenia screening tool developed by the European Geriatric Medical Society (EUGMS) Consensus Committee on defining sarcopenia, which employs both gait speed and handgrip strength measurements, although other validated methods of assessing sarcopenic status can be used (51). By assessing patients for both malnutrition and sarcopenia, healthcare practitioners can administer treatments for both conditions, which requires a combination of dietary interventions and muscle strengthening exercises. Additionally, MSS can be diagnosed in both underweight and overweight or obese patients. Furthermore, integrating muscle loss as a diagnostic marker of malnutrition is an important step forward as it highlights the vital role of muscle not only as a structural organ but also for its endocrine, metabolic and immunological functions, and that muscle loss can occur independent of overall body weight (e.g., sarcopenic obesity) making body mass index (BMI) alone as inaccurate marker of overall nutrition health. The updated definition of sarcopenia elevated low muscle strength to the forefront as a primary indicator of sarcopenia and identified poor physical performance as indicative of severe sarcopenia (52). Integrating measures and function in the definition of sarcopenia addresses the technical challenges of availability of muscle mass measurements (e.g., DEXA, MRI, CT) in the hospital setting and permits easier to implement measures of muscle strength and function (e.g., hand-grip strength, chair stand test).

Although MSS has not yet been widely evaluated in health settings, its potential value for predicting poor outcomes in clinical practices has been illustrated in several studies (53, 54). Consistently, other frameworks such as AND/ASPEN have incorporated the measurement of muscle mass as a key diagnostic criterion for malnutrition diagnosis. Similarly, two nutritional screening tools for both conditions have been recently published, Remote—Malnutrition APP (R-MAPP) and PROtocol for NuTritional risk in Oncology (PRONTO) (55, 56).

2.4 AND/ASPEN diagnostic criteria 2012

In 2012 (Figure 1), the Academy of Nutrition and Dietetics collaborated with ASPEN to recommend a standardized set of diagnostic characteristics to be used to identify and document adult malnutrition in the clinical setting (13). The consensus statement adopts the approach of Jensen et al., by recommending that patients should first be categorized based on their inflammation status, which can be assessed by a combination of biochemical markers such as serum levels of albumin, prealbumin, C-reactive protein (CRP), or white blood cell count, and clinical signs of inflammation such as fever, hypothermia, or systemic inflammatory responses (e.g., tachycardia, hyperglycemia). Once inflammation status is determined, the clinician can diagnose malnutrition if two or more out of six total characteristics are present. The six characteristics put forward include insufficient energy intake, weight loss, loss of subcutaneous fat, localized or generalized fluid accumulation that may mask weight loss, loss of muscle mass, and diminished functional status as measured by hand grip strength (Table 2). However, measurable numerical guidelines are only put forth for energy intake and weight loss, leaving loss of body fat or muscle mass, fluid accumulation, and reduced grip strength up to the clinician's interpretation of whether to rate as "mild," or "moderate to severe." By incorporating inflammatory status and measures of muscle mass and function, the AND/ASPEN consensus statement represents a significant step forward in the development of a universal framework for the diagnosis of malnutrition.

2.5 ESPEN diagnostic criteria 2015

In 2015 (Figure 1), ESPEN appointed an international expert group to reach a consensus on a set of generally applicable diagnostic criteria for the diagnosis of malnutrition, independent of etiologic

10.3389/fnut.2024.1169538

TABLE 2 Criterion used by recent malnutrition guidelines.

	AND/ASPEN 2012		ESPEN 2015	GLIM 2018	
Severity	Non-severe (moderate) malnutrition	Severe malnutrition	Not included	Moderate malnutrition[c]	Severe malnutrition[c]
Decreased BMI (kg/m^2)	Not included		Alternative 1[b] < 18.5 kg/m^2 Alternative 2[b] < 20 if <70 yr, or < 22 if ≥70 yr	< 20 if <70 yr, or < 22 if ≥70 yr	<18.5 if <70 yr, or < 20 if ≥70 yr
Decreased energy intake	In the context of acute injury or illness[a]		Not included	≤ 50% of EER for >1 week, or	
	< 75% EER for >7d	≤ 50% EER for ≥5d			
	In the context of chronic illness[a]			any reduction for >2 weeks, or	
	< 75% EER for ≥1 mo	< 75% EER for ≥1 mo			
	In the context of social or environmental circumstances[a]			any chronic GI condition that adversely impacts food assimilation or absorption[d]	
	< 75% EER for ≥3 mo	≤ 50% EER for ≥1 mo			
Weight loss	In the context of acute injury or illness		Alternative 2[b] 5% over last 3 mo, or 10% indefinite of time	5–10% within the past 6 mo, or 10–20% beyond 6 mo	>10% within the past 6 mo, or > 20% beyond 6 mo
	1–2% in 1 wk	2% in 1 wk			
	5% in 1 mo	5% in 1 mo			
	7.5% in 3 mo	7.5% in 3 mo			
	In the context of chronic illness				
	5% in 1 mo	5% in 1 mo			
	7.5% in 3 mo	7.5% in 3 mo			
	10% in 6 mo	10% in 6 mo			
	20% in 1 y	20% in 1 y			
	In the context of social or environmental circumstances				
	5% in 1 mo	5% in 1 mo			
	7.5% in 3 mo	7.5% in 3 mo			
	10% in 6 mo	10% in 6 mo			
	20% in 1 y	20% in 1 y			
Loss of subcutaneous fat	In the context of acute injury or illness		Not included	Not included	
	Mild	Moderate			
	In the context of chronic illness				
	Mild	Severe			
	In the context of social or environmental circumstances				
	Mild	Severe			
Localized or generalized fluid accumulation	In the context of acute injury or illness		Not included	Not included	
	Mild	Moderate to Severe			
	In the context of chronic illness				
	Mild	Severe			
	In the context of social or environmental circumstances				
	Mild	Severe			

(Continued)

mechanisms and applicable to patients from all clinical settings (14). The guidelines recommend that patients at risk of malnutrition be screened by any validated screening tool. If found to be at risk, the committee recommends the assessment of three variables considered to reflect nutritional status most accurately, namely weight loss, BMI, and free fat mass index (FFMI) (Table 2). The group furthermore

TABLE 2 (Continued)

	AND/ASPEN 2012		ESPEN 2015	GLIM 2018	
Loss of muscle mass	In the context of acute injury or illness		Alternative 2[b] FFMI <15 and 17 kg/m2 in women and men, respectively	Mild to moderate deficit[e]	Severe deficit[e]
	Mild	Moderate			
	In the context of chronic illness				
	Mild	Severe			
	In the context of social or environmental circumstances				
	Mild	Severe			
Loss of muscle function	In the context of acute injury or illness		Not included	Not included	
	N/A	Measurably reduced			
	In the context of chronic illness				
	N/A	Measurably reduced			
	In the context of social or environmental circumstances				
	N/A	Measurably reduced			

[a]Acute or injury or disease-related malnutrition is defined by the presence of a marked inflammatory response. Malnutrition in the context of a chronic illness is defined by inflammation of a mild to moderate degree. Malnutrition in the context of social or environmental circumstances is defined by no inflammatory response.
[b]ESPEN proposes two alternative ways to diagnose malnutrition; one exclusively based on reduced BMI, and another based on reduced BMI, weight loss, and loss of muscle mass.
[c]The GLIM guidelines grade severity using three phenotypic criteria: % weight loss, reduced BMI, or reduced muscle mass. Patient must have 1 phenotypic criteria met within the moderate or severe cutoffs.
[d]Decreased energy intake is not included in GLIM severity grading.
[e]GLIM provides guidance on the measurement of muscle mass by validated tools such as appendicular lean mass index (ALMI, kg/m^2) by dual-energy absorptiometry or corresponding standards using other body composition methods like bioelectrical impedance analysis (BIA), CT or MRI, or if not available, anthropometric measurements.

provides two alternatives for the diagnosis of malnutrition based on the use of these variables: (1) diagnosis solely based on a BMI, or (2) the combined finding of unintentional weight loss together with either reduced BMI or a low FFMI using sex-specific cut-offs. The inclusion of FFMI reflects the continued appreciation of muscle mass as an important indicator of nutritional status and necessitated the use of modern techniques for body composition analysis. Importantly, the consensus provided numerical cut-offs for each indicator, enabling uniform diagnosis across clinical settings. Regarding inflammation, the consensus group determined that it should be regarded as an etiologic factor rather than a diagnostic feature of malnutrition. This differed from the approach of AND/ASPEN, which considered inflammatory status to be one of the primary differentiators of malnutrition severity and allowed for the use of etiologic variables in the diagnosis of malnutrition.

2.6 Global leadership initiative on malnutrition 2018

The discrepancies between malnutrition diagnostic criteria suggested by the two major nutrition societies, ASPEN and ESPEN, called for an opportunity to publish a unified consensus diagnostic criteria set for malnutrition. In 2018 (Figure 1), the Global Leadership Initiative on Malnutrition (GLIM) convened to build a global consensus for diagnostic criteria for malnutrition in adults applicable in diverse global settings (15). Comprised of members from several major global clinical nutrition societies, including ASPEN, ESPEN, the Latin American Federation for Nutritional Therapy (FELANPE), and the Parenteral and Enteral Nutrition Society of Asia (PENSA), the GLIM initiative set its primary aim to "combine clinical accuracy and consistency with a simple implementation that could be applied by nonspecialized healthcare personnel in everyday practice." As such, the GLIM guidelines represent the most current and comprehensive malnutrition criteria.

Following in the footsteps of the ESPEN 2015 recommendations, the GLIM guidelines recommend an initial screening with a validated screening tool to identify "at risk" status. If a subject is determined to be at risk of malnutrition, it is recommended that clinicians move on to assessment, consisting of malnutrition diagnosis and grading of severity. Malnutrition diagnosis according to GLIM relies on the presence of one etiologic and one phenotypic criterion. Recommended etiologic indicators according to GLIM include reduced food intake (Table 2). Like the ASPEN 2012 guidelines, GLIM also incorporates inflammation as an etiologic criterion, whether related to acute disease/injury or related to chronic disease. The inclusion of inflammation is an important provision that includes new research demonstrating the critical role that systemic inflammation plays in the pathophysiology of malnutrition. To judge whether systemic inflammation is chronic or severe, GLIM recommends the measurement of C-reactive protein (CRP) as a biomarker, although low albumin/prealbumin levels are also included.

Phenotypic criteria include non-volitional weight loss, low BMI, or reduced muscle mass (Table 2). Like ESPEN 2015, GLIM recommends that muscle mass be measured by compositional analysis, such as the analysis of FFMI by dual-energy absorptiometry (DXA). However, recognizing that the availability of analytical equipment varies with geography, physical examination, or standard anthropometric methods such as mid-arm muscle or calf circumference can be used with thresholds adapted to race. Akin to the ASPEN/AND guidelines of 2012, GLIM uses phenotypic criteria to grade the severity of malnutrition as "moderate" or "severe" based

on numerical cutoffs of weight loss, BMI, or reduced muscle mass. Even so, the GLIM criteria are less subjective, more clinically intuitive, and include characteristics such as weight loss, muscle mass, and BMI that are more congruent with established ideas of non-severe and severe malnutrition. As malnutrition is not an indexed term in ICD-10, if moderate malnutrition is identified, code E46 (unspecified malnutrition) may be used. If severe malnutrition is documented, code E43 (severe malnutrition) can be employed. It should be noted that, unlike ICD-10, GLIM does not incorporate a mild malnutrition diagnosis (Table 1). Efforts should be made to unify ICD codes with the GLIM guidelines, to ensure that clinicians across the globe diagnose malnutrition by the same criteria.

However, among the criteria included in the GLIM diagnosis, assessment of skeletal muscle mass is least often applied, while BMI continues to be the most applied (57). Recently (Figure 1), the GLIM consortium appointed a working group to provide guidance on the assessment of skeletal muscle mass and the use of muscle function as a diagnostic indicator of malnutrition. The guidance reinforces their original recommendations to utilize a technical approach for measurement of muscle mass [e.g., dual energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), computerized tomography (CT)] when available, but to use a clinical approach (e.g., anthropometrical measures such as calf circumference or mid-upper arm circumference) if not. Although the working group agreed with the original GLIM guidelines that muscle function cannot serve as a surrogate marker of muscle mass, they leave open the option for physicians to assess for sarcopenia as a phenotypic assessment of malnutrition severity, either as an objective measure of muscle mass or muscle strength.

2.7 World Health Organization

According to the WHO, the term malnutrition addresses 3 broad groups of conditions: Undernutrition, which includes wasting (low weight-for-height), stunting (low height-for-age, mainly applicable to the pediatric population), and underweight (low weight-for-age) (58), micronutrient-related malnutrition, which includes micronutrient deficiencies (a lack of sufficient vitamin and mineral intake) or micronutrient excess, and overweight, which includes obesity and diet-related noncommunicable diseases (such as heart disease, stroke, diabetes, and some cancers). While modern frameworks such as GLIM do well to account for malnutrition due to undernutrition and obesity, the WHO framework provides the broadest definition of malnutrition by incorporating malnutrition due to micronutrient abnormalities. While no numerical cutoff values or diagnostic criteria are provided, the WHO framework is an important step for future diagnostic frameworks that account for all the causes of malnutrition.

2.8 An integrated malnutrition diagnosis framework

Considering the complex history of the definition and diagnosis of malnutrition, we propose that adult malnutrition be defined as a clinical syndrome caused by the imbalance of decreased nutrient intake and increased nutrient demand and characterized by the presence of weight loss, decreased muscle mass and/or function, and/or micronutrient deficiency in the setting of chronic semi-starvation, acute or chronic disease, or obesity. We also propose that the GLIM and WHO frameworks for diagnosing malnutrition be integrated into a single scheme integrating the three forms of malnutrition: undernutrition, obesity and micronutrient deficiency (Figure 2). Integration of loss of muscle (lean) mass (and strength/function) enables clinicians to diagnose malnutrition without solely relying on body weight and BMI (e.g., diagnosis of sarcopenic obesity). According to this proposed and unified framework, symptoms and clinical signs of malnutrition will be assessed as part of clinical examination. Clinicians should routinely assess their patients for history of reduced food intake, weight loss, loss of muscle (lean) mass/strength/function, micronutrient deficiency, obesity and faltered growth/stunting (in children), Integrating the three forms of malnutrition (triple burden) in clinical care could enable early diagnosis and proper treatment of such a significant disease. Global adoption of an integrated framework with validated methodology and cutoff values for each criterion would enable consistent diagnosis of malnutrition irrespective of geography, improve malnutrition research outcomes and interpretability, and an overall goal of improved patient outcomes.

Although not the main focus of this paper, it is important to note that within the past 5–10 years there have been multiple consensus statements on pediatric malnutrition, and a global integrated framework would be beneficial in this population as well. In 2015, the Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition published a recommended standardized set of diagnostic indicators to be used to identify and document pediatric malnutrition (undernutrition) in routine clinical practice (59). The recommended indicators include z scores for weight-for-height/length, body mass index-for-age, or length/height-for-age or mid–upper arm circumference when a single data point is available; and further, when 2 or more data points are available, indicators may also include weight gain velocity (<2 years of age), weight loss (2–20 years of age), deceleration in weight for length/height z score, and inadequate nutrient intake (59). In 2022, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) published a position statement on identifying pediatric disease-associated undernutrition (60). This position statement provided an updated descriptive definition of pediatric disease-associated undernutrition as "Undernutrition is a condition resulting from imbalanced nutrition or abnormal utilization of nutrients which causes clinically meaningful adverse effects on tissue function and/or body size/composition with subsequent impact on health outcomes (60)." This position statement recommended that in addition to commonly used criteria for undernutrition such as z score < -2 for weight-for-age, weight-for-length, or body mass index < -2, an unintentional decline of >1in these z scores over time should be considered as an indicator requiring further assessment to establish a diagnosis (60).

3 Discussion

Recently, traditional diagnostic indicators of malnutrition such as BMI have faced criticism for their lack of applicability to the population treated in Western hospitals. The use of a low BMI as a phenotypic criterion for malnutrition diagnosis varies significantly by

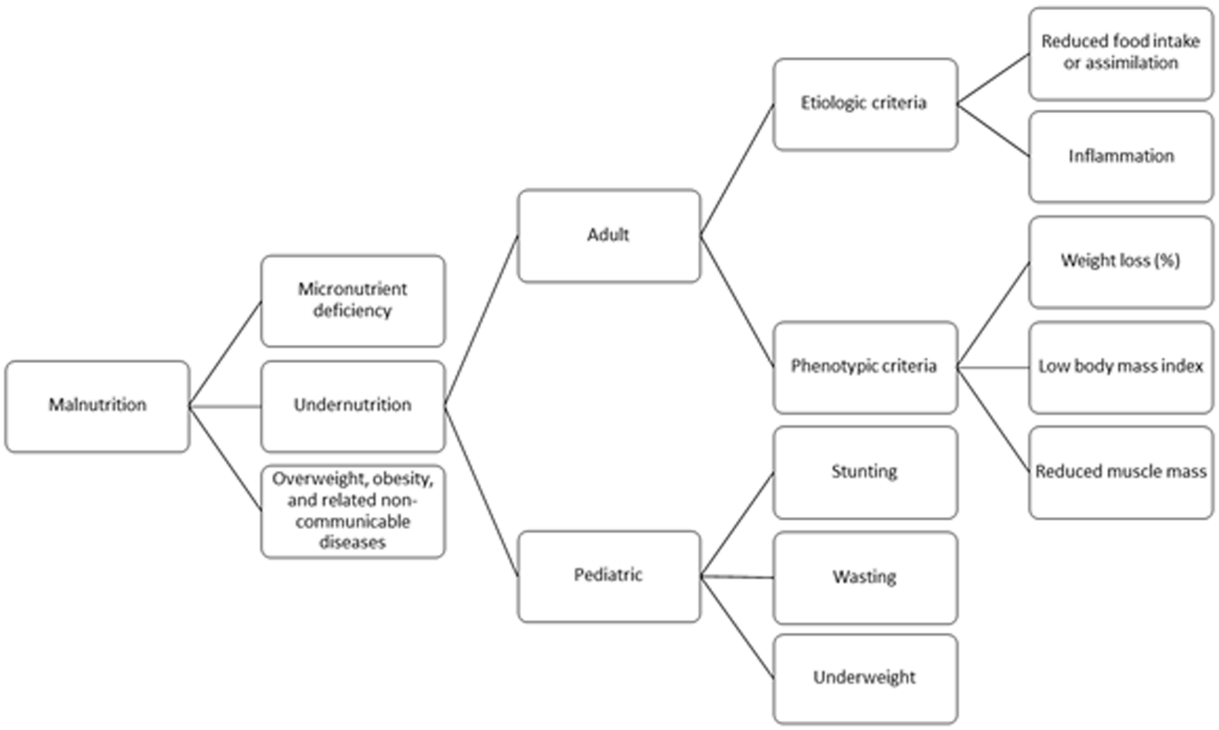


FIGURE 2
Malnutrition diagnosis algorithm.

region. Individuals from America are frequently overweight or obese and would need to lose a significant amount of weight before receiving a low BMI designation. However, a low BMI cutoff is still included in the GLIM guidelines because of its ease of measurement and common use in other areas of the globe. On the other hand, the loss of muscle mass is an emerging criterion that is gaining support for inclusion in malnutrition diagnostic guidelines from the clinical nutrition community. Having been included in ASPEN 2012, ESPEN 2015, and GLIM 2018, the methodology for measuring muscle mass and defining what is 'reduced' has undergone considerable optimization over the past decade. A primary issue that confronts the use of muscle mass as a global criterion for diagnosing malnutrition is the lack of availability of advanced measurement instruments such as DXA, CT, or BIA. Another limitation is the fact that technology-based methods are often unable to physically accommodate persons with very high body mass. Furthermore, their accuracy is also decreased when used on obese individuals (61). Fortunately, further guidance provided by GLIM points to the anthropometric assessment of muscle mass by calf or mid-arm muscle circumference as being adjustable for persons with high BMI (62). To develop the use of muscle mass as a widely accepted indicator of malnutrition, appropriate cutoff values adjusted for sex and ethnicity must continue to be developed for each methodology, that technology-based methods undergo further refinement and standardization, and, most importantly, that promotion spurs wider clinical awareness of muscle mass as a criterion.

While reduced muscle mass has gained wide acceptance as an indicator of malnutrition, the role of inflammation is less clear. It is commonly accepted that acute or chronic inflammation results in altered body composition and reduced biological function (7, 63), which contributes to malnutrition in several ways, including reduced food intake, increased resting energy expenditure, and muscle catabolism. Based on the work of Jensen et al. (7), modern guidelines for diagnosing malnutrition such as AND/ASPEN 2012 and GLIM 2018 incorporate screening and classification of patients based on their inflammatory status. Although this helps integrate inflammation into the diagnosis of malnutrition, it is not yet clinically well-defined, and biomarkers for detecting the severity of inflammation are not yet agreed upon nor widely utilized as a part of the current clinical practice. In addition, disorders labeled as chronic starvation are not devoid of subtle inflammatory stress.

The present usage of inflammation does not categorize patients with severe illness or acute tissue damage into risk groups to properly decide on the severity of the illness, and therefore the nutritional intervention. For instance, under the current diagnostic framework, all critically ill patients should be classified as having a severe acute injury or disease-related malnutrition. However, pre-admission comorbidities play a major role in determining the clinical outcome of critically ill or acutely injured patients and therefore dictate the appropriate nutritional intervention plan. Two questions need to be further addressed; whether the nutritional requirements of patients with moderate inflammation differ from those of patients with severe inflammation and whether nutrients with anti-inflammatory properties could exert beneficial effects in patients with inflammation-related malnutrition as compared to standard nutrition interventions.

Micronutrient deficiency, frequently overlooked in existing definitions of malnutrition, should be an integral component of malnutrition diagnosis. Patients suffering from both starvation and inflammatory diseases are more likely to be deficient in micronutrients due to inadequate intake and/or increased requirements. Additionally, obese patients have been shown to have deficiencies in almost all

micronutrients both before and after bariatric surgery. Clinicians recognize this as the classic combination of macronutrient excess and micronutrient deficiency. Given their essential vital function for normal metabolism, we suggest that micronutrient deficiency become an integral part of a universal malnutrition diagnostic framework. For instance, zinc is a cofactor for the function of several enzymes in glucose, protein, and lipid metabolism, and is crucial for the utilization of glucose by muscle and fat cells. The functions and methods of diagnosis of micronutrient deficiency and treatment have been nicely reviewed by Berger et al. in the 2022 ESPEN micronutrient guideline (64).

An appreciation for the history of the definition and diagnosis of malnutrition, along with continued advancement and unification of the diagnostic frameworks, will provide nutrition experts and clinicians the required foundation to tackle the age-old challenge of properly recognizing and successfully treating malnutrition.

WHO and GLIM diagnostic frameworks are great milestones towards harmonization of the definition and diagnosis of malnutrition. The current proposed framework further builds on these two milestones by integrating the four main forms of malnutrition (adult, pediatric, starvation-related, and disease-related) into one framework. Integrating micronutrient deficiency and obesity-related chronic diseases as integral components of malnutrition diagnosis could further unify efforts to address malnutrition globally. Future research is warranted to validate the cutoffs required for making the diagnosis and classification of malnutrition and coining risk-based therapeutic interventions in different clinical settings. Additionally, the availability of reliable and accessible tools to measure body composition (low muscle/lean mass and high fat to lean mass ratio) and muscle function in clinical settings will enable clinicians to diagnose malnourished patients, tailor treatment plans to their existing phenotype, and monitor effectiveness.

Author contributions

RH, AM, and AS all contributed to the ideation, creation, and editing of this article. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

RH and AS employee and stockholder of Abbott. The material presented in this article is based on the best-known clinical evidence and is not affected by this financial relationship.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dietz WH. Climate change and malnutrition: we need to act now. *J Clin Invest*. (2020) 130:556–8. doi: 10.1172/JCI135004

2. Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, et al. The global Syndemic of obesity, undernutrition, and climate change: the lancet commission report. *Lancet*. (2019) 393:791–846. doi: 10.1016/S0140-6736(18)32822-8

3. Lustig RH, Collier D, Kassotis C, Roepke TA, Kim MJ, Blanc E, et al. Obesity I: overview and molecular and biochemical mechanisms. *Biochem Pharmacol*. (2022) 199:115012. doi: 10.1016/j.bcp.2022.115012

4. Ethgen O, Beaudart C, Buckinx F, Bruyere O, Reginster JY. The future prevalence of sarcopenia in Europe: a claim for public health action. *Calcif Tissue Int*. (2017) 100:229–34. doi: 10.1007/s00223-016-0220-9

5. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. *J Cachexia Sarcopenia Muscle*. (2016) 7:507–9. doi: 10.1002/jcsm.12167

6. Maleta K. Undernutrition. *Malawi Med J*. (2006) 18:189–205.

7. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the international consensus guideline committee. *Clin Nutr*. (2010) 29:151–3. doi: 10.1016/j.clnu.2009.11.010

8. Itoh M, Tsuji T, Nemoto K, Nakamura H, Aoshiba K. Undernutrition in patients with COPD and its treatment. *Nutrients*. (2013) 5:1316–35. doi: 10.3390/nu5041316

9. Vandevijvere S, Chow CC, Hall KD, Umali E, Swinburn BA. Increased food energy supply as a major driver of the obesity epidemic: a global analysis. *Bull World Health Organ*. (2015) 93:446–56. doi: 10.2471/BLT.14.150565

10. Bal BS, Finelli FC, Shope TR, Koch TR. Nutritional deficiencies after bariatric surgery. *Nat Rev Endocrinol*. (2012) 8:544–56. doi: 10.1038/nrendo.2012.48

11. Reynolds E. Vitamin B12, folic acid, and the nervous system. *Lancet Neurol*. (2006) 5:949–60. doi: 10.1016/S1474-4422(06)70598-1

12. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: a new form of malnutrition? Part A Vitamins. *Obes Surg*. (2008) 18:870–6. doi: 10.1007/s11695-007-9349-y

13. White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy Malnutrition Work G, et al. Consensus statement: Academy of nutrition and dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr*. (2012) 36:275–83. doi: 10.1177/0148607112440285

14. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition—an ESPEN consensus statement. *Clin Nutr*. (2015) 34:335–40. doi: 10.1016/j.clnu.2015.03.001

15. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition—a consensus report from the global clinical nutrition community. *Clin Nutr*. (2019) 38:1–9. doi: 10.1016/j.clnu.2018.08.002

16. Guggenheim KY. *Nutrition and nutritional diseases*. Lexington, MA: The evolution of concepts: DC Heath & Co. (1981).

17. Theoharides TC. Galen on marasmus. *J Hist Med Allied Sci*. (1971) 26:369–90. doi: 10.1093/jhmas/XXVI.4.369

18. Fischer M, JeVenn A, Hipskind P. Evaluation of muscle and fat loss as diagnostic criteria for malnutrition. *Nutr Clin Pract*. (2015) 30:239–48. doi: 10.1177/0884533615573053

19. Demaitre L. The medical notion of "withering" from Galen to the fourteenth century: the treatise on marasmus by Bernard of Gordon. *Traditio*. (1992) 47:259–307. doi: 10.1017/S036215290000725X

20. Bayles G. The malady of innutrition. *N Y Med J*. (1877) 15:13–21.

21. Ruis AR. "children with half-starved bodies" and the assessment of malnutrition in the United States, 1890-1950. *Bull Hist Med*. (2013) 87:378–406. doi: 10.1353/bhm.2013.0044

22. Kruse HD. Medical evaluation of nutritional status. *JAMA J Am Med Assoc*. (1943) 121:584–91. doi: 10.1001/jama.1943.62840080005007a

23. Turner CE, Fellow PH. Precision and reliability of underweight measurement. *Amer J Pub Health*. (1929) 19:969–79. doi: 10.2105/AJPH.19.9.969

24. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The biology of human starvation. Volume II*. Washington, DC: Am J Public Health Nations Health. (1950).

25. Massry SG, Smogorzewski M. The hunger disease of the Warsaw Ghetto. *Am J Nephrol*. (2002) 22:197–201. doi: 10.1159/000063761

26. Jelliffe DB. The assessment of the nutritional status of the community (with special reference to field surveys in developing regions of the world). *Monogr Ser World Health Organ*. (1966) 53:3–271.

27. Leevy CM, Cardi L, Frank O, Gellene R, Baker H. Incidence and significance of hypovitaminemia in a randomly selected municipal hospital population. *Am J Clin Nutr*. (1965) 17:259–71. doi: 10.1093/ajcn/17.4.259

28. Waterlow JC. Classification and definition of protein-energy malnutrition. *Monogr Ser World Health Organ*. (1976) 62:530–55.

29. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. *Am J Surg*. (1980) 139:160–7. doi: 10.1016/0002-9610(80)90246-9

30. Butterworth CE. The skeleton in the hospital closet. *Nutrition*. (1994) 10:442.

31. Bistrian BR, Blackburn GL, Hallowell E, Heddle R. Protein status of general surgical patients. *JAMA*. (1974) 230:858–60. doi: 10.1001/jama.1974.03240060028025

32. Bollet AJ, Owens S. Evaluation of nutritional status of selected hospitalized patients. *Am J Clin Nutr*. (1973) 26:931–8. doi: 10.1093/ajcn/26.9.931

33. Frisancho AR. Triceps skin fold and upper arm muscle size norms for assessment of nutrition status. *Am J Clin Nutr*. (1974) 27:1052–8. doi: 10.1093/ajcn/27.10.1052

34. Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, Smith MF. Nutritional and metabolic assessment of the hospitalized patient. *JPEN J Parenter Enteral Nutr*. (1977) 1:11–21. doi: 10.1177/014860717700100101

35. Seltzer MH, Bastidas JA, Cooper DM, Engler P, Slocum B, Fletcher HS. Instant nutritional assessment. *JPEN J Parenter Enteral Nutr*. (1979) 3:157–9. doi: 10.1177/014860717900300309

36. Hooley RA. Clinical nutritional assessment: a perspective. *J Am Diet Assoc*. (1980) 77:682–6. doi: 10.1016/S1094-7159(21)03591-1

37. Grant JP, Custer PB, Thurlow J. Current techniques of nutritional assessment. *Surg Clin North Am*. (1981) 61:437–63. doi: 10.1016/S0039-6109(16)42430-8

38. Heymsfield SB, McManus C, Stevens V, Smith J. Muscle mass: reliable indicator of protein-energy malnutrition severity and outcome. *Am J Clin Nutr*. (1982) 35:1192–9. doi: 10.1093/ajcn/35.5.1192

39. Steffee WP. Malnutrition in hospitalized patients. *JAMA*. (1980) 244:2630–5. doi: 10.1001/jama.1980.03310230032019

40. Gassull MA, Cabre E, Vilar L, Alastrue A, Montserrat A. Protein-energy malnutrition: an integral approach and a simple new classification. *Hum Nutr Clin Nutr*. (1984) 38:419–31.

41. Guarnieri GF, Toigo G, Situlin R, Del Bianco MA, Crapesi L, Zanettovich A. Direct biochemical analysis of human muscle tissue in hospital malnutrition. *JPEN J Parenter Enteral Nutr*. (1987) 11:55S–63S. doi: 10.1177/014860718701100507

42. Rosenberg IH. Summary comments. *Am J Clin Nutr*. (1989) 50:1231–3. doi: 10.1093/ajcn/50.5.1231

43. Guess CW, Werth R, Pollard M, Wood CD. An assessment of nutritional depletion following major colonic surgery. *Dis Colon Rectum*. (1984) 27:669–71. doi: 10.1007/BF02553362

44. Russell DM, Jeejeebhoy KN. The assessment of the functional consequences of malnutrition. *Curr Concepts Nutr*. (1984) 13:113–35.

45. Van Bokhorst-De Van Der Schueren MA, Guaitoli PR, Jansma EP, De Vet HC. Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting. *Clin Nutr*. (2014) 33:39–58. doi: 10.1016/j.clnu.2013.04.008

46. Mears E. Outcomes of continuous process improvement of a nutritional care program incorporating serum prealbumin measurements. *Nutrition*. (1996) 12:479–84. doi: 10.1016/S0899-9007(96)91721-9

47. Kondrup J, Allison SP, Elia M, Vellas B, Plauth MEducational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. *Clin Nutr*. (2003) 22:415–21. doi: 10.1016/S0261-5614(03)00098-0

48. Kaiser MJ, Bauer JM, Uter W, Donini LM, Stange I, Volkert D, et al. Prospective validation of the modified mini nutritional assessment short-forms in the community, nursing home, and rehabilitation setting. *J Am Geriatr Soc*. (2011) 59:2124–8. doi: 10.1111/j.1532-5415.2011.03659.x

49. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc EWG. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. (2003) 22:321–36. doi: 10.1016/S0261-5614(02)00214-5

50. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. (1999) 15:116–22. doi: 10.1016/S0899-9007(98)00171-3

51. Vandewoude MF, Alish CJ, Sauer AC, Hegazi RA. Malnutrition-sarcopenia syndrome: is this the future of nutrition screening and assessment for older adults? *J Aging Res*. (2012) 2012:1–8. doi: 10.1155/2012/651570

52. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. (2019) 48:16–31. doi: 10.1093/ageing/afy169

53. Hu X, Zhang L, Wang H, Hao Q, Dong B, Yang MJ. Malnutrition-sarcopenia syndrome predicts mortality in hospitalized older patients. *Sci Rep*. (2017) 7:1–9. doi: 10.1038/s41598-017-03388-3

54. Juby AG, Mager DR. A review of nutrition screening tools used to assess the malnutrition-sarcopenia syndrome (MSS) in the older adult. *Clin Nutr ESPEN*. (2019) 32:8–15. doi: 10.1016/j.clnesp.2019.04.003

55. Krznarić Z, Vranešić Bender D, Laviano A, Cuerda C, Landi F, Monteiro R, et al. A simple remote nutritional screening tool and practical guidance for nutritional care in primary practice during the COVID-19 pandemic. *Clin Nutr*. (2020) 39:1983–7. doi: 10.1016/j.clnu.2020.05.006

56. Muscaritoli M, Bar-Sela G, Battisti NML, Belev B, Contreras-Martínez J, Cortesi E, et al. Oncology-led early identification of nutritional risk: a pragmatic, evidence-based Protocol (PRONTO). *Cancers*. (2023) 15:380. doi: 10.3390/cancers15020380

57. Compher C, Cederholm T, Correia M, Gonzalez MC, Higashiguch T, Shi HP, et al. Guidance for assessment of the muscle mass phenotypic criterion for the global leadership initiative on Malnutrition diagnosis of malnutrition. *JPEN J Parenter Enteral Nutr*. (2022) 46:1232–42. doi: 10.1002/jpen.2366

58. Organization WH. *Fact sheet–Malnutrition*. World Health Organization. (2021).

59. Becker P, Carney LN, Corkins MR, Monczka J, Smith E, Smith SE, et al. Academy of nutrition and dietetics, American Society for Parenteral and Enteral Nutrition. Consensus statement of the Academy of nutrition and dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr Clin Pract*. (2015) 30:147–61. doi: 10.1177/0884533614557642

60. Hulst JM, Huysentruyt K, Gerasimidis K, Shamir R, Koletzko B, Chourdakis M, et al. Special interest group clinical Malnutrition of ESPGHAN. A practical approach to identifying pediatric disease-associated undernutrition: a position statement from the ESPGHAN special interest group on clinical Malnutrition. *J Pediatr Gastroenterol Nutr*. (2022) 74:693–705. doi: 10.1097/MPG.0000000000003437

61. Price KL, Earthman CP. Update on body composition tools in clinical settings: computed tomography, ultrasound, and bioimpedance applications for assessment and monitoring. *Eur J Clin Nutr*. (2019) 73:187–93. doi: 10.1038/s41430-018-0360-2

62. Gonzalez MC, Mehrnezhad A, Razaviarab N, Barbosa-Silva TG, Heymsfield SB. Calf circumference: cutoff values from the NHANES 1999-2006. *Am J Clin Nutr*. (2021) 113:1679–87. doi: 10.1093/ajcn/nqab029

63. Evans DC, Corkins MR, Malone A, Miller S, Mogensen KM, Guenter P, et al. The use of visceral proteins as nutrition markers: an ASPEN position paper. *Nutr Clin Pract*. (2021) 36:22–8. doi: 10.1002/ncp.10588

64. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. *Clin Nutr*. (2022) 41:1357–424. doi: 10.1016/j.clnu.2022.02.015

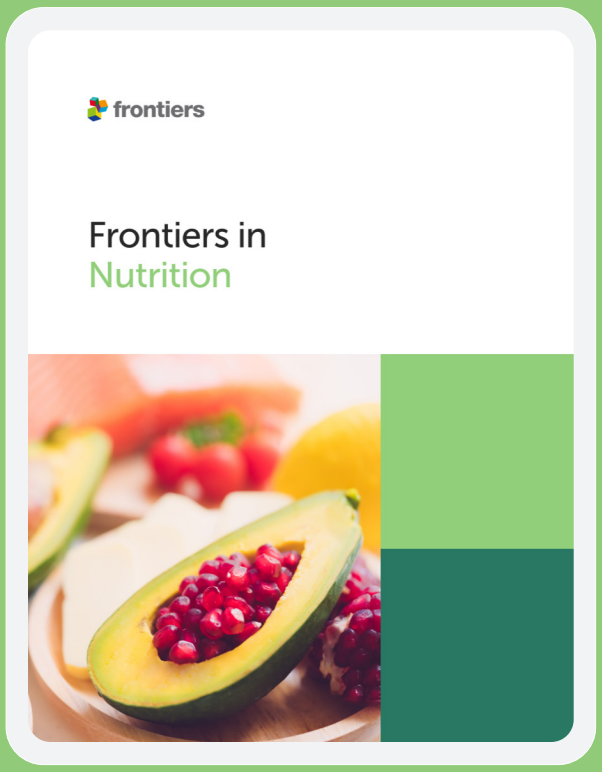
Frontiers in Nutrition

Explores what and how we eat in the context of health, sustainability and 21st century food science

A multidisciplinary journal that integrates research on dietary behavior, agronomy and 21st century food science with a focus on human health.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact