FB09-Agrarwissenschaften, Ökotrophologie und Umweltmanagement

Institute for Nutrition

Nutrition in Prevention and Therapy

Individualization of nutritional treatment through use of biomarkers in polymorbid medical inpatients

Dissertation

Submitted for the degree of doctor trophologiae (Dr. troph.)

to the Faculty of Agricultural Sciences, Nutritional Sciences and Environmental Management

Justus-Liebig-University Giessen

Submitted by

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From: Weesen, Switzerland

Giessen, 2024

This dissertation was accepted as a doctoral dissertation in fulfilment of the requirements for the degree of doctor trophologiae by the Faculty of Agricultural Sciences, Nutritional Sciences and Environmental Management, Justus-Liebig-University Giessen.

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Date of Defence: 31.07.2024

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(Carla Wunderle)

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Abbreviations

ADMA, asymmetric dimethylarginine

BMI, body mass index

CRP, c-reactive protein

DRM, disease related malnutrition

EBM, evidence-based medicine

EFFORT, Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial

eGFR, estimated glomerular filtration rate

EPaNIC, Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients

ERN-ERA European Renal Nutrition Group of the European Renal Association

ESPEN, European Society of Clinical Nutrition and Metabolism

GABR, global arginine bioavailability ratio (GABR=arginine / (ornithine + citrulline))

GDF15, growth-differentiation factor-15

GLIM, Global Leadership Initiative on Malnutrition

HGS, handgrip strength

ICU, intensive care unit

IGF1, insulin-like growth factor-1

IL-1β, interleukin 1β

IL-6, interleukin 6

MNA, Mini Nutritional Assessment - Long Form

mTOR, mammalian target of rapamycin

NNT, number needed to treat

NO, nitric oxide

NRS, Nutritional Risk Screening 2002

ONS, oral nutritional supplement

OR, Odds Ratio

PN, parenteral nutrition

QoL, quality of life

RCT, randomized controlled trial

SOP, standard operating procedure

T4, thyroxine

T3, triiodothyronine

TNFα, tumor necrosis factor α

1. Abstract

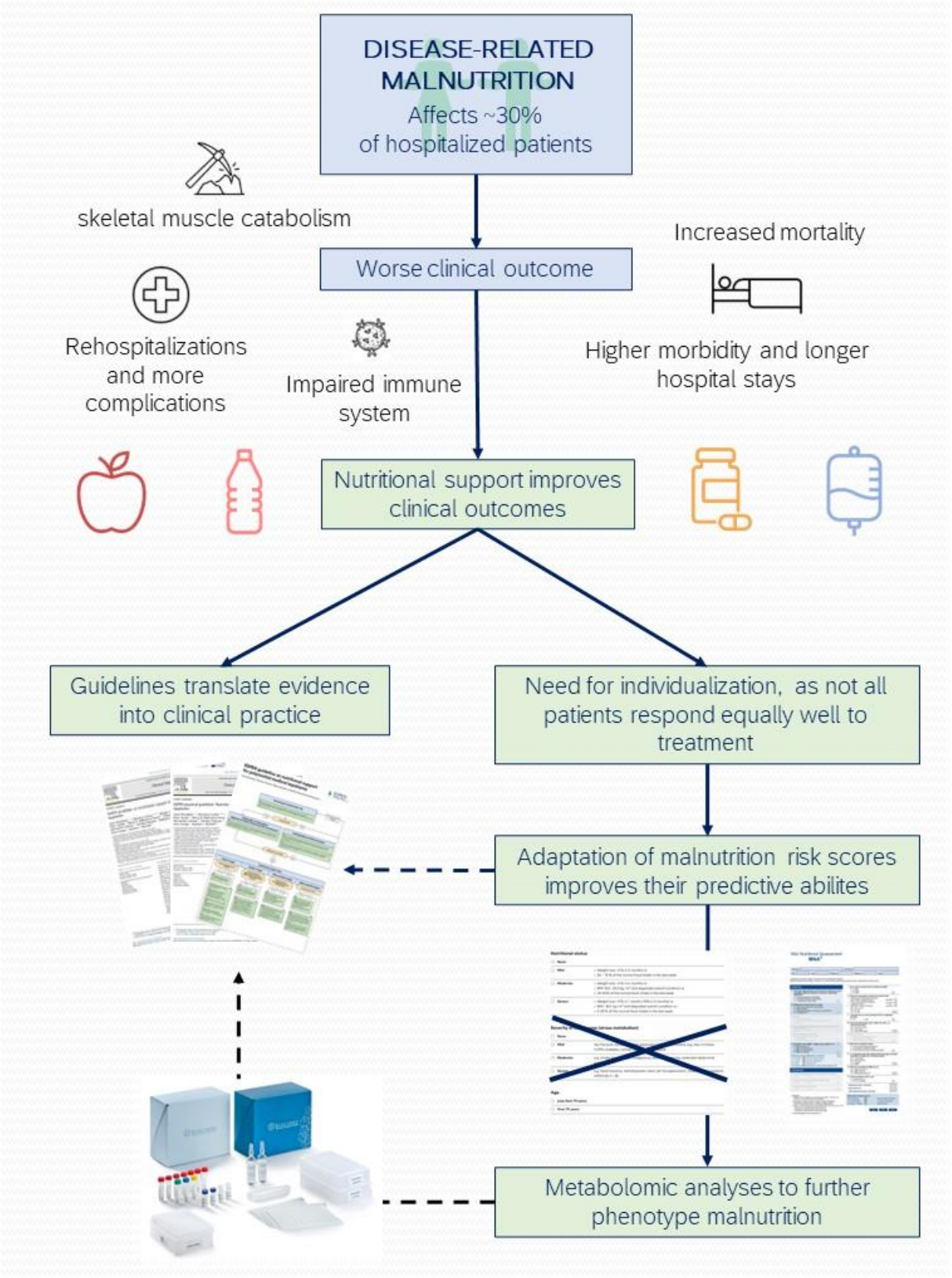
Background: Disease-related malnutrition in medical inpatients is highly prevalent and associated with significantly increased morbidity, disability, short- and long-term mortality, impaired recovery from illness, and cost of care. Nutritional support has been shown to be an effective treatment to reduce these risks. Yet, there is growing evidence suggesting that not all patients respond equally to nourishment and individualization to the patient's specific situation is needed. Addressing the heterogeneity in treatment responses and translating the findings into clinical practice through evidence-based recommendations are thus two major challenges for improving nutritional care in the future.

Methods: This work combines two different methodological approaches, including (a) updating the treatment guideline for nutritional support of polymorbid patients in collaboration with the European Society of Clinical Nutrition and Metabolism (ESPEN) based on a systematic review and meta-analysis process with development of recommendations regarding individualization of treatment, and (b) using clinical data from the randomized controlled Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT) to investigate the use of specific biomarkers and amino acids (i.e., arginine, glutamine and tryptophan) as well other parameters to improve the prediction of treatment response.

Results: In 2023, we updated the ESPEN guideline based on new evidence. It now comprises 32 instead of 22 recommendations covering several aspects of nutritional support including indication, route of feeding, energy and protein targets, micronutrient requirements, monitoring, and intervention procedures, as well as three new recommendations on individualization of nutritional therapy. In several analyses using the EFFORT trial data, we found that the metabolism of the amino acids arginine, glutamine and tryptophan provided prognostic information on the occurrence of adverse clinical outcomes but did not help to predict response to nutritional treatment. In an additional analysis, we found that adapting nutritional risk scores, by removing parameters reflecting disease severity, improved their predictive value for treatment response. Patients having high adapted scores showed a significant survival benefit from nutritional support, whereas this was not observed for patients having low adapted scores.

Conclusion: This work focuses on the individualization of nutritional care for medical inpatients through the elaboration of clinical guidelines and specific analysis of new parameters in a large treatment trial. This is an important step in translating new research findings on malnutrition phenotyping, underlying pathophysiology and treatment response into clinical practice and may help to improve treatment of patients in the near future.

1.1 Graphical abstract



1.2 Abstract German

Hintergrund: Krankheitsbedingte Mangelernährung bei stationären Patienten ist weit verbreitet und geht mit einer deutlich erhöhten Morbidität, kurz- und langfristigen Mortalität, einer beeinträchtigten Genesung und hohen Behandlungskosten einher. Es konnte gezeigt werden, dass die Ernährungstherapie eine wirksame Behandlung zur Verringerung dieser Risiken darstellt. Es gibt jedoch zunehmend Hinweise darauf, dass nicht alle Patienten gleichermaßen auf die Ernährungsintervention ansprechen und dass eine individuelle Anpassung an die spezifische Situation des Patienten erforderlich ist. Der Umgang mit der Heterogenität im Therapieansprechen und die Umsetzung der Erkenntnisse in die klinische Praxis durch evidenzbasierte Empfehlungen sind daher zwei wesentliche Herausforderungen für die Verbesserung der zukünftigen Ernährungsversorgung.

Methoden: In dieser Arbeit werden zwei verschiedene methodische Ansätze kombiniert: (a) die Aktualisierung der Behandlungsleitlinie zur Ernährungstherapie polymorbider Patienten in Zusammenarbeit mit der *European Society of Clinical Nutrition and Metabolism* (ESPEN) auf Grundlage einer systematischen Übersichtsarbeit und Metaanalyse mit der Entwicklung von Empfehlungen zur Individualisierung der Behandlung und (b) die Verwendung klinischer Daten aus der randomisierten kontrollierten Studie *Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial* (EFFORT), um die Verwendung spezifischer Biomarker und Aminosäuren (bspw. Arginin, Glutamin und Tryptophan) sowie anderer Parameter zu untersuchen, um die Vorhersage des Behandlungserfolgs zu verbessern.

Ergebnisse: Die aktualisierte Leitlinie enthält 32 anstatt 22 Empfehlungen, die verschiedene Aspekte der Ernährungstherapie abdecken, darunter Indikation, Art der Ernährung, Energie- und Proteinziele, Mikronährstoffbedarf, Überwachung und Interventionsverfahren, sowie drei neue Empfehlungen zur Individualisierung der Ernährungstherapie. In mehreren Analysen mit Daten der EFFORT-Studie stellten wir fest, dass die Metabolite des Aminosäurestoffwechsels von Arginin, Glutamin und Tryptophan zwar prognostische Informationen über das Auftreten negativer klinischer Outcome liefert, aber nicht zur Vorhersage des Ansprechens auf eine Ernährungstherapie beiträgt. In einer weiteren Analyse, die einen anderen Ansatz verfolgte, zeigte sich, dass ein umgerechneter Screening-Score für Mangelernährung, der keine Punkte für krankheitsspezifische Faktoren berücksichtigt, das Therapieansprechen besser vorhersagt. Patienten mit einem hohen umgerechneten Score hatten einen deutlichen Überlebensvorteil durch die Ernährungstherapie, während dies bei Patienten mit einem niedrigen angepassten Score nicht der Fall war.

Schlussfolgerung: Diese Arbeit konzentriert sich darauf, die Ernährungstherapie für stationäre, medizinische Patienten zu individualisieren, indem sie eine klinische Leitlinie aktualisiert und neue Parameter zu Individualisierung in einer großen Behandlungsstudie analysiert. Dies ist ein wichtiger Schritt um neue Forschungsergebnisse zur Phänotypisierung von Mangelernährung, ihrer zugrunde liegenden Pathophysiologie und dem Therapieansprechen in die klinische Praxis zu übertragen und kann somit zu einer zukünftig besseren Behandlung von Patienten beitragen.

2. Introduction

2.1 Malnutrition

2.1.1 Relevance, classification, pathogenesis

As stated by the World Health Organization, malnutrition encompasses deficiencies, excesses, or imbalances in an individual's consumption of energy or nutrients. This includes three categories of conditions: undernutrition, micronutrient-related malnutrition, overweight, and diet-related non-communicable diseases. [1] The European Society of Clinical Nutrition and Metabolism (ESPEN) defines malnutrition as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease". [2] However, there is no universally valid definition. Due to the demographic change and with advances in medical treatment, there is a rising number of patients who are older than 65 years and will have a complex combination of chronic diseases and comorbidities. [3] Particularly in this patient population disease-related malnutrition has become a matter of growing concern. In Europe, data reveals that up to a third of inpatients suffer from malnutrition or are at risk of malnutrition upon admission to the hospital. [4, 5] In addition, a patient's nutritional status often deteriorates during hospitalization due to illness-related loss of appetite, the necessary fasting for diagnostic studies, side-effects from medication, diseases affecting the normal function of the gut, inadequate inpatient nutrition management, and disease-related and disuse-related wasting. [6] Malnutrition, especially in the mostly elderly, chronically ill medical patients contributes to harmful metabolic consequences, such as catabolism and muscle wasting and poses a substantial burden on health, social, and aged-care systems. [3, 7] Additionally, there is a strong association between malnutrition and an increased risk of adverse clinical outcomes, including increased morbidity and mortality, functional decline, and prolonged hospitalization. [8, 9] These associations do not depend on the underlying medical condition and thus emphasize the need for appropriate nutritional support as part of holistic hospital care. [10]

Malnutrition may result from several factors: starvation, illness (e.g., polypharmacy, inflammatory mechanisms, and impaired absorption or assimilation of nutrients), immobility-induced muscle wasting, [11] and older age or social isolation. [12] The pathogenesis is complex and multifactorial. However, inflammation has been discovered as a main driver of malnutrition, influencing our metabolism in many ways. The systemic response to a stressor or disease [13] involves a variety of processes that are evolutionarily conserved [14] and

particularly affect the immune system, the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. [15-17] The activation of this cascade stimulates the release of stress hormones like catecholamines such as adrenalin and noradrenalin or cortisol, catecholamines. On the other hand, sex hormones, thyroid hormones and other peripheral hormones decrease. [15] The conversion of thyroxine (T4) to triiodothyronine (T3) through deiodination is decreased as part of an endocrine adaption. This observed drop in T3 levels is related to the severity of disease and could be seen as a metabolic mechanism to lower energy consumption and reduce catabolism. [18] Depending on the strength of the reaction, however generally, the entire neuroendocrine and inflammatory reaction together lead to the mobilization of energy stores. [13] Fatty acids are released from lipolysis, glucose is degraded from glycolysis, glycogenolysis and gluconeogenesis, and in the muscle amino acids are released from proteolysis. Muscle wasting is one of the serious consequences of depleting energy reserves and is exacerbated by excess cortisol, which impairs protein synthesis. [13, 19, 20] At the same time insulin-dependent glucose transporters in the peripheral tissue are downregulated thereby causing stress hyperglycemia [21]. Meanwhile pro-inflammatory cytokines such as interleukin 6 (IL-6), interleukin 1β (IL-1β) and tumor necrosis factor α (TNFα) are released, initiating various processes that contribute to the pathogenesis of malnutrition. For example, they have an anorectic effect on brain circuits, reduce appetite, delay gastric emptying, and have a catabolic effect on skeletal muscle, which leads to a loss of muscle mass. [6, 16, 22, 23]. The effects of the above-mentioned proinflammatory cytokines on skeletal muscle are mediated by numerous mechanisms, such as inhibition of muscle protein synthesis, activation of the ubiquitin-proteasome system and autophagy, two mechanisms involved in muscle breakdown and impairing myogenesis. [24]

2.1.2 Screening and diagnosing malnutrition

Defining or classifying malnutrition has historically been a challenge due to the lack of a true gold standard. However, in 2016, the Global Leadership Initiative on Malnutrition (GLIM) was launched by several of the major global clinical nutrition societies, bringing together global experts who agreed on a two-step approach to diagnosing malnutrition in 2019. [25] In a first step, nutritional screening is recommended to identify patients at risk of malnutrition with a validated tool. Today, several easy-to-use screening tools for assessing the malnutrition risk exist, which differ in terms of target group, validity, agreement, and reliability. [3, 26] Among these scores, the screening tool Nutritional Risk Screening (NRS) 2002 [27] and the assessment tool Mini Nutritional Assessment (MNA) [28] are widely used and quick to perform. Both were developed and validated on the basis of prospective studies that showed a prediction of the development of malnutrition or generally adverse clinical outcomes with the tools.

The second step is to apply more specific criteria. At least one phenotypic criterion (unintentional weight loss, low body mass index (BMI), and reduced muscle mass) and one etiologic criterion (reduced food intake or assimilation, and inflammation or disease burden) must be present to diagnose malnutrition. [6, 25] The GLIM criteria have been derived based on a strong pathophysiological rationale and their prognostic value is well documented in several studies. [29, 30] However, current definitions for malnutrition or risk for malnutrition conflate wasting due to disease and wasting due to starvation [25, 31], potentially limiting their ability to accurately predict the effectiveness of nutritional interventions.

2.2 Evidence-based treatment approach

2.2.1 Decision making in clinical practice

The concept of evidence-based decision making in clinical practice was raised in the 1970s and 1980s and at that time mainly related to medicine. Key players such as David Sackett, David Eddy, and Archie Cochrane emphasized the importance of strengthenin the empirical practice of medicine and proposed initial rules for guiding clinical decisions. [32] In 1991 the specific term of evidence-based medicine (EBM) was introduced with focus on helping clinicians to understand the results of clinical studies, and to determine how to apply the results to their everyday practice. [33] The concept was fundamentally criticized for suppressing clinical freedom. However, the concept has evolved and now comprises three main pillars in the process of decision-making: First, the clinical judgement of the patient's multidisciplinary care team, which summarizes the individual clinical expertise. Secondly, the relevant scientific evidence, which ranges from basic science and clinical trials to comprehensive meta-analyses and systematic reviews, and thus represents the best available external evidence. Good clinicians use both own clinical expertise and the best available external evidence, and both alone are not enough, because thirdly we need to incorporate patients' values and preferences into our decision for or against a particular treatment or intervention (**Figure 1**). [34, 35]

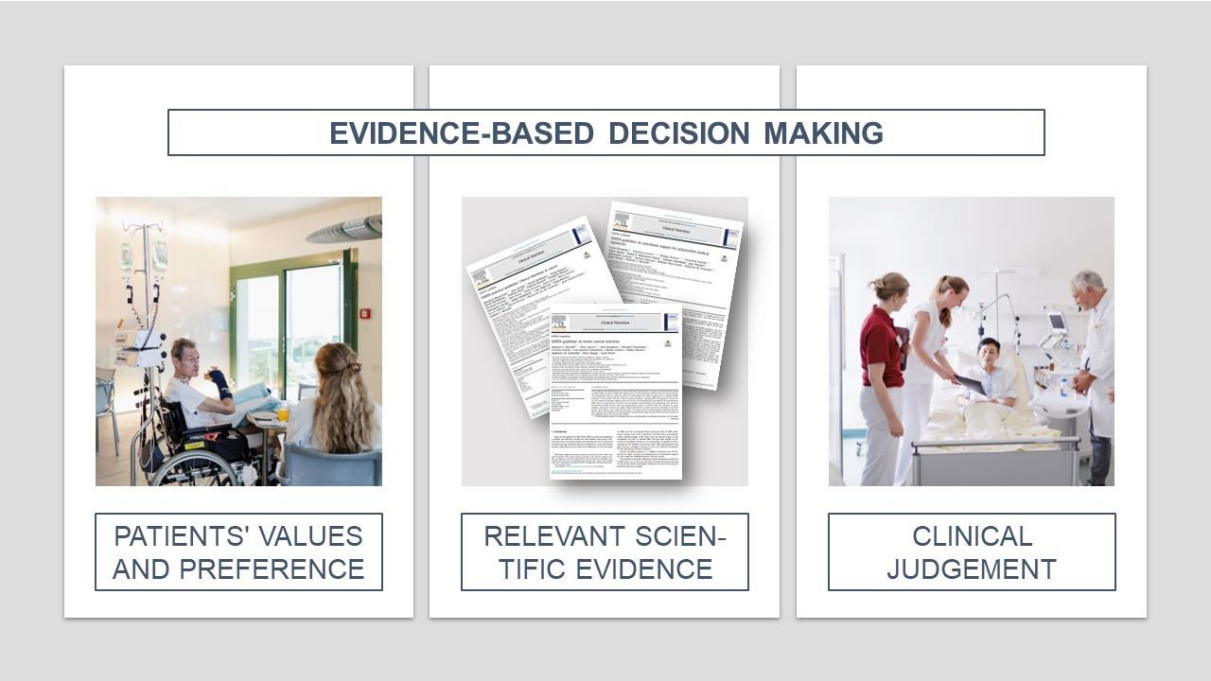


Figure 1: Pillars for evidence-based clinical decision-making. Own illustration; copyright photos: Philipp Schuetz

EBM has fundamentally changed the way we practice medicine today in many ways. Just as medical interventions adhere to EBM, decision making related to nutrition therapy should also align with these principles, since all three pillars overlap. [36] Access to well-conducted randomized controlled trials and meta-analyses is therefore a prerequisite to guide medical nutritional science towards evidence-based decision making. While certain goals may remain unmet, medical nutritional research has made important advances in the last years, particularly in medical ward patients. [37]

2.2.2 The role of clinical practice guidelines

In the 1980s a further advance has adopted, and researchers started to produce trustworthy clinical practice guidelines. [35] In the last thirty years, the number of indexed Medline publications has risen to more than 5,000 per month [38] and by 2023 the number of citations has exceeded one million. [39] This amount of data makes it difficult, if not impossible, for a clinician to integrate relevant information into their daily practice in such a way that patients can benefit from the wealth of new knowledge. [38] In Europe, for example, the survival rate for cancer patients varies greatly from country to country due to differences in treatment policies and accessibility of healthcare facilities. Such fluctuations cannot be explained solely by differences in disease or patient demographics, have been documented in almost all medical disciplines and depend primarily on the quality of treatment. [40] Therefore, the translation of research findings into clinical practice and their continuous use in health care

have led to major quality improvements. Clinical practice guidelines are among the most effective tools that have been developed to address this issue. [38]

The European Society for Clinical Nutrition and Metabolism (ESPEN) is an international Society that promotes the development of clinical nutrition guidelines since 1997. In the early days of clinical nutrition guidelines, the methodology and quality of these guidelines varied considerably. For this reason, ESPEN launched a new four-year guideline concept in 2010 which, in addition to separating enteral and parenteral nutrition, focuses on medical nutrition in general and takes a disease-specific approach. [41] Based on the previous work and experiences ESPEN has published a standard operating procedure (SOP) in 2015, in which they have defined a rigorous methodology to create or update a guideline. The key milestones are: Proposal submission, selection of a working group, creation of a list of topics/PICO questions, primary systematic literature search, assignment of level of evidence to literature, creation and grading of statements and recommendations, consensus process with first round of voting, revision of statements and recommendations, second round of voting, consensus conference, creation of evidence tables, and finalization of manuscript. [42] Due to the strict methodology described, clinical practice guidelines contain reliable and valid recommendations and represent a critical review of the current state of knowledge. They are used for decision-making not only in clinical practice but also in policy-making bodies and insurance companies or medical education. [38]

2.2.3 Single disease approaches and facing the challenge of a polymorbid patient population

As stated by Lefevre et al., "we know, for example, how to educate a diabetic patient, a chronic bronchitis patient, and a hypertensive patient, but we do not know, in practical terms, how to educate a patient with all three diseases". [43] Initially, it was uncertain whether the screening, assessment, and treatment of disease-related malnutrition in polymorbid medical inpatients should differ from those with a single disease, as the studies were mainly conducted in a narrowly defined homogeneous patient population. Yet, the large randomized controlled trials (RCTs) of the last decade have provided important new evidence showing that nutritional support can indeed reduce mortality and other complications in polymorbid patients. [44, 45]

Although there is no universally accepted definition of polymorbidity or the synonym multimorbidity, there are authors that define it as being the co-occurrence of at least two chronic health conditions in the same person. [43, 46, 47] The impacts of several diseases on health and nutrition differ from the corresponding interactions between disease and ageing. Polymorbidity is highly prevalent, affecting more than 70% of the hospitalized adult population,

and is associated with higher mortality and healthcare burden. [48] Other consequences of polymorbidity include disability, functional decline, poor quality of life (QoL) as well as higher healthcare costs. [47] Surprisingly, more than half of those affected are under 65 years old, although prevalence rises with age. [49] The current approach, focusing on individual diseases in clinical guidelines, neglects polymorbidity. [49] Fried et al. showed that clinicians struggle with applying disease-specific guidelines to their patients with multiple conditions and would therefore benefit from tools to assist them in decision making for this population. [50] In the current nutritional guidelines, which focus on individual diseases (e.g. nutritional support for patients with cancer) or patient groups (e.g. older adults), polymorbidity is only given limited consideration, if any at all. To date, it is unknown whether there is a synergistic negative effect of several diseases on nutritional status, or on clinical outcome. When considering polymorbidity, polypharmacy must also be taken into account, since polymorbid patients require multiple medications to manage their diseases and comorbidities. This is undoubtedly an essential pillar of their treatment, but carries a high risk of potential drug-drug and drug-nutrient interactions and the possible effects on nutritional status. [51] Polypharmacy is associated with an increased risk of malnutrition [52] and sarcopenia [53] most commonly due to adverse drug effects [54, 55], making this population particularly vulnerable to nutritional impairment. The effects of drugs on our metabolism are complex and include loss of appetite, nausea, diarrhea, weight changes, taste alterations, decrease or increase in saliva secretion, modifications in lipid profile, alterations in electrolyte balance, and changes in glucose metabolism. [56] Therefore, there is a need to create evidence-based consensus on how to provide nutritional support for the polymorbid medical inpatient population.

2.3 The importance of individualization and addressing heterogeneity in the response to nutritional therapy

2.3.1 Malnutrition as a partly modifiable risk factor – nutritional support influences clinical outcomes

Malnutrition is a well-established risk factor for adverse clinical courses and mortality. [8, 10] However, next to data from observational studies, several randomized controlled trials in the last decade have provided evidence that nutrition interventions reduce these risks significantly. [37, 45] Particularly, the field of nutrition care for medical inpatients has raised significantly in recent years. In the past, insufficient trial data on the best approach to treating malnutrition meant that clinicians often paid little attention to the problem of malnutrition. [36] However recently, several trials studying the role of nutrition support in the medical inpatient have changed our understanding. A 2019 systematic review and meta-analysis of 27 study including

6,803 patients, reported that nutrition support provided during hospitalization is associated with a 25 percent reduction in both mortality and non-elective hospital readmissions. [37] Interestingly, the subgroup of trials using a high protein intervention and were providing therapy in the long-term showed best results in terms of mortality reduction, suggesting that these are key elements of nutrition care. [57] Consistent with this finding, a large placebo-controlled, clinical trial by Deutz et. al in 2016 demonstrated that the use of a high-protein oral nutritional supplement (ONS) was able to improve survival in medical patients hospitalized for congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease. In particular, the nutritional intervention significantly lowered 90-day mortality with a relative risk reduction of 50 percent. [45]

2.3.2 Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial [58]

The largest RCT so far in medical patients that also demonstrated a survival benefit of nutritional support was the Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT) trial. The study was conducted in eight Swiss hospitals between April 2014 and February 2018. The Ethics Committee of Northwest and Central Switzerland approved the study protocol in January 2014 (registration ID 2014_001). The trial was registered at ClinicalTrial.gov (NCT02517476) in August 2015. Adult inpatients (≥18 years of age) at nutritional risk (NRS total score ≥ 3 points) and with an expected hospital stay of >4 days who were willing to sign an informed consent form participated in the EFFORT study. Exclusion criteria were an initial hospitalization in intensive care units or surgical wards; unable to ingest oral nutrition; already receiving nutritional support at admission; with a terminal condition; admitted to hospital because of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, or stem-cell transplantation; after gastric bypass surgery; with contraindications for nutritional support; and previously included in the trial. Treatment of intervention group patients was initiated within 48h after hospitalization based on a previous published consensus protocol and in accordance with international guidelines [59, 60] to reach energy and protein goals. A trained registered dietitian defined an individual nutrition plan for each patient with calculated energy and protein targets. For energy requirements the Harris-Benedict equation [61] was used and protein goals were set at 1.2-1.5 g/kg body weight per day, except in patients with kidney failure, where it was 0.8 g/kg body weight per day. [62] The nutrition plan was initially based on oral nutrition provided by the hospital kitchen and oral nutrition supplements. An escalation to enteral tube feeding or parenteral feeding was recommended if at least 75% of the protein and energy targets could not be reached within 5 days through oral feeding. A reassessment was done every 24-48

hours. Patients in the control group obtained usual hospital food without nutritional consultation or supplementation (appetite guided approach). The primary composite endpoint of the trial was severe complications, mortality, admission to the intensive care unit, cardiovascular and gastrointestinal complications, functional decline, and hospital readmissions.

In this trial, nutritional support resulted in a significantly higher intake of energy, protein, and micronutrients from day one. In addition to this finding, the authors found nutrition support to be highly effective in reducing the risk of 30-day all-cause mortality (adjusted odds ratio (OR) 0·65 [0·47–0·91], p=0·011), with a number needed to treat (NNT) of 37, which reflects that one death can be prevented in 37 patients treated with nutritional support. For adverse events there was an almost 30 percent risk reduction, resulting in an adjusted odds ratio [OR] 0·79 [95% CI 0·64–0·97], p=0·023. No specific adverse side effects of the intervention were observed in this study. [58] In addition, the nutritional intervention proved to be cost-effective in the calculations in a Markov model. [63] These results strongly support the concept of systematically screening medical inpatients on admission to hospital for nutritional risk, irrespective of any underlying conditions, followed by a nutritional assessment and introduction of individualized nutritional support in at risk patients.

2.3.3 Heterogeneity in the response to nutritional support

Despite the broad evidence for the beneficial effects of nutritional support in medical inpatients, there are certainly differences in the response to a nutritional intervention in patients with a variety of clinical conditions, such as high inflammation or severely ill patient population. A Cochrane review with a heterogenic patient population from 2017, also including acutely ill patients from the intensive care unit (ICU) or surgical patients, found only little positive effects of nutritional treatment on clinical outcomes [64]. On this topic, Casaer et al. published a review on nutrition in the acute phase of critical illness in the New England Journal of Medicine in 2014, in which they compared the latest large, adequately powered trials conducted on critically ill patients. Although several nutritional interventions with different approaches led to an increase in energy, protein (and micronutrients) intake, none of them could demonstrate a beneficial effect on mortality or other relevant clinical outcomes. The authors concluded that there is no clear evidence that feeding protocols targeting full-replacement nutrition early in the course of critical illness result in clinical benefits. [65] This is a common phenomenon that is also observed in advanced cancer cachexia. [66] Nevertheless, even in the acute but less severely ill patient population on the medical ward, there are subgroups that do not benefit from nutritional support. Indeed, the response to nutritional therapy depends among other factors on the inflammatory status. As an acute-phase protein, c-reactive protein (CRP) is one of the most popular biomarkers for inflammation. The production and release of acute-phase

proteins in the liver is induced by pro-inflammatory cytokines after a certain stressor. [67] CRP levels of >100 mg/l, indicating high inflammation, have been shown to be associated with lower treatment response in malnourished medical inpatients, not showing significantly positive effects of nutritional therapy in EFFORT on mortality. Meanwhile 30-day mortality in patients with low and moderate CRP levels below 100 mg/l was significantly reduced by individualized nutritional support [68]. A comparison of CRP values in the subgroup of cancer patients also showed that patients with a CRP value of >100 mg/l did not respond to treatment, indicating that inflammation is also an important factor for response in a fulminant disease such as cancer. [69] These results are in line with former trials, e.g. the one by Gariballa and Forster, in which severity of acute-phase response had significant negative effects on nutritional status and clinical outcome. [70]

2.3.4 Predictive biomarkers and the path to personalized nutrition

Next to inflammation, there has been research on other biomarkers to predict the response to nutritional interventions. The stress response cytokine growth-differentiation factor-15 (GDF15) [71] is a potential promising biomarker, which elevates during aging and acute illness [72] and leads to illness-induced anorexia, emesis and an aversive reaction to food. [73] A recent secondary analysis of the ICU trial Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) [74] investigated the potential of low GDF15 to identify patients who benefit from early parenteral nutrition, who tolerate enteral nutrition, and who resume spontaneous oral intake in critically ill patients. While high GDF15 was strongly associated with severity of illness and poor prognosis, GDF15 could not identify patients who may benefit from or be harmed by early parenteral nutrition (PN), and the association with enteral feeding (in)tolerance was weak. [71] However, GDF15 is still elevated during recovery and convalescence after acute illness compared to aged-matched controls and associated with poorer outcome. [72] This might indicate that it can also be useful to investigate the prognostic value of GDF15 not only in critical care but also in recovery period or even in acute illness without previous ICU stay to predict response to nutrition support.

Further secondary analysis of the EFFORT trial showed that there are other biomarkers besides that identify patients who benefit from nutritional support, while others have failed to do so. For example, a worsening kidney function was found to be associated with a higher benefit from nutritional therapy. [75] In addition, another functional parameter that predicts treatment response and may help to personalize nutrition therapy is handgrip strength (HGS). In fact, HGS has been proposed as an easy-to-use, noninvasive, objective, and inexpensive tool to detect and monitor changes in nutritional status and to predict functional decline during hospitalization and post-discharge. [76-78] While the prognostic value of HGS has been

demonstrated in several studies, a new study also showed that an individualized nutritional support is most effective in reducing mortality in patients with very low HGS (i.e., ≤8 kg for females and ≤16 kg for males). [79] HGS may thus help to select patients for a more intensive feeding intervention. An ability that does not apply to patients diagnosed with sarcopenia on CT scans, as sarcopenia was associated with a poorer prognosis but not with a greater benefit from nutritional support. [80]

Yet, there are other markers that have not proven to enhance the identification of patients most likely benefiting from treatment. Historically, circulating albumin levels on hospital admission have been considered useful biochemical markers for the nutrition assessment, because albumin levels are also influenced by nutritional intake. However, there is increasing evidence that the influence of nutritional factor in an acute phase of disease is small. In fact, a recent study suggested that low admission albumin in hospitalized patients at nutritional risk have prognostic implications and indicate higher mortality risk but are not helpful in selecting patients regarding nutritional treatment interventions. [81] These results are in line with a consensus paper and a meta-analysis concluding that albumin levels should be used in the evaluation of severity of disease but not to assess nutritional status or diagnose malnutrition. [82-84] This may be explained by albumin serum concentrations being affected by a variety of non-nutritional factors, mostly reflecting acute disease or inflammation but not available plasma proteins or nutritional status in an acute disease or exacerbation. [85] The visceral protein albumin is a negative acute-phase protein and albumin levels are inversely correlated to CRP levels. [84] Normalization of albumin levels may therefore not depend on nutritional treatment, protein intake or albumin treatment, but rather on the resolution of inflammation. [86]

In addition, yet there are no convincing data demonstrating that the addition of genomics, transcriptomics, proteomic or metabolomic data would improve the phenotyping of patients regarding malnutrition and response to treatment. [87] Gut microbiota or nutrigenetics are other tools that could possibly be used to advance the concept of personalized nutrition. But again, there is lack of studies proofing their benefit for the management of patients.

It is worth noting that there is a wide range of possible biomarkers that have been studied to assess malnutrition. In addition to common serum visceral proteins like albumin or prealbumin, also transferrin or retinol-binding protein have been considered. Other laboratory markers that are associated with malnutrition are urinary creatinine, urinary 3-methylhistidine, serum cholesterol, blood lymphocyte count, serum insulin-like growth factor-1 (IGF1), serum leptin and many more. Also, several proteomic und metabolomic markers have been studied. [87, 88] Due to their association with malnutrition these different markers may be considered potential candidates for predicting response to nutritional treatment, but it is important to consider individual limitations of each marker. [89]

It seems clear, that in order to improve nutritional care of patients, the question is not only whether nutritional support is effective in reducing risks and negative consequences associated with malnutrition, but also the mechanisms underlying these effects and whether we can identify parameters to better tailor nutritional support to the specific needs of patients. Using biomarkers to stratify patients according to their malnutrition phenotype and their treatment response will be key to advance the concept of traditional treatment to individualized and personalized treatment.

3. Articles

3.1.1 Letter to the editor: Is nutritional support effective in malnourished polymorbid medical inpatients? [90]

Author contributions:

CW, Carla Wunderle (born Gressies); PS, Philipp Schuetz, NKB, Nina Kaegi-Braun, FG, Filomena Gomes

CW and PS designed the research. CW conducted the research and analyzed data/performed statistical analysis. CW wrote the paper. PS, CW, NKB, and FG had primary responsibility for final content. PS was responsible for resources, supervision, and funding acquisition. All authors read and approved the final version of the manuscript.

Clinical Nutrition 42 (2023) 45–52

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Letter to the Editor

Letter to the Editor: Is nutritional support effective in malnourished polymorbid medical inpatients?

Keywords:
Nutritional support
Polymorbid patients
Inhospital

Dear Editor,

There is now growing evidence demonstrating that nutritional support is effective in lowering mortality and other adverse clinical outcomes in medical inpatients [1–3]. However, studies have been heterogenous in regard to the specific patient population and it has remained somewhat unclear whether these results are also true for the subgroup of polymorbid patients – a particularly vulnerable population that causes high healthcare costs [4]. As a result, evidence on nutritional support in recent guideline recommendations for this specific population has been limited due to lack of large-scale trials and meta-analyses from such trials [5]. We are now in the process of reevaluating and updating these guidelines and thus conducted a reanalysis and update of the recent meta-analysis on nutritional support of medical inpatients, with a focus on the polymorbid patient population. Thus, from the Kaegi-Braun 2021 [2] meta-analysis, we identified the included studies that were conducted in polymorbid medical populations, and we additionally performed a search update in October 2022 using the previous methodology and search strategy to identify additional eligible papers published since 2021 and 2022 [2,3]. We used the same definition for polymorbidity as specified in the ESPEN guidelines on nutritional support for polymorbid patients [5]. Overall, we found 16 randomized trials investigating nutritional support in the population of malnourished polymorbid medical inpatients (see Appendix for details on the methodology and additional results). When compared to patients not receiving nutritional support (control group), nutritional intervention (mostly oral and enteral nutrition) was associated with a significant reduction in mortality (8.7% (209 of 2395) compared to 12.0% (288 of 2400), OR 0.68 (95%CI 0.51 to 0.91, p = 0.009) with moderate heterogeneity I^2 = 37% (Fig. 1). We also found significant beneficial effects in other outcomes particularly a reduction in the risk of unplanned hospital readmission (OR of 0.64 (95% CI 0.45 to 0.90, p = 0.01) with substantial heterogeneity I^2 = 65% (Fig. 2), but also improvements in several nutritional outcomes including a higher energy and protein intake and an increase in body weight (Appendix).

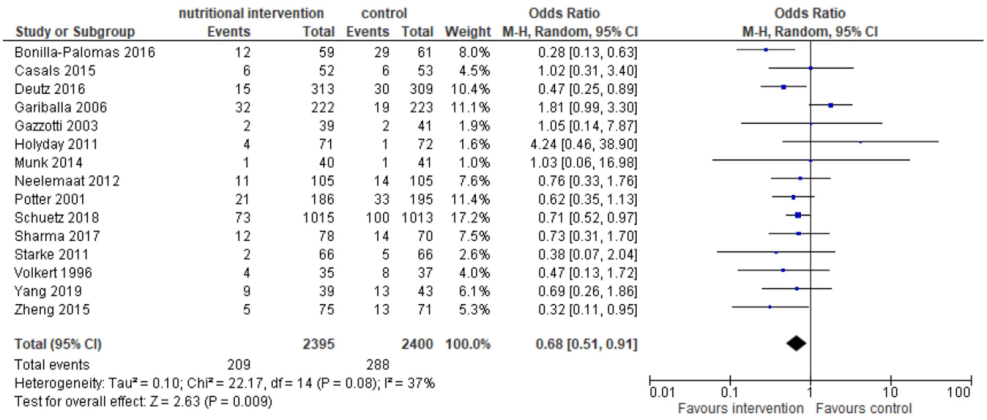


Fig. 1. Forest plot comparing nutritional intervention versus control for mortality in polymorbid medical inpatients. A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95%CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95%CIs. OR indicates odds ratio.

https://doi.org/10.1016/j.clnu.2022.11.007

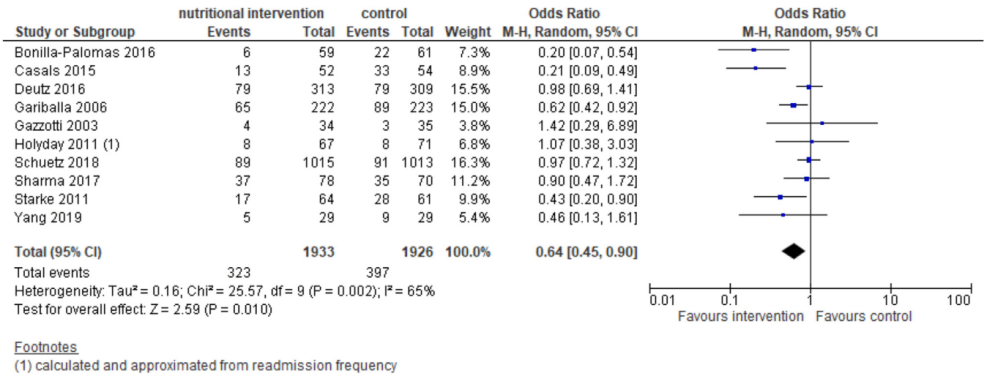


Fig. 2. Forest plot comparing nutritional intervention versus control for non-elective hospital readmissions in polymorbid medical inpatients. A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95%CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95%CIs. OR indicates odds ratio.

Despite the fact that the medical population of mainly elderly polymorbid patients with complex combinations of diagnoses has an increased risk for mortality, morbidity and causes the majority of health care cost, they are the least studied [4]. Herein our reanalysis and update of an existing meta-analysis demonstrates that nutritional support is an effective way to improve survival and lower hospital readmission rates of malnourished polymorbid medical inpatients, which likely contributes to lower healthcare costs. This analysis should be considered during the planned update of the ESPEN guidelines for polymorbid patients.

Funding

This study was supported in part by the Swiss National Science Foundation, Switzerland (SNSF Professorship, PP00P3_150531/1) and the Research Council of the Kantonsspital Aarau, Switzerland (1410.000.044).

Conflict of interest

PS is supported by grants of the Swiss National Science Foundation, Switzerland (SNSF Professorship, PP00P3_150531) and the Research Committee of the Kantonsspital Aarau, Switzerland (1410.000.058 and 1410.000.044). Dr P Schuetz's institution has previously received unrestricted grant money from Nestle Health Science and Abbott Nutrition. All other authors report no conflicts of interest within the last 36 months.

Appendix

Definition of polymorbidity used in this analysis

Polymorbid inpatients population as defined by

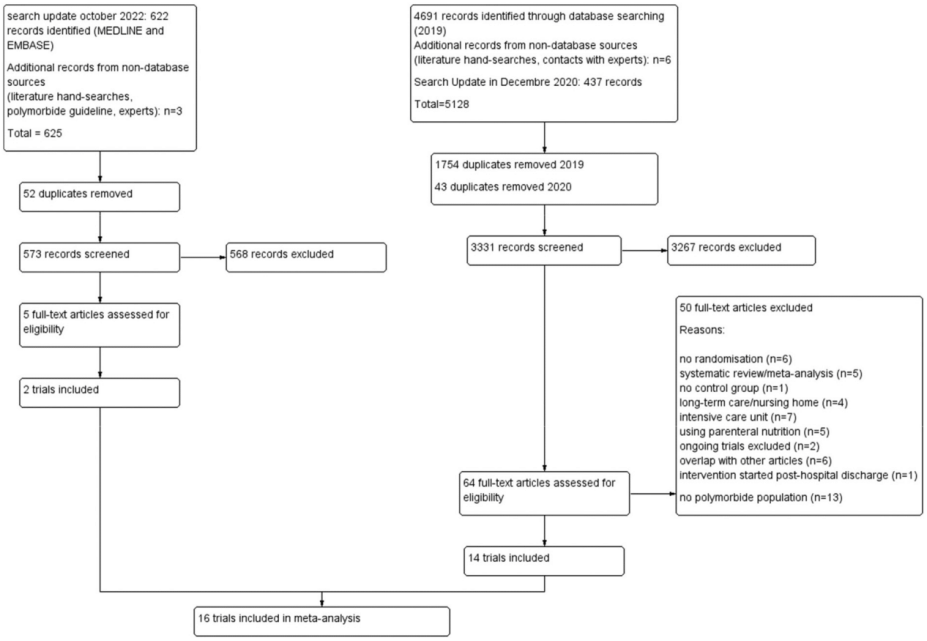
a) at least 2 co-occurring chronic diseases are present in at least 50% of the study population or
b) mean number of diseases or drugs/medication or the Charlson comorbidity index in the study population as being more than 1.5

In case of uncertainties about the way comorbidities are reported, the trials' authors were contacted in order to get more information; if contact is not possible, the working group made a consensus decision about the inclusion/exclusion of the studies [1].

Search strategy used in Medline

1. exp *PROTEIN-ENERGY MALNUTRITION/or malnutrition.mp. or exp *MALNUTRITION/
2. maln*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. undern*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. 1 or 2 or 3
5. exp *Nutrition Therapy/or exp *Enteral Nutrition/or nutritional therapy.mp.
6. exp *Nutritional Support/or nutrition support.mp.
7. (nutrition* adj3 (support or therapy)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. dietary advice.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. food fortification.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. oral nutrition* supplement*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

11. (enteral adj1 (nutrition or feeding)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. hospital.mp. or exp *Hospitals/
14. hospital*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. ward*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. in?patient*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. 13 or 14 or 15 or 16
18. 4 and 12 and 17
19. limit 18 to yr = "2021–2022"



eFig. 1. Study Flow Chart

eTable 1
Overview of the characteristics of the included trials

Source	Sample size (n)	Patient population	Type of intervention	Proof of polymorbidity	Type of control	Endpoints crucial for the analysis
Bonilla-Palomas et al. [6], 2016 Spain	120	>18 y, acute heart failure and malnutrition (MNA score)	Food optimization, specific recommendations, and nutritional supplement prescriptions (± ONS)	Charlson Comorbidity Index (CCI) > 3.8	Usual hospital food	Mortality, readmissions
Casals et al. [7], 2015 Spain	106	>18 y, hospitalization, medium or high risk of malnutrition on the MUST scale	Nutritional counselling	Agreement with ESPEN working group	Usual care	Mortality, readmission, LOS, barthel index, weight change
Deutz et al. [8], 2016 Matheson et al. [9], 2021 USA	652	≥65 y, recent hospital admission, primary diagnosis of CHF, AMI, pneumonia, or COPD, SGA class B or C	474 ml/d ONS (700 kcal/d, 40 g protein/d, 3 g calcium-beta-hydroxybeta-methylbutyrate/d, 160 IU vitamin D_3/d, and other essential micronutrients), for 90 days	CCI > 2	474 ml/d placebo ONS (96 kcal/d)	Mortality, readmission, LOS, handgrip strength
Feldblum et al. [10], 2010 Israel	259	≥65 y, MNA score <10, weight loss of more than	Individual nutritional treatment using ONS, glucose polysaccharides for	CCI > 2	Usual hospital food or dietary advice once during hospitalization	Mortality

(*continued on next page*)

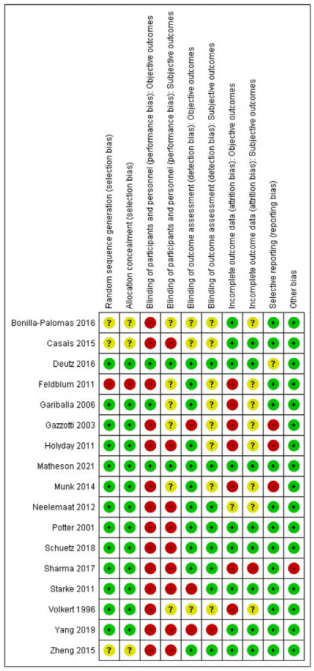
eTable 1 (*continued*)

Source	Sample size (n)	Patient population	Type of intervention	Proof of polymorbidity	Type of control	Endpoints crucial for the analysis
		10% during the 6 months prior the study period	caloric fortification and, vitamin and mineral supplements if intake of micronutrients was <75% DRI			
Gariballa et al. [11], 2006 UK	445	>65 y, medical and selected (non-gastric) surgical patients, BMI <40 kg/m^2, able to swallow, able to sign an IC (abbreviated mental test >6)	400 ml/d ONS (995 kcal/d, 100% DRI for vitamins) in addition to the standard hospital diet for 6weeks	Chronic illnesses >1.5/ Patient, drug intake 3.5/ Patient	Placebo	Mortality, function, infections, readmissions, LOS
Gazzotti et al. [12]; 2003 Belgium	80	>75 y, admitted for acute conditions, MNA score 17 –23.5	400 ml/d sweet or salty sip feed (500 kcal/d, 21 g protein/d) throughout hospitalization and convalescence	Number of drug intake >5/patient	Usual hospital food	Mortality, readmissions, LOS
Holyday et al. [13], 2012 Australia	143	All admitted patients were considered for the study, exclusion criteria: expected LOS <72h, palliative patients, patients who were unable to be nutritionally assessed and patients already seen by a dietitian during the admission	Individualized modification of hospital food (texture modification and fortification), prescription of nutrition supplements, assistance with meals, education	CCI > 5	Malnutrition care plan only if referred by clinical staff (usual hospital food)	Mortality, readmissions, LOS
Munk et al. [14], 2014 Denmark	84	≥18 y, oncology, orthopedics, and urology wards, nutritional risk, able to eat orally, an anticipated LOS of ≥3 days, sufficient language skills	Protein-supplemented food service concept	Agreement with ESPEN working group	Usual hospital food	Mortality, LOS
Neelemaat et al. [15], 2012 Netherlands	210	≥60 y, malnourished, admitted to an acute hospital	Energy- and protein-enriched diet (extra 750 kcal/d, 30 g protein/d), 2 ONS/d (600 kcal/d, 24 g protein/d), 400 IU Vit D3/d, 500 mg calcium, telephone counseling by a dietitian	Polymorbidity confirmed by author	Usual hospital food	Mortality, LOS
Potter et al. [16], 2001Scotland	381	>60 y, medicine for the elderly unit, BMI <75th percentile	360 ml/d ONS (540 kcal/d, 22.5 g protein/d)	Agreement with ESPEN working group	Usual hospital food	Mortality, LOS
Schuetz et al. [17], 2019 Switzerland	2088	Medical inpatients, NRS score ≥3	Protocol-guided individualized nutritional support to reach protein (1.2–1.5 g/kg/d and caloric goals (according to the weight-adjusted Harris-Benedict equation)	Polymorbidity confirmed by author	Usual hospital food	Mortality, function, infections, readmissions, LOS
Sharma et al. [18], 2017 Australia	148	>60 y, PG-SGA class B or C (PG-SGA: Patient Generated-SGA)	Individualized nutrition care plan plus monthly post-discharge telehealth follow-up	CCI > 2	Usual hospital food	Mortality, readmissions, LOS
Starke et al. [19], 2011 Switzerland	132	NRS score ≥3, general medical patients	Individual nutritional care, including a detailed nutritional assessment, individual food supply, fortification of meals and ONS, all according to the individual TEE and to reach protein 1.0 g/kg/d	Number of drug intake >6/patient	Usual hospital food	Mortality, infections, readmissions, LOS
Volkert et al. [20], 1996 Germany	72	≥75 y, undernourished	400 ml/d ONS (500 kcal/d), 200 ml/d ONS (250 kcal/d) for 6 months after discharge	Multiple diagnoses shown in publication	Usual hospital food	Mortality, function
Yang et al. [21], 2019 Taiwan	82	>65y, pneumonia, BMI <18.5k g/m^2 or MNA-SF score ≤7 (MNA-SF: MNA-Short Form)	Individualized nutritional intervention program	Multiple diagnoses and comorbidities shown in publication	Usual hospital food	Mortality, readmissions, LOS
Zheng et al. [22], 2015 China	146	Cerebral infarction, intracranial hemorrhage or both, focal neurological signs and dysphagia	Nasogastric nutrition	>2 co-occurring chronic diseases in >50% of study population	Family managed nutrition	Mortality, Infections

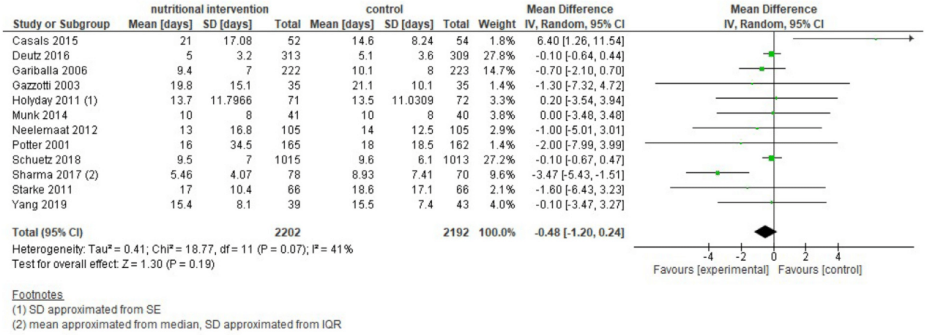
Mini Nutritional Assessment (MNA); Charlson Comorbidity Index (CCI); Length of stay (LOS); Malnutrition Universal Screening Tool (MUST); European Society for Clinical Nutrition and Metabolism (ESPEN); Oral Nutrition Supplements (ONS); Body Mass Index (BMI); Subjective Global Assessment (SGA); Nutrition Risk Screening (NRS); daily recommended intake (DRI).

eTable 2
Selected outcomes

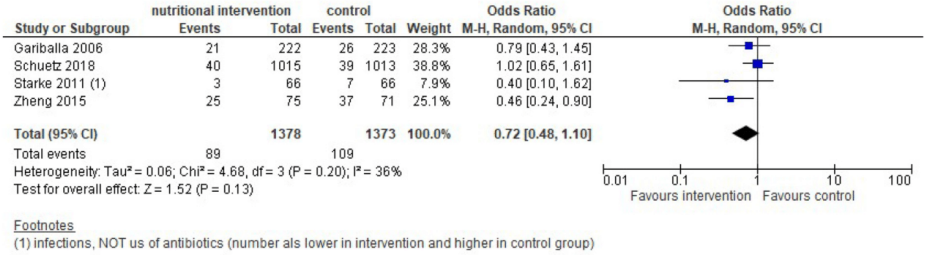
	Mortality	Infections	Non-elective readmissions	Length of hospital stay (days)
	OR (95%CI)	OR (95%CI)	RR (95%CI)	Mean difference (95%CI)
Intervention, events/total (%) or mean (No)	209/2395 (8.7)	89/1378 (6.5)	323/1933 (16.7)	12.9 (2202)
Control, events/total, (%) or mean (No)	288/2400 (12.0)	109/1373 (7.9)	397/1926 (20.6)	13.2 (2192)
Overall estimate	0.68 (0.51, 0.91)	0.72 (0.48, 1.10)	0.64 (0.45, 0.90)	−0.48 (−1.20, 0.24)
Heterogeneity, test for overall effect	*I2 = 37%, p = 0.009*	*I2 = 36% p = 0.13*	*I2 = 65%, p = 0.01*	*I2 = 41%, p = 0.19*



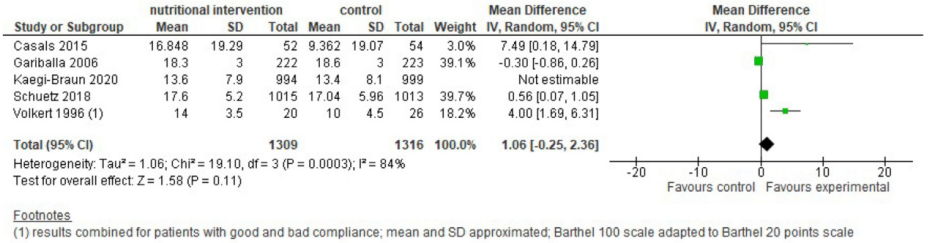
eFigs. 2 and 3. The risk of bias assessment.



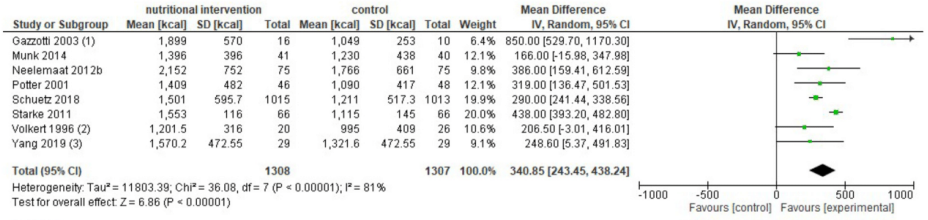
eFig. 4. Length of stay.



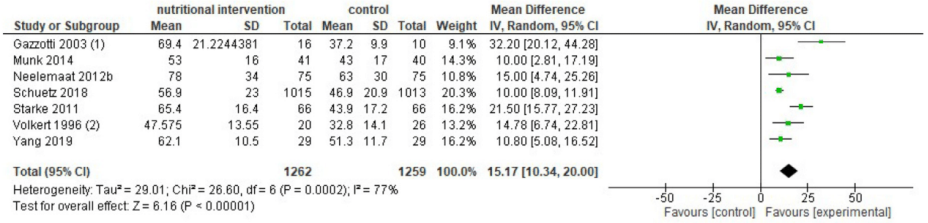
eFig. 5. Infections.



eFig. 6. Barthel index.

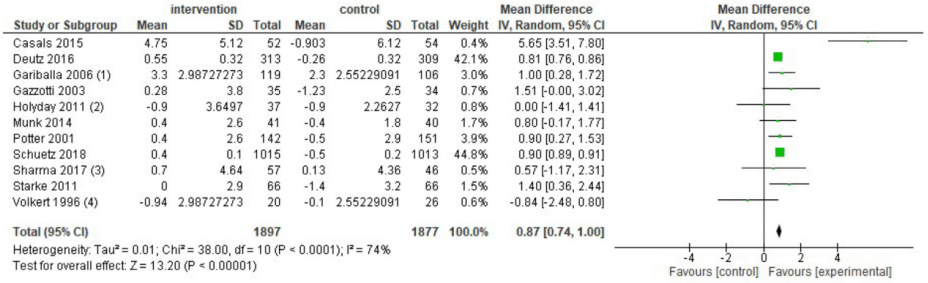


eFig. 7. Caloric intake.



Footnotes
(1) SD intervention group combined spontaneous intake and supplement intake
(2) intervention: groups combined (good and bad supplement acceptance)

eFig. 8. Protein intake.



Footnotes
(1) calculated from baseline-weight and weight at follow up, SD approximated from SD other publications
(2) SD approximated from SE
(3) SD approximated from 95% CI
(4) SD approximated from SD other publications

eFig. 9. Weight change.

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4 November 2022

3.1.2 ESPEN guideline on nutritional support for polymorbid medical inpatients [91]

Author contributions:

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CW, FG, SB and PS designed the research. CW conducted the systematic literature search. CW and FS screened abstracts for eligibility and assessed bias assessment. All authors wrote the commentary for one question and rated the corresponding level of evidence. PS, CW, FG, and SB had primary responsibility for final content, including introduction and discussion. PS and SB were responsible for resources, supervision, and funding acquisition. All authors read and approved the final version of the manuscript.

Clinical Nutrition 42 (2023) 1545–1568

Contents lists available at ScienceDirect

Clinical Nutrition

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ESPEN Guideline

ESPEN guideline on nutritional support for polymorbid medical inpatients

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ARTICLE INFO

Article history:
Received 16 June 2023
Accepted 20 June 2023

Keywords:
Guideline
Polymorbidity
Multimorbidity
Nutritional support
Hospitalized patients

SUMMARY

Background: Disease-related malnutrition in polymorbid medical inpatients is a highly prevalent syndrome associated with significantly increased morbidity, disability, short- and long-term mortality, impaired recovery from illness, and cost of care.
Aim: As there are uncertainties in applying disease-specific guidelines to patients with multiple conditions, our aim was to provide evidence-based recommendations on nutritional support for the polymorbid patient population hospitalized in medical wards.
Methods: This update adheres to the standard operating procedures for ESPEN guidelines. We did a systematic literature search for 15 clinical questions in three different databases (Medline, Embase and the Cochrane Library), as well as in secondary sources (e.g. published guidelines), until July 12th. Retrieved abstracts were screened to identify relevant studies that were used to develop recommendations (incl. SIGN grading), which was followed by submission to Delphi voting.
Results: From a total of 3527 retrieved abstracts, 60 new relevant studies were analyzed and used to generate a guideline draft that proposed 32 recommendations (7x A, 11x B, 10x O and 4x GPP), which encompass different aspects of nutritional support including indication, route of feeding, energy and protein requirements, micronutrient requirements, disease-specific nutrients, timing, monitoring and procedure of intervention. The results of the first online voting showed a strong consensus (agreement of >90%) on 100% of the recommendations. Therefore, no final consensus conference was needed.
Conclusions: Recent high-quality trials have provided increasing evidence that nutritional support can reduce morbidity and other complications associated with malnutrition in polymorbid patients. The timely screening of patients for risk of malnutrition at hospital admission followed by individualized nutritional support interventions for at-risk patients should be part of routine clinical care and

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https://doi.org/10.1016/j.clnu.2023.06.023

multimodal treatment in hospitals worldwide. Use of this updated guideline offers an evidence-based nutritional approach to the polymorbid medical inpatients and may improve their outcomes.

Abbreviations

BI	Barthel Index
βHMB	β-hydroxy β-methylbutyrate
CG	Control Group
DRM	Disease-Related Malnutrition
EN	Enteral Nutrition
GLIM	Global Leadership Initiative on Malnutrition
HGS	Handgrip strength
IC	Indirect Calorimetry
IG	Intervention Group
LOS	Length Of hospital Stay
MNA(-SF)	Mini Nutritional Assessment (short form)
MUST	Malnutrition Universal Screening Tool
NRS 2002	Nutritional Risk Screening 2002
NST	Nutrition Support Team
ONS	Oral Nutritional Supplement(s)
PICO	Population of interest, Interventions, Comparisons, Outcomes
PN	Parenteral Nutrition
QoL	Quality Of Life
REE	Resting Energy Expenditure
RCT	Randomized Controlled Trial
SF-12	12-Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
SGA	Subjective Global Assessment
SIGN	Scottish Intercollegiate Guidelines Network
SNAQ	Short Nutritional Assessment Questionnaire
TEE	Total Energy Expenditure
WG	Working Group

1. Introduction

The present guideline represents an update of the original guideline on polymorbid patients from 2018 [1] and follows the Standard Operating Procedures (SOP) from European Society for Clinical Nutrition and Metabolism (ESPEN) [2]. Compared to the original guideline, the Working Group (WG) decided to keep the same twelve PICO questions for which the recommendations and associated evidence were updated and reviewed, to formulate evidence-based recommendations also for the three non-PICO questions, and to add a new question regarding biomarkers to predict treatment response to address heterogeneity as certain patients do not show the same benefit from nutritional support.

1.1. What is the definition of polymorbidity?

Although there is no universally accepted definition of polymorbidity (also known as multimorbidity), some authors define it as being the co-occurrence of at least two chronic health conditions in the same person. That is also the definition used for the purposes of this guideline, based on literature recommendations [3–5] and discussions within the guideline WG.

The health and nutrition implications of suffering from more than one disease at the same time differ from the corresponding interactions between disease and aging. Polymorbidity is often, but not necessarily, observed in older persons, in contrast to the geriatric context when multimorbidity is always combined with functional limitations and other age-related degenerative expressions. As life expectancy increases and individuals acquire a variety of chronic illnesses, polymorbidity becomes one of the main challenges that many healthcare and social services face worldwide. Additionally polymorbidity is associated with increased health service utilization and poorer health outcomes [6,7], demonstrating the relevance of proper treatment for polymorbid patients.

1.2. Why do we need to develop nutritional support guidelines for polymorbid medical inpatients?

As stated by Lefevre et al., "we know, for example, how to educate a diabetic patient, a chronic bronchitis patient, and a hypertensive patient, but we do not know, in practical terms, how to educate a patient with all three diseases" [3]. In fact, we did not know if the screening, assessment and treatment of disease-related malnutrition (DRM) in polymorbid medical inpatients should differ from the approach used in patients with a single disease. Yet, recent large randomized controlled trials (RCT) over the last five years have provided important new evidence showing that nutritional support can reduce morbidity and other complications in polymorbid patients, which may help us to answer these question and formulate evidence-based recommendations [8,9].

Polymorbidity is highly prevalent, affecting more than 70% of the hospitalized adult population, and is associated with higher mortality and healthcare burden [10]. Other consequences of polymorbidity include disability, functional decline, poor quality of life (QoL) and higher healthcare costs [5]. Whilst the prevalence increases with age, more than half of all people affected with this problem are younger than 65 years [11]. In this context, the current single-disease healthcare approach has been challenged, as clinical guidelines are largely created for individual diseases and rarely account for polymorbidity [11]. Fried et al. showed that clinicians struggle with the uncertainties of applying disease-specific guidelines to their patients with multiple conditions, and would therefore benefit from a number of tools to assist them in decision making for this population [12]. Limited, if any, accounting for polymorbidity applies to current nutritional guidelines that focus on single diseases (e.g. nutritional support in renal failure) or on patient groups (e.g. older adults). To date, it is unknown whether there is a synergistic negative effect of several diseases on nutritional status, or on clinical outcome. Therefore, there is a need for an updated evidence-based consensus on how to provide nutritional support for the

polymorbid medical inpatient population and to strengthen recommendations that now have a solid evidence base.

2. Materials and methods

2.1. Pragmatic definition of polymorbidity for the current project

This guideline is based on clinical trials that investigate the effects of nutritional support on different outcomes. Because these population-based trials usually report an average number of comorbidities or number of drugs/medications, a pragmatic definition of the polymorbid medical inpatient population was established and does not differ from the original guideline.

- at least two co-occurring chronic diseases present in at least 50% of the study population (in a few of the studies it is stated that x % of the study population suffers from disease A, y% of the study population suffers from disease B, and so on)

or, alternatively,

- a Charlson comorbidity index in the study population as being more than 1.5
- a mean number of diseases or drugs (medications) over 1.5

Polypharmacy is considered to be an important and acceptable marker of polymorbidity, with polypharmacy and polymorbidity having been described as being "two sides of the same coin" [13]. Additionally, it has been shown that the greater the number of medications, the higher the risk of weight loss and manifest malnutrition, which suggests that polypharmacy has a potentially negative effect on nutritional status. The Charlson comorbidity index is the most extensively studied comorbidity index and is considered a valid and reliable method to measure comorbidity that can be used in clinical research [6,14].

In cases of uncertainty about the way that comorbidities were reported, the study authors were contacted in order to obtain additional information. In the event that they could not be reached, a blinded consensus decision within the guideline WG was taken about whether or not to include the study. Some of the included studies were conducted in older populations, since many polymorbid patients are also of an older age. For each included study, the criteria used to consider the study population as being polymorbid was recorded (and reported in the evidence table, in appendix 1).

However, the rigorous methodical approach used came up with some limitations regarding selecting trials and has led to a lower number of included trials. Thus it guarantees that our findings are valid for the population of polymorbid medical inpatients.

2.2. Guideline development

We conducted the update of the guideline with a multidisciplinary team of 14 European specialist in nutritional support from which twelve have already been authors of the original paper from 2018 following the SOP for the development of ESPEN guidelines [2]. The WG decided to keep the previously defined clinical questions as well as the inclusion and exclusion criteria (Table 1). Most of the relevant clinical topics are covered by twelve questions in the PICO format (indication, route of feeding, energy and protein requirements, micronutrients requirements, disease-specific nutrients, timing, monitoring and procedure of intervention). However three topics of interest could not be developed as a PICO-question (underlying disease, polypharmacy and treatment response). The previous question b (duration of intervention) is now incorporated into recommendations 20 to 23 (continued support).

The same search strategies used in the original guidelines were used in the literature searches in 2022. Similar to the original guideline, a systematic literature search was conducted, first in secondary sources by searching published guidelines and systematic reviews potentially relevant for each question, followed by a search in primary sources. On the 12th of July the primary source search update was conducted by the same author in three databases (Medline, Embase and the Cochrane Library) since April 2016.

For all questions, the results from each database were combined and exported to Endnote, followed by removal of duplicates. The abstracts were screened by either one of two WG members in a standardized and systematic way – potential studies (full texts) were then reviewed by both members. Discrepancies were resolved through consensus or recourse to a third review author.

Many studies required the assessment of the full paper to ascertain whether it met all of the inclusion criteria, and for a proportion of the papers (n = 16), the authors were contacted and requested to provide more information, which was usually to clarify whether their study population suffered from multiple

Table 1
Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Patients characteristics	- Human adults aged ≥18 years - Patients hospitalized in acute care wards	- Non human, ≤18 years, pregnant women - Patients admitted to critical/intensive care units - Surgical patients - Patients living on long-term care facilities - Outpatients - Patients receiving end of life care - Healthy population - Less than 50% of the study population has two co-occurring diseases
	- Polymorbid inpatients population as defined by a) at least two co-occurring chronic diseases are present in at least 50% of the study population or b) mean number of diseases or drugs/medication or the Charlson comorbidity index in the study population as being more than 1.5 In case of uncertainties about the way comorbidities are reported, the trials' authors are contacted in order to get more information; if contact is not possible, the WG makes a consensus decision about the inclusion/exclusion of the studies.	
Outcomes	Nutritional outcomes (e.g. weight, energy and protein intake) Clinical outcomes (e.g. mortality, infections) Patient-centered outcomes (e.g. quality of life) Healthcare resources	
Language and year	English; no restriction on publication year	

comorbidities. For those studies whose authors could not be reached (n = 11), seven were included and four excluded, according to the WG consensus decision.

Each WG member was allocated with one or two clinical questions and was responsible for: validation of the literature, quality assessment and assignment of level of evidence for each paper relevant for the recommendations (e.g. using SIGN checklists), generation of first draft of recommendations, including the supporting text and grade of recommendation. The classification of the literature into levels of evidence and grades of recommendation were performed according to the SIGN grading system [15], as exemplified in Tables 2 and 3.

In the original guideline from 2018 a total of 4532 abstracts were screened, 38 relevant studies were analyzed and used to generate a guideline draft that proposed 22 recommendations and four statements. The search update in July 2022 identified 4234 additional possible eligible abstracts; after removing the duplicates, a number of 3527 abstracts were screened. The details of the search update can be found in Table 4. As a result of the update and the conversion of the statements to recommendations, a total of 100 studies are now included.

An evidence table with the number of studies allocated to each question, study details, evidence of polymorbidity for each study population, study type and level of evidence is presented in Appendix 1 (supplementary data: evidence table). These studies can also be identified in the present document through the assignment of the respective evidence level in the text below each recommendation, in bold, e.g. **Level of evidence 2+**.

The WG generated a guideline draft with a total of 32 recommendations (approved by the WG and the ESPEN Guidelines Editorial Board office, which was followed by the start of the consensus procedure, by sending that draft to the members of the ESPEN guideline project, ESPEN members and other experts in clinical nutrition for online voting (Delphi method) in April 2023. The results of this online voting were a strong consensus (agreement of >90%) in 100% of recommendations, which is so far unique in ESPEN guideline development. Nevertheless the feedback received during the online voting was used to make minor changes and improvements to recommendations and supportive text. Due to the large agreement on the first vote, no final consensus conference took place.

3. Results

Question 1. Does nutritional support based on screening and/or assessment versus no screening and/or assessment improve outcomes in polymorbid medical inpatients?

Table 2
Levels of evidence (SIGN grading system) [15].

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

3.1. Recommendation 1

In polymorbid medical inpatients, a quick and simple nutritional screening method using a validated tool should be applied to identify malnutrition risk.

Grade of recommendation B – Strong consensus 97% agreement.

Commentary

Polymorbid medical inpatients are at high risk of malnutrition. Several prospective cohort studies showed a prevalence of approximately 40–50% in a hospitalized population of tertiary centers [16,17]. Observational studies have shown the frequency of complications in untreated at-risk patients to be three times higher than in patients not at-risk, and furthermore length of hospital stay (LOS) is 50% longer, which has a negative influence on clinical outcomes [18]. Further, in the one-day cross-sectional study of Beck et al. patients at nutritional risk were more likely to be readmitted within 30 days (45% vs. 27%, p = 0.024) and had a higher mortality within 30 days after discharge (23% vs. 10%., p = 0.0285) [19]. Also, in a prospective observational cohort study, Lengfelder et al. were able to show higher odds for malnourished patients having a LOS of ≥3 days (2.38, 95% CI, 1.45 to 3.88; p < 0.001) and for readmission within 30 days (2.28, 95% CI, 1.26 to 4.12; p < 0.006) [20]. The same effect was shown by Li et al. in patients with community acquired pneumonia [21] **(Level of Evidence 2-)**. The latter also showed a significant increase in the prevalence of nutritional risk measured by the Nutritional Risk Screening 2002 (NRS 2002) within two weeks after admission (40.61% vs. 48.93%; p = 0.036).

Scoring systems for determining nutritional risk, such as NRS 2002 and the Mini Nutritional Assessment Short-Form (MNA-SF) link nutritional risk assessment to treatment by predicting that nutritional interventions will have a positive influence on variable outcomes [22–25]. Both of these tools are rapid, easily undertaken and show a high degree of content validity and reliability, thereby making them suitable in polymorbid medical inpatients including those patients with cognitive dysfunction [26,27].

In a secondary analysis of the multicenter, randomized clinical EFFORT trial [8], Stalder et al. investigated the ability of five different nutrition screening and partly also assessment instruments (NRS 2002 [22], Subjective Global Assessment (SGA) [28], Short Nutritional Assessment Questionnaire (SNAQ) [29], MNA-SF [24] and Malnutrition Universal Screening Tool (MUST) [30]) to predict 1-year mortality and response to nutritional treatment. While high nutritional risk was associated with higher mortality in all tools, SGA and MNA-SF showed the strongest association with adjusted odds ratios of 3.17 (95% CI, 2.18 to 4.61, p < 0.001) and 3.45 (95% CI, 2.28 to 5.22, p < 0.001). When comparing mortality in intervention group (IG) patients to the control group (CG) stratified by severity of malnutrition, there was overall no clear trend towards more benefit in patients with more severe malnutrition, with NRS 2002 and SGA showing the most pronounced relationship between the severity of malnutrition and reduction in mortality as a response to nutritional support [31].

3.2. Recommendation 2

In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to allow an early adequate nutritional therapy and to define quality outcome measures.

Grade of recommendation B – Strong consensus 97% agreement.

Commentary

If patients screen positive, diagnosis should be established according to GLIM criteria – the Global Leadership Initiative on Malnutrition (GLIM) proposes a two-step approach for the malnutrition diagnosis, which includes a validated screening and second, a

Table 3
Grades and forms of recommendations (SIGN grading system).

a. Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1 ++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 +, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ++, directly applicable to the target population; or A body of evidence including studies rated as 2 +, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 ++ or 1 +
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 ++ or 2 +
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

b. Forms of recommendation	
Judgment	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

Table 4
Number of abstracts retrieved for each question, in each database, and number of studies included for analysis (original and updated searches).

	Number of abstracts found in the updated searches (2022):				Previous included studies	Total included studies (2016 + 2022)
	Medline	Embase	Cochrane Library	Total (without duplicates)		
Question 1	159	8	271	421	2	3
Question 2	217	274	186	494	11	21
Question 3	159	236	76	357	1	1
Question 4	15	13	0	19	1	2
Question 5	14	14	141	156	2	5
Question 6	23	95	58	161	0	0
Question 7	66	92	176	282	2	4
Question 8	270	259	252	576	2	6
Question 9	4	3	240	238	10	24
Question 10	76	288	245	542	2	5
Question 11	6	8	112	120	2	6
Question 12	30	34	114	161	3	7
Total				**3527**	**38**	**84**
Question 13					2	10
Question 14					0	0
Question 15					0	6
Total						**100**

detailed assessment with phenotypic and etiologic criteria for diagnosis and grading the severity of malnutrition [32]. This guideline did not focus specifically on the assessment and diagnosis with GLIM criteria in polymorbid medical inpatients but generally on assessments to identify pathogenic factors which should be used to develop a treatment plan. The effectiveness of the care plan should be measured by a subsequent monitoring including dietary intake, body weight, and measurements of mental and physical function and of clinical outcome.

In a controlled trial, Rypkema et al. demonstrated that a standardized, early nutritional intervention in older polymorbid medical inpatients at nutritional risk, determined by the MNA-SF, is effective and does not significantly increase hospital costs. The intervention resulted in both a more pronounced weight gain (0.92 ± 0.27 kg in the IG (IG) vs. −0.76 ± 0.28 kg in the CG, $p < 0.001$) and a significant lower rate of nosocomial infections (23.6% vs. 36.7%, $p = 0.01$) **(Level of evidence 2+)**.

In a prospective, non-randomized cohort study, Jie et al. found nutritional support was beneficial for polymorbid medical inpatients at nutritional risk as defined by the NRS 2002 [17] **(Level of evidence 2+)**. The overall complication rate was significantly lower in the group with nutritional therapy than in the no-support group (20.3% vs. 28.1%, $p = 0.009$), primarily because of the lower rate of infectious complications (10.5% vs. 18.9%, $p < 0.001$). These effects were robust after multivariate adjustment. Also, in the same study, the effects of each medical nutrition therapy were analyzed separately, and significantly lower complication rates were found only in patients who received enteral nutrition (EN) compared to the group without nutritional support (8.2% vs. 28.1%, $p < 0.001$).

Question 2. In polymorbid medical inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements, with or without nutritional counseling, versus no oral nutritional supplements, improve outcomes?

3.3. Recommendation 3

In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely receive oral nutrition, individualized provision of nutritional support via oral nutritional supplements (ONS) to reach energy and protein requirements shall be offered to improve their nutritional status, QoL and overall survival.

Grade of recommendation A − Strong consensus 100% agreement.

Commentary

Provision of ONS in acutely ill hospitalized patients or inpatients at risk of developing malnutrition has been found to improve

nutritional intake in terms of energy and protein and have a positive impact on nutritional status, clinical outcomes and overall survival. Hegerová el al. conducted a prospective RCT in 200 inpatients from an internal medicine department and found that the provision of ONS (combined with physiotherapy) increased the overall nutritional intake, mainly energy (1954 ± 429 kcal in the IG vs. 1401 ± 364 kcal, $p < 0.001$) and protein (76.3 in the IG ±16.1 vs. 55.5 in the CG ±13.7, $p < 0.001$), without negatively affecting the hospital food consumption (72.8% in the IG vs. 71.3% in the CG, $p = 0.528$) [33] **(Level of evidence 1++).** This supplementation resulted in significant preservation of muscle mass (lean body mass difference between admission and three months after discharge was −3.5 kg in CG patients, and +1.3 in the IG) and independence (the difference in the Barthel Index (BI) values between admission and three months showed a statistically significant decline in the CG ($p < 0.01$) vs. a non-significant decline in the IG). Therefore, ONS have a supplemental role in the provision of nutrition during hospitalization. Schuetz el al., in the EFFORT trial, reported a lower risk of adverse clinical outcome in the IG compared to controls (adjusted OR 0.79, 95% CI 0.64 to 0.97, $p = 0.023$) and a lower risk of mortality (adjusted OR 0.65, 95% CI 0.47 to 0.91, $p = 0.011$), with no statistically significant difference in side effects between both groups [34] **(Level of evidence 1++). Similarly,** improved survival in medical inpatients receiving nutritional support was reported in the meta-analysis by Gomes et al. where the analysis of 27 trials resulted in lower mortality rates in patients receiving nutritional care vs. the controls (230 of 2758 [8.3%] vs. 307 of 2787 [11.0%]; OR 0.73; 95% CI, 0.56–0.97) [35]. Nutrition support was also associated with lower non-elective hospitalizations 14.7% vs. 18.0%; RR 0.76; 95% CI 0.60 to 0.96) improved energy and protein intake (mean difference of 365 kcal, 95% CI 272–458 kcal for energy and mean difference of 17.7 g, 95% CI 12.1–23.3 g for protein), and improvements in nutritional and functional status **(Level of evidence 1++).** A meta-analysis by Gressies et al. conducted in 2022 that was an update and re-analysis of Gomes et al. included trials exclusively conducted within the population of polymorbid patients using the exact same definition as used in this guideline. The analysis showed again a significant reduction in mortality risk (OR 0.68; 95% CI 0.51–0.91) (Fig. 1) and hospital readmissions (OR 0.64; 95% CI 0.45–0.90) proofing the effectiveness of nutritional support in this vulnerable patient group with complex combinations of diagnoses [36] (**Level of evidence 1++**).

The long-term effects of individualized nutritional support during hospitalization are also of interest. According to a secondary analysis of the EFFORT trial by Kaegi-Braun et al., the positive effects of individualized nutritional support provided during hospitalization which were observed at 30 days, were not sustained at six months after discharge when nutrition was not continued [37] **(Level of evidence 1++).** Therefore, the effect of long-term provision of individualized nutritional support continuing as homecare should be a subject of future research.

3.4. Recommendation 4

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, high protein nutrient specific ONS should be administered, when they may help maintain functional status and muscle mass, reduce mortality and improve QoL.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary

Several nutrient specific ONS have been tested for their effectiveness on the improvement of outcomes in hospitalized patients. High protein ONS containing – β-Hydroxy β-Methylbutyrate (βHMB) have been tested for their effect on muscle mass and functionality. According to the NOURISH study, a multicenter RCT which included 652 malnourished inpatients, high protein βHMB ONS may not yield a difference when compared with placebo on readmission rates, but may help with the maintenance of muscle mass during hospital stay and result in a significant decrease in post-discharge mortality (90-day mortality was 4.8% in the IG vs. 9.7% in the CG; RR 0.49, 95% CI 0.27 to 0.90, $p = 0.018$) [9] **(Level of evidence 1++).** The effects of this ONS were also positive in a subgroup of patients with chronic obstructive pulmonary disease (COPD) from the same study, where the IG had significant decreased mortality risk compared to the CG (1.83%, 2.75%, 2.75% vs. 6.67%, 9.52% and 10.48%, $p = 0.0395, 0.0193, 0.0113$, respectively). Moreover, COPD patients receiving the high protein βHMB ONS showed an increase in handgrip strength (HGS) from discharge to 30 days (1.56 kg vs. −0.34 kg, $p = 0.0413$) and increased body weight (0.66 kg vs. −0.01 kg, $p < 0.05$) [38] **(Level of evidence 1++).** Improved functionality measured by HGS was also observed in other subgroup analyses from the NOURISH study, including patients with cardiovascular and pulmonary disease. Patients receiving specialized ONS showed in a greater extent improvement in HGS, nutritional and performance status, compared to the controls receiving the placebo ONS (49% vs. 31%, $p = 0.0003$) [39] **(Level of evidence 1++).**

In addition, provision of ONS containing 995 kcal from macronutrients and covering 100% of the RDA for healthy older adults in vitamins and minerals led to a lower incidence of depressive symptoms ($p = 0.021$) in older medical inpatients, with no other

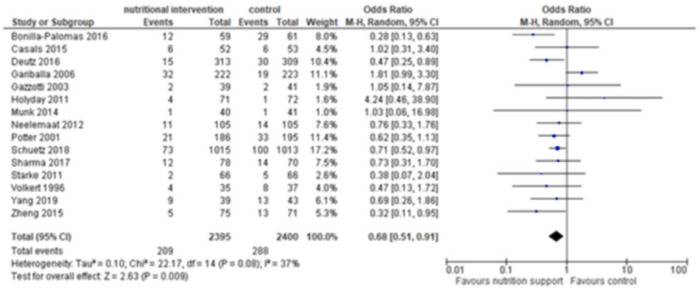

Fig. 1. Forest plot comparing nutritional intervention versus control for mortality in polymorbid medical inpatients [36].A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95% CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95% CIs. OR indicates odds ratio.

effect on their cognitive performance but with a significant positive effect on their self-reported QoL (i.e. the treatment effect in QoL scores using the SF-36 form at 6 months was 7.0, 95% CI 0.5 to 13.6, p = 0.04 for physical function, 10.2, 95% CI 0.1 to 20.2, p = 0.047 for role physical, and 7.8, 95% CI 0.0 to 15.5, p = 0.05 for social function domains, compared to placebo) [40,41] **(Level of evidence 1++ for both).**

Wound-specific ONS have also been tested for their effectiveness in polymorbid patients during rehabilitation. A supportive retrospective analysis of data collected from 341 patients showed that the daily provision of wound-specific ONS resulted in a significant greater decrease in the wound area, compared to the patients who did not receive nutritional support (61.1% in the IG vs. 34.5% in the CG, p = 0.01) [42]. Although these results are interesting and promising, the available studies remain limited.

3.5. Recommendation 5

In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely receive nutrition orally, ONS shall be offered as a cost-effective way of intervention towards improved outcomes.

Grade of recommendation A − Strong consensus 100% agreement.

Commentary

Early detection and intervention against DRM has been shown to improve nutritional status and reduce complications during hospital stay and non-elective readmissions [9,43] **(Level of Evidence 1++ for both).** According to a cost-effectiveness analysis by Philipson et al., in a retrospective study from 2000 to 2010, the provision of ONS to malnourished medical inpatients resulted in a reduction in LOS of 2.3 days, 95% CI -2.42 to −2.16 that subsequently decreased annual hospital costs by 4734 $, 95% CI -4754 $ to −4714 $, and reduced the readmission rate by 6.7%, from 34.3% to 32.0% [44] **(Level of evidence 2++).** The greatest benefit was recorded in the most severely ill patients, which was a finding in general agreement with the "Feed Or Ordinary Diet" multi-center RCT, in which routine ONS (independent of baseline nutritional status) did not offer significant benefits to a mostly well-nourished stroke patient population (OR of death or poor outcome was 1.03, 95% CI 0.91 to 1.17 for the overall group and 0.78, 95% CI 0.46 to 1.35 in the small undernourished subgroup). This stresses the importance of providing nutritional support to those most in need [45] **(Level of Evidence 1++).**

The cost analysis of the multicenter, randomized clinical EFFORT trial showed that nutritional support for polymorbid medical inpatients is a highly cost-effective intervention to reduce risks for ICU admissions and hospital-associated complications, while improving patient survival. Overall costs of care within 30 days of admission averaged 27,240 € per-patient in the IG versus 27,439 € in the CG resulting in per-patient cost savings of 199 €. The economic benefits calculated to prevent adverse outcomes were 256 € for one severe complication, 2490 € for one day in ICU, and 7423 € for one death [46] **(Level of Evidence 2+).**

For polymorbid medical inpatients who are malnourished or at nutritional risk, the economic analysis using modelled cost-savings calculations of several RCTs reflect reductions in infectious complications, LOS, and non-elective readmissions, as measures for the effectiveness of in-hospital nutritional support. In the meta-analysis of Schuetz et al. the overall costs of care within the model timeframe of 6 months averaged 63,227 $ per patient in the IG vs. 66,045 $ in the CG, which correlate to per patient cost savings of 2818 $. These cost benefits were mostly due to reduced infection rates and shorter lengths of stay. The authors also calculated 820 $ to prevent a hospital-acquired infection and 733 $ to avoid a non-elective readmission [47].

Positive results were also reported in a meta-analysis of RCTs on hospitalized patients at high risk of developing pressure ulcers, by Tuffaha et al. Provision of nutritional support resulted in a cost saving of 425 $ per patient and a marginal improvement of quality adjusted life years of 0.005, compared to the usual care [48] **(Level of evidence 1++).**

Regarding the provision of nutrient specific ONS, Zhong et al. conducted an economic evaluation of NOURISH study. According to this analysis the provision of high protein βHMB ONS had an incremental cost-effectiveness ratio (ICER) of 524 $/life years, concluding that this intervention was cost effective and positive in terms of survival for the patients [49] **(Level of Evidence 1++).** Moreover, a similar analysis was conducted by Ballesteros-Pomar et al. from the perspective of the Spanish National Health System in the patients included in NOURISH study. According to their analysis the intervention proved to be cost effective, improved survival and marginally reduced cost of treatment [50] **(Level of evidence 1+).**

Question 3. In patients where nutritional requirements cannot be met orally, does the use of enteral nutrition compared to parenteral nutrition (total or supplemental) result in improved outcomes in polymorbid medical inpatients?

3.6. Recommendation 6

In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN before parenteral nutrition (PN) can be administered to ensure reaching nutritional goals.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary

Reaching energy goals in medical inpatients is important to prevent weight loss and the loss of muscle mass that may lead to poorer functional outcomes. However, in the acute care setting many obstacles may prevent patients from meeting their nutritional requirements orally. These obstacles include loss of appetite due to acute illness, delayed gastric emptying causing both nausea and early satiety, inability to swallow, and vomiting, among others. In these situations, use of EN or PN can help increase nutritional intake until oral intake is sufficient [51,52]. Several randomized studies have compared the effect of nutritional support on outcomes of medical inpatients. A 2019 systematic review and meta-analysis on nutritional support in medical inpatients found significantly improved clinical outcomes in those receiving adequate nutritional support. The review included 27 RCTs from several countries comprising 6803 medical inpatients, and reported a 27% reduction in mortality and non-elective hospital readmissions [35]. The review also found significantly higher energy and protein intake, as well as beneficial effects on weight when comparing nutritional support (including counseling and oral and enteral feeding) to CG patients.

3.7. Recommendation 7

In polymorbid medical inpatients whose nutritional requirements cannot be met orally, the use of EN may be superior to PN because of a lower risk of infectious, non-infectious complications and maintenance of gut integrity.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary

Several studies are using nutritional strategies typically providing a combination of oral nutrition, EN and/or PN compared to usual care or other feeding strategies in the medical inpatient setting [53–55]; these studies, however, did not directly compare the two feeding modalities. There are also several studies that investigated whether EN compared to PN resulted in better outcomes. While most studies examined the critical care setting and patients with acute pancreatitis [56–58], there is some observational evidence for the polymorbid medical inpatient population [17]. This observational evidence consists of one large, prospective, non-randomized study (briefly described in the clinical question 1) from three institutions in the US and China including patients at nutritional risk, as defined by the NRS 2002, that investigated the outcomes of patients receiving either EN or PN to patients without nutritional support [17] (**Level of evidence: 2+**). Approximately two thirds of the patients were medical patients from the department in respiratory and gastrointestinal diseases. Because the study was non-randomized, the authors used multiple logistic regression analysis to evaluate the influence of nutritional support on the risk of infectious and non-infectious complications. Overall, the study found a significantly lower risk of overall complications and infectious complications associated with nutritional support (adjusted OR 0.54, 95% CI 0.38 to 0.77), $p < 0.001$ and adjusted OR 0.42, 95% CI 0.27 to 0.64, $p < 0.001$, respectively). When the nutritional support group was further divided into those receiving PN and those receiving EN, the overall complication rate and the rates of infectious complications and non-infectious complications were significantly lower in those patients receiving EN than in those patients with no nutritional support ($p = 0.001$). However, no difference in the complication rates was found between patients with PN and patients with no nutritional support ($p = 0.29$). Because of differences in the patient population, this analysis was also repeated in patients undergoing major abdominal surgery who had PN or no nutritional support. Again, no significant difference in the complication rate was found between PN patients and control patients. This study has a number of important limitations regarding the observational, non-randomized design with important differences in study populations between PN and EN patients (as well as no-nutritional support patients), differences in hospital characteristics between the Chinese and US hospitals and the lack of a standardized follow-up. Thus, causal inferences cannot be drawn. Still, the study suggests that EN may be more beneficial than PN, due to fewer infectious and non-infectious complications.

Albeit outside the scope of these guidelines, studies from critical care demonstrated that EN compared to PN results in similar mortality but lower complication risk. Specifically, a recent meta-analysis of 18 RCTs studying 3347 patients did not find benefits in terms of mortality. In that meta-analysis, EN compared to PN was associated with a significant reduction in infectious complications (RR 0.64, 95% CI 0.48 to 0.87, $p = 0.004$) and with a significant reduction in ICU LOS (weighted mean difference [WMD] −0.80, 95% CI -1.23 to −0.37, $p = 0.0003$, $I^2 = 0\%$), while no significant differences in hospital LOS and mechanical ventilation were observed. Authors stated that these results may be explained by the benefit of reduced macronutrient intake (avoidance of overfeeding) rather than the enteral route itself [59]. Similarly for pancreatitis, a meta-analysis including eleven trials and 562 patients found that compared with PN, EN was associated with decreased mortality (relative risk 0.43, 95% CI 0.23 to 0.78, $p = 0.006$), a lower risk of infection and complications (RR 0.53, 95% CI 0.39 to 0.71, $p = 0.000$) and a reduction in mean LOS (mean difference = −2.93, 95% CI -4.52 to −1.34, $p = 0.000$) [60].

In summary, several trials found that the addition of either EN or PN to oral nutrition improves outcomes, but high-quality randomized studies comparing EN and PN head-to-head in the polymorbid medical inpatient setting are scarce. Still, when also considering high-quality evidence from critical care and in patients with pancreatitis as well as observational evidence from polymorbid medical inpatients, there are several arguments for the use of EN as a first line therapy as compared to PN due to lower risks for infectious and non-infectious complications. A physiological rational is also the prevention of intestinal mucosal atrophy by EN compared to PN [61].

> Question 4. Does the estimation of energy requirements with a prediction equation versus a weight-based formula improve outcomes of polymorbid medical inpatients requiring nutritional support?

3.8. Recommendation 8

Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula, although the accuracy of prediction equations in this population is low.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary

The estimation of energy requirements is an important part of the patient assessment process and requires the determination of an individual's total energy expenditure (TEE) i.e. the sum of resting energy expenditure (REE), diet-induced thermogenesis and the energy expended during physical activity. The gold standard to measure REE is IC and for TEE the gold standard is doubly labelled water. However, these methods are rarely available in the clinical setting (almost never for the latter) and require considerable expertise [62]. Practitioners therefore tend to rely on either published prediction equations (e.g. Harris-Benedict [63] or Ireton-Jones [64]) or weight-based formulae (e.g. 25–30 kcal/kg body weight), to estimate energy requirements. In prediction equations, energy requirements are estimated from a number of different parameters e.g. weight, age, gender, ventilation status, heart rate etc.; in weight-based formulae the prediction is based solely on patient body weight. No single, validated method for estimating requirements exists, and the evidence-base for all prediction methods currently in use is poor [65]. In the absence of IC, there is a debate about which of the two estimation methods is the most valid for use in the clinical setting. However, no studies were identified that answered this specific question.

While both published prediction equations and weight-based formulae provide valid estimates of energy requirements for groups of patients, both methods are subject to significant bias and imprecision when applied to individuals [66,67]. More than 200 prediction equations have been published in the literature, with accuracy rates ranging from 36% to 75% when compared with IC and no single equation emerges as being the most accurate in polymorbid medical inpatients [66]. Practitioners should therefore exercise a considerable degree of clinical judgment when determining the energy requirements of a polymorbid medical inpatient.

This also includes the choice of activity or stress factors, which relies on the clinical judgment, knowledge, and experience of the individual calculating the predicted requirements − it should be undertaken with caution since their misapplication can lead to clinically significant errors.

Individuals requiring nutritional support range from paralyzed and sedated, critically ill patients to fully mobile patients on the ward or in the community. To date, however, there is a relative lack of research on the effects of illness and injury on physical activity levels, although a recent consensus document concluded that since

acute illness is usually accompanied by a decrease in physical activity that compensates for any increase in BMR, TEE is rarely above that of healthy, sedentary individuals of the same sex and age [68]. In a study designed to evaluate the accuracy of prediction equations against IC in hospitalized patients, REE was measured by IC in 395 inpatients referred for nutritional support. REE measurements were compared with three prediction equations including one specifically for obese individuals [63,64,69] and one weight-based formula recommended by the American College of Chest Physicians (25 kcal/kg body weight). The mean age of the population was 56 ± 18 years and the mean BMI was 24 ± 5.6 kg/m^2. Measured REE was 1617 ± 355 kcal/day for the entire group and 1790 ± 397 kcal/day in the obese group (n = 51). In this study the authors concluded that no single prediction equation was accurate (i.e. within 90–110% of measured REE) in the majority of the population. Another recent study conducted in 23 malnourished polymorbid, older hospitalized patients (mean age of 81.8 ± 8.1 years and mean BMI of 23.4 ± 4.0 kg/m^2) confirmed these results: the average REE predicted by the Harris–Benedict formula exceeded the REE measured by IC (after an overnight fast) on admission and at discharge by 29% and 11%, respectively, suggesting that the Harris–Benedict formula is not accurate in this patient population [70] **(Level of evidence 2+)**.

Clinicians should be aware of the limitations of using precise numbers on weight-based formulae (or prediction equations) since in all studies there is considerable variation around the effect estimate. They should recognize that all prediction methods are imprecise when applied to individuals and therefore should only be used as a starting point when estimating requirements. In fact, this highlights the need for input from a suitable and experienced healthcare professional to adequately assess the nutritional needs of the patient, e.g. a dietitian.

3.9. Recommendation 9

In the absence of IC, TEE for polymorbid older patients (aged ≥65 years) can be estimated at approximately 27 kcal/kg actual body weight/day. REE can be estimated at 18–20 kcal/kg actual body weight/day with the addition of activity or stress factors to estimate TEE.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

In a review designed to determine the energy requirements of frail older people [71], including polymorbid patients, 33 studies (2450 subjects) were identified where REE was measured by IC in subjects aged 65 years or more and the results were compared with healthy older individuals **(Level of evidence 2++)**. Only studies that measured REE by IC after a fast and at rest were considered eligible for inclusion in the review. The mean age was 73.0 ± 6.6 years, with no significant difference in BMI between the healthy and sick cohorts (25.6 ± 1.5 kg/m^2 and 25.2 ± 2.5 kg/m^2 respectively) and no differences in fat mass or fat-free mass. The weighted mean for the whole group was 20.4 kcal/kg actual body weight whereas the weighted mean for the polymorbid hospitalized older group was lower at 18.5 kcal/kg body weight. The mean TEE in sick older individuals was 27 ± 1.8 kcal/kg body weight and the weighted physical activity level in these patients was 1.36 ± 0.03 reflecting the relative physical inactivity of this population. The results of this review should be interpreted with caution since relatively few data were available in the sick older individuals (n = 248) compared with the healthy older individuals (n = 1970). Furthermore the methods described in the paper failed to comply fully with guidelines for the conduct of systematic reviews [72]. For example, only one database (MEDLINE) was searched when it is recommended that at least three should be searched, and only studies published in English were included.

3.10. Recommendation 10

In the absence of IC, REE for severely underweight patients can be estimated at 30 kcal/kg actual body weight.

Grade of recommendation 0 – Strong consensus 96% agreement.

3.11. Recommendation 11

This target of 30 kcal/kg actual body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary

In a study designed to determine the energy requirements of severely underweight hospitalized patients energy expenditure was measured by IC in 14 patients [73]. Mean BMI was 15.8 ± 1.8 kg/m^2 and mean age was 66.5 ± 13.9 years. In this study mean REE by IC was 1300 ± 160 kcal/day equating to 31.4 kcal/kg body weight. These results should be interpreted with caution since the sample size was very small. Furthermore, patients received continuous EN or PN during IC and thus measured energy expenditure included not only REE but also diet-induced thermogenesis.

The target of approximately 30 kcal/kg body weight in severely underweight patients may need to be achieved with caution, as this is a population at high risk of refeeding syndrome. The diagnostic criteria and the factors proposed for screening of refeeding syndrome have been proposed elsewhere [74].

From the review of the literature, it is not possible to determine which method of estimating energy requirements (or which prediction equation) is the best in terms of promoting better outcomes in the polymorbid medical inpatient population.

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation 11 is limited to the subgroup of polymorbid older patients. For further information regarding the nutritional care of older patients, please refer to the existing ESPEN guidelines on clinical nutrition and hydration in Geriatrics [75].

Question 5. Do protein targets higher than 1.0 g/kg body weight/day versus a lower target improve outcomes in polymorbid medical inpatients requiring nutritional support?

3.12. Recommendation 12

Polymorbid medical inpatients requiring nutritional support shall receive 1.2–1.5 g protein/kg of body weight per day as a cost-effective and highly efficient measure to prevent body weight loss, to reduce complications, to improve functional outcome and QoL.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Protein targets of at least 1.0 g/kg body weight have been recommended in the past [1], e.g. supported by a high-quality RCT with 132 polymorbid patients (**Level of evidence 1++**). More recent and larger RCTs, such as the EFFORT trial (**Level of Evidence 1++**) including 2028 polymorbid patients, support a higher daily protein target of 1.2–1.5 g/kg body weight [8,37,46]. Compared to the usual care CG, odds for adverse outcomes and 30-day mortality were significantly lower in patients receiving individualized nutrition with these protein targets (OR 0.79, 95% CI 0.64 to 0.97

and OR 0.65, 95% CI 0.47 to 0.91 respectively), while functional status via BI, and QoL significantly increased. An economic evaluation of EFFORT indicates that the high-protein nutritional support was highly cost-effective with per-patients savings of 199 € of overall costs of care within 30 days of admission; and 18 € in full cost analysis (**Level of Evidence 1**++) [46].

To reach high protein targets of 1.2–1.5 g/kg body weight, several strategies were used in the trials and interchangeably combined to respect patients individual preferences including ONS, protein-rich hospital menu, food fortification, and high-protein deserts and snacks [8,76,77].

The results of a recent meta-analysis from 2021 demonstrated that high protein intake was one of the strongest predictors for beneficial mortality effects of nutritional interventions: trials using high-protein strategies in medical inpatients at nutritional risk, had significantly stronger effects on mortality compared to trials with low-protein interventions (OR 0.57, 95% CI 0.44 to 0.74 vs. 0.93, 95% CI 0.73 to 1.19). High-protein interventions were considered when ONS with more than 20% protein were used or individual protein goals above 1 g of protein per kilogram body weight was defined [78]. In line with this finding, the recommendations from guideline on nutritional therapy by the American College of Gastroenterology [56] and other expert groups [51,79,80] for older patients and general inpatients are advocating daily protein targets of at least 1.2 g/kg body weight and even higher intake for individuals with severe illness [79].

Regarding combination of nutrition with exercise, several societies recommend to combine high-protein intervention with physical activity, to maintain or enhance muscle mass in malnourished older patients, including the ESPEN guideline for geriatrics and an ESPEN expert group on protein requirements in older adults [75,79]. This combination has been shown effective for the prevention and treatment of sarcopenia in several trials [81–85]. For instance, one RCT of 47 malnourished polymorbid patients participating in a rehabilitation program on a geriatric ward, compared whey supplementation vs. no whey supplementation and demonstrated positive effects on daily protein intake (1.48 vs. 1.05 g/kg body weight) and muscle strength [76] (**Level of Evidence 1**+). Still, there is remaining uncertainty regarding the specific role of exercise in high-protein interventions in the group of polymorbid medical inpatients at nutritional risk, because there is a lack of trials comparing head-to-head protein supplementation with exercise vs. without exercise [76,86,87].

3.13. Recommendation 13

For polymorbid medical inpatients at nutritional risk with impaired kidney function (eGFR <30 ml/min/1.73 m^2) who are not on kidney replacement therapy, a low amount of protein of 0.8 g protein/kg body weight/day should be targeted.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary

In the case of polymorbid medical inpatients with impaired kidney function, protein requirements should be lower [51]. ESPEN Guideline on clinical nutrition for kidney disease recommends setting protein targets preferably guided by protein catabolic rate. Referring to body weight, it is recommended to start with a protein intake of 1 g/kg body weight per day and gradually increase up to 1.3 g/kg body weight for medical inpatients with acute kidney injury (AKI) or chronic kidney disease (CKD) without kidney replacement therapy (KRT). Different recommendations are made for patients with other renal conditions, e.g. 0.6–0.8 g for patients with CKD without acute illness or 1.2 g/kg body weight/day if those patients are on conventional intermittent chronic KRT and higher intakes for critically ill patients [88]. However, those recommendations do not refer specifically to polymorbid patients with kidney diseases.

Within EFFORT [8], protein targets of 1.2–1.5 g were lowered to 0.8 g/kg body weight/day for patients with eGFR <30 ml/min/1.73 m^2 according to earlier guidelines [1,88]. However, the degree of kidney impairment was a strong predictor for response to nutritional support and patients with eGFR of 15–29 l/min/1.73 m^2 receiving 0.8 g and those with 30–59 ml/min/1.73 m^2 receiving 1.2–1.5 g/kg body weight/day showed the strongest benefits on 30-day mortality (OR 0.37, 95% CI 0.14 to 0.95 and 0.39, 95% CI 0.21 to 0.75, respectively) (**Level of Evidence 1**++) [89]. This finding supports the concept of adjusting protein goals in polymorbid patients with renal conditions and impaired kidney function for eGFR and using targets from 0.8 g/kg body weight if eGFR is < 30 ml/min/1.73 m^2 and at 1.2–1.5 g with eGFR if ≥ 30 ml/min/1.73 m^2. However, based on our search, there is a lack of trials comparing higher vs. lower protein targets in the polymorbid patient population with impaired kidney function. A recent critical review supported by the European Renal Nutrition Group of the European Renal Association (ERN-ERA) and ESPEN also recommends that renal status be prioritized in patients with advanced CKD (stages 4 and 5) [90]. However, they conclude that patients with CKD need a personalized approach depending on nutritional status and renal condition, and that renal and nutritional priority (protein restriction vs. no protein restriction) may substitute for each other over time.

Question 6. In patients exclusively fed orally, does micronutrient (vitamins and trace elements) supplementation compared to no supplements improve outcomes in polymorbid medical inpatients?

3.14. Recommendation 14

In polymorbid medical inpatients exclusively fed orally, an adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients may be at risk of micronutrient deficiency as a result of decreased intake or greater micronutrient utilization, which can compromise health as well as recovery from illness or disease. Some studies suggest beneficial outcomes from supplementation of micronutrients: for example, a study relating micronutrients to COVID-19 infection by James et al. reported limited evidence that supplementation of certain micronutrients can prevent severe disease or shorten time to recovery [91]. In another study, a Swiss group reported fewer adverse effects in medical inpatients ≥18 years outside of intensive care from early implementation of individualized nutrition support goals which included micronutrient provision, although any role the specific micronutrient goal had is unclear [8]. Just as underprovision of micronutrients could compromise polymorbid medical inpatients so too could overprovision. For example, a meta-analysis of mixed study populations found additional micronutrient supplementation to a therapeutic diet [74] already supplemented in micronutrients did not reduce mortality and may have increased LOS by approximately one day (albeit with borderline statistical significance) [92].

General micronutrient supplementation, with or without supplementation of specific micronutrients, based only on the provision of multivitamins rather than a combined multivitamin and multi-trace element appears to be common, and often based on financial cost of the supplement. However, if a subject may have general micronutrient depletion or generally increased

micronutrient requirements then there is likely to be a need to provide trace elements as well as vitamins. Therefore, in the absence of specific toxicity risks or known micronutrient adequacy, supplementation should aim to deliver a complete range of both multivitamins and multi-trace elements rather than multivitamins alone. Complete micronutrient supplementation to meet reference nutrient intakes or otherwise estimated daily requirements could be particularly important in polymorbid medical inpatients due to the potential for any deficiencies to affect multiple and already compromised organ systems. Micronutrient requirements in older adults, frail or unwell subjects are unclear, but these groups may be particularly at risk of deficiencies [75]. ESPEN provides practical advice on micronutrient status affecting disease and vice versa, micronutrient provision and monitoring, and potential micronutrient deficiencies resulting from medicine administration such as vitamin B12 or iron with proton pump inhibitors, or thiamine with diuretic therapy [93]. The mechanisms by which these deficiencies could occur vary according to the medicine and nutrient. No studies were identified that reported the supplementation of multivitamins (with or without trace elements) compared to no supplements in polymorbid medical inpatients exclusively fed orally.

3.15. Recommendation 15

In polymorbid medical inpatients exclusively fed orally, documented or suspected micronutrient deficiencies should be repleted.

Grade of recommendation GPP − Strong consensus 96% agreement.

Commentary

The need for micronutrient supplementation is often based on clinical assessment of the subject and in some cases estimated daily micronutrient requirements may temporarily exceed recommended daily intakes in order to account for depleted stores and/or increased utilization (particularly in patients who are exclusively fed orally). For example, a study by Joosten et al. found hospital inpatients >65 years of age likely to be deficient in vitamin B12, folate and/or vitamin B6, even though the same subjects had apparently normal reported levels of the same micronutrients [94]. A study by Kilonzo et al. [95] on self-reported morbidity from infections in free-living patients (rather than inpatients) aged >65 years, randomized to receive either a daily vitamin and mineral supplement or placebo, found fewer QALYs per person in the supplemented group. This result is counter-intuitive; however, incomplete supplements not designed to replete micronutrient stores were used despite almost one third of the participants being judged at risk of micronutrient deficiency on recruitment. Daily micronutrient supplementation in free living individuals ≥60 years old did not improve incidence and severity of acute respiratory tract infections [96], although since the subjects were well-nourished they perhaps did not benefit from the supplementation. Another study of frail subjects in the community ≥65 years found a reduction in frailty with increased dietary intake but not with supplementation of only micronutrients [97]. However, the potential influence of increased micronutrient intake associated with the higher dietary intake in this study is unclear and the micronutrients-only group received estimated daily needs rather than repletion. Supplementation of some nutrients could affect supplementation of others, although there was no reduction in nutrient intake from food with increased micronutrient intake in those aged ≥65 years consuming high-protein ONS post discharge [98].

Question 7. Does disease-specific nutritional supplementation (e.g. fiber, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard formulations improve outcomes in polymorbid medical inpatients?

Many specialized ONS/EN feeds have been developed for specific diseases that usually involve chronic/acute inflammation, specific micronutrient deficiency or specific metabolic disorders [99]. However, most studies were not conducted in identified hospitalized polymorbid patients, even though some of these patients may well be polymorbid, and the number of useable studies identified is extremely low.

3.16. Recommendation 16

In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and βHMB can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.

Grade of recommendation 0 − Strong consensus 92% agreement.

Commentary

Pressure ulcers are responsible for protein loss, hypermetabolism and hypercatabolism, and are often associated with malnutrition, including nutrient deficiencies that are critical to the different phases of wound healing (conditionally essential amino acids and antioxidant micronutrients). A RCT from Singapore that included 26 polymorbid patients hospitalized for more than two weeks [100] showed a marginal albeit significant effect of an arginine/glutamine/βHMB mixture on the healing of pressure ulcers (greatest improvement of viable tissues at two weeks in the IG, by 43% vs. 26%, $p = 0.02$) **(level of evidence 1+)**. The amino acid mixture (14 g arginine, 14 g glutamine and 2.4 g calcium βHMB per day) was not part of a nutritional formula, but all patients were fed per recommendations for hypermetabolic and hypercatabolic patients (30–35 kcal and 1.2–2.0 g protein/kg body weight/day according to the stage of the ulcer). As the basic nutritional needs were covered in both groups, the supplement (administered orally or enteral) was likely responsible for the beneficial effects observed. In another RCT from Hong Kong, 87 polymorbid malnourished older adults with pressure ulcers were randomized to receive or not the same mix of arginine/glutamine/βHMB for four weeks, besides an adapted nutritional support (at least 30 kcal and 1.2 g protein/kg body weight/day) [101], (**level of evidence 1+**). A statistically significant reduction in pressure ulcer size ($p = 0.048$) and depth ($p = 0.002$) was observed in the IG while the Pressure Ulcer Scale for Healing (PUSH score) showed a significant improvement in the CG ($p < 0.001$). However, there was no between group difference on pressure ulcer healing in term of pressure ulcer area, depth, undermine and PUSH score.

Other positive studies have been published using an oral nutritional supplement enriched in arginine, zinc and antioxidants in patients outside the scope of these guidelines [102,103].

3.17. Recommendation 17

In polymorbid medical older inpatients requiring EN, EN formulas enriched in a mixture of soluble and insoluble fibers can be used to improve bowel function.

Grade of recommendation 0 − Strong consensus 96% agreement.

Commentary

Diarrhea and constipation are the most frequent complications of EN in hospitalized patients. A Belgian study of 145 older patients receiving enteral feeding [104] found positive effects of a formula enriched with 30 g fiber including 33% insoluble (cellulose and hemicellulose A) and 67% soluble (pectin, hemicellulose B, inulin) fiber (IG) vs. the CG, which received the same EN with no fiber **(level of evidence 1++)**. The frequency of stools was lower (4.1 ± 2.6 per week versus 6.3 ± 4.7 per week; $p < 0.001$) and the

stool consistency higher in the IG (31% had solid form stools in the IG vs. 21% in the CG, and 2% had liquid-watery stool in the IG vs. 13% in the CG, $p < 0.001$); however, patients in the CG received more laxatives during the study period than patients in the fiber group. A global 4-week mortality of 24% underlines the severity of the patients' conditions.

The effects on bowel function associated with the absence of detrimental metabolic effect argue for a recommendation for a first intention use of EN formulae enriched with a mixture of soluble and insoluble fibers (supposed to match the multiple sources of fibers in normal food). The same recommendation has been made in ESPEN's clinical nutrition and hydration guidelines in geriatrics [75].

Recommendation 17 was downgraded from grade of recommendation B to 0, due to the limited number of available studies in identified polymorbid medical inpatients**.**

3.18. Recommendation 18

We cannot recommend the use of other disease-specific nutritional supplementation in polymorbid medical inpatients.

Grade of recommendation 0 – Strong consensus 100% agreement.

The scarcity of quality intervention studies in populations adequately described as polymorbid does not allow to recommend the use of other disease-specific nutrients.

One of such prospective studies with negative findings was conducted in Japan in 50 patients with exacerbation of COPD [105] (**Level of evidence 1**+). They were randomized to receive either ONS with 1.1 g of eicosapentaenoic acid (EPA) or a comparable one without n-3 fatty acid during their hospitalization, both groups receiving a total of 30–35 kcal/kg/day. At discharge (after 12–13 days of supplementation in both groups), there was a non-significant increase in lean body mass index and skeletal muscle mass index in the EPA group compared with the CG (lean body mass index: +0.35 vs. +0.19 kg/m^2, $p = 0.60$, and skeletal muscle mass index: +0.2 vs. −0.3 kg/m^2, $p = 0.17$, respectively). The changes in skeletal muscle mass index were significantly correlated with the LOS in the EPA group, but not in the CG ($r = 0.53$, $p = 0.008$, and $r = -0.32$, $p = 0.31$, respectively).

Question 8. Does early nutritional support (i.e. provided less than 48 h post hospital admission) compared to later nutritional support improve outcomes in polymorbid medical inpatients?

3.19. Recommendation 19

Early nutritional support (i.e. provided in less than 48 h post hospital admission) compared to later nutritional support shall be performed in polymorbid medical inpatients, as mortality and adverse events are lower and lean body mass loss could be decreased and self-sufficiency could be improved.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients are at high risk of developing DRM, so it is possible that this population could benefit from early nutritional support during hospital admission to avoid worsening of DRM with subsequent negative outcomes.

The use of early nutritional support is debated in different clinical scenarios and patient populations. From the available literature addressing this question in medical inpatient populations with confirmed polymorbidity, six studies were identified.

The previous described large EFFORT trial [8] addressed this question as the IG got their therapy initiated within 48h. By 30 days, patients in the IG experienced 21% less adverse clinical outcomes and 35% lower mortality (adjusted OR 0.65 [0.47 to 0·91], $p = 0.011$) **(Level of evidence 1++).**

In a subgroup analysis of EFFORT, patients with aging-related vulnerability receiving individualized early nutritional support compared with routine hospital food showed a >50% reduction in the risk of 30-day mortality (OR 0.48 95% CI 0.31 to 0.76; $p = 0.002$) [106]. In patients with chronic heart failure included in the EFFORT trial, Hersberger et al., 2021, reported that mortality over 30 days was 66% lower in the IG (OR 0.44 95% CI 0.26 to 0.75; $p = 0.002$) [107].

The above mentioned prospective RCT from Hegerová et al. [33] aimed to determine whether early nutritional therapy and exercise would influence the development of sarcopenia and impaired self-sufficiency during acute illness. Patients randomized to the CG received standard treatment, while in the IG ONS (600 kcal, 20 g/day protein) was added to the standard diet from day 1 of hospitalization (with a simultaneous intensive rehabilitation program). The amount of lean body mass in CG patients decreased during their hospital stay but did not change in the IG. Three months post-discharge, lean body mass was 3.5 kg lower in the CG but only 0.4 kg lower in the treated group. Lean body mass did not reach its original value even twelve months post-discharge in the CG, but it did in the IG. Regarding self-sufficiency (measured by independency in the activities of daily living through the BI, it diminished during the course of annual monitoring in both groups of patients, but the decline was sharper in the CG (**Level of evidence 1**++).

Zheng et al. [108] compared early EN (started on first day, $n = 75$) with "family managed nutrition" ($n = 71$) in a RCT of patients with acute stroke and dysphagia. The infection rate in the IG was significantly lower than that in the CG (33.3% vs. 52.1%, $p = 0.022$). Also, the IG showed a better NIHSS score than that of the CG after 21 days (12.04 ± 2.55) vs. 10.78 ± 2.69); $p = 0.008$). However, patients were admitted to the stroke unit in the IG and to the regular ward in the CG, which entails a high risk of bias (**Level of evidence 1-**).

Using a nationwide inpatient database with 432,620 eligible patients hospitalized for acute heart failure after propensity score matching, Kaneko et al. showed that delayed initiation of feeding (later than two days after admission) was associated with higher in-hospital mortality (OR 1.32, 95% CI1.26 to 1.39), longer LOS and higher incidence of pneumonia and sepsis when compared to earlier initiation of feeding (**Level of evidence 2-**) [109].

Two studies addressed budget impact analysis, performed using previously published outcomes data. Buitrago et al. in a secondary analysis applied to a Colombian population, found that average total costs over 60 days were 3770 $ for patients with delayed nutrition therapy vs. 2419 $ for patients with early nutrition therapy (started within 24–48 h of hospital admission) – a savings of 1351 $ (35.8% decrease) per nutrition-treated patient (**Level of evidence 2**++) [110]. A similar budget-impact analysis, applied to a Mexican population, reported average total healthcare costs over 30-days 3527 $ for patients with early nutrition therapy vs. 6032 $ for patients with standard nutrition therapy – a savings of 2505 $ per early nutrition-treated patient (41.5% lower). Cost differences between the groups were 2336 $ vs. 3065 $ for hospital-associated costs (23.8% lower), 262 $ vs. 780 $ for 30-day readmissions (66.4% lower) and 1348 $ for malnutrition-associated infections (**Level of evidence 2**++) [111].

Question 9. Does the continued use of nutritional support after discharge compared to nutritional support during inpatient stay alone affect the outcome of polymorbid patients?

For the present question, only interventions initiated in the hospital (and continued after discharge) were considered for inclusion. In case of doubt, authors were contacted to confirm this information.

3.20. Recommendation 20

In malnourished polymorbid medical inpatients or those at risk of malnutrition, nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients are commonly malnourished and frequently nutritional status does not improve but instead deteriorates during their hospital stay. As a result, many patients leave the hospital malnourished, or more malnourished, which increases the risk for functional decline, loss of independence and greater morbidity. Poor nutritional status is acknowledged to contribute to the recently described post hospital syndrome that represents a 30-day "generalized transient vulnerability following hospital discharge" leading to higher morbidity and an increased rate of unplanned readmissions [112]. Therefore, ensuring adequate nutritional intake during the transition from hospital to home is an important goal in malnourished patients. Systematic reviews found evidence for improved body weight and nutritional status in older patients after discharge either with individualized nutritional support [113] or intervention with ONS [114]. A recent meta-analysis also demonstrated that caloric intake but also protein intake was significantly higher in patients receiving nutritional support after hospital discharge (**Level of evidence: 1++**) [115]. Very few studies have, however, directly compared nutritional intervention in and after hospital discharge vs. nutritional support in hospital alone.

One study by Feldblum et al. which directly compared 6-month individualized nutritional support from a dietitian in hospital followed by three home visits after discharge [group 1, n = 66 (IG)] to either a single consultation with the dietitian in hospital or standard care [group 2 and 3, n = 102 (CG)], showed that continued nutritional support in malnourished patients aged ≥65 years resulted in a significantly higher change in mean MNA score, compared to the combined group 2 and 3 (3.01 ± 2.65 in the IG vs. 1.81 ± 2.97 in the CG, p = 0.004) [116] **(Level of evidence 1-).** Similarly, in a prospective RCT of 80 patients aged 75 years or more admitted for acute disease and at risk for malnutrition, a 60-day intervention with ONS which started in hospital and was continued at home or in the nursing home resulted in maintained body weight and improved MNA scores (3.01 ± 2.65 vs. 1.81 ± 2.97), p = 0.004), whereas CG patients continued to lose weight [117] **(Level of Evidence 1++).**

Similar results were obtained in other RCTs. In a RCT of malnourished hospital inpatients (n = 47 in the IG and n = 46 in the CG) by Casals et al., the intervention resulted in increased body weight (4.750 ± 5.12 kg in the IG vs. −0.903 ± 6.12) kg in the CG, p < 0.001) and improved the MUST score (−2.457 ± 1.39 in the IG vs. −1.170 ± 1.67) in the CG, p < 0.001) after six months of continued nutritional counseling by case manager nurses (frequency of visits depending on severity of malnutrition, either every month or every second month) **(Level of Evidence 1-)** [118] and similarly, in a RCT of malnourished patients (according to the MNA-SF) aged 85 ± 6 years, individualized nutritional support for four months after discharge maintained body weight in the intention-to-treat analysis (difference in mean weight from baseline to 4-month follow-up was 0.6 kg in the IG vs. −1.5 kg in the CG, p < 0.001), although a high dropout rate was reported **(Level of Evidence 1+)** [119]. A sub-analysis of the NOURISH study showed an increase in nutrient intake in IG patients without decrease in dietary intake **(Level of Evidence 1-)** [98].

3.21. Recommendation 21

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and QoL.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

Improving functional status is one of the most important goals of nutritional therapy after discharge to prevent prolonged recovery, unplanned readmissions or loss of autonomy. Functional status can be assessed by objective measures such as HGS or walking speed, or by subjective measures, for example through the use of questionnaires on mobility and physical ability. QoL is a multidimensional construct to evaluate the success of treatments which has been increasingly used in RCTs of nutritional interventions. Due to the many influencing factors on health-related QoL, sufficient sample sizes are needed and effects of nutritional therapy on QoL might depend on the subjects' age, the underlying disease or the duration of nutritional therapy.

In one RCT conducted in malnourished adults aged ≥60 years admitted to an acute hospital for medical or surgical conditions, 3-month nutritional intervention (with energy and protein rich diets, ONS and calcium + vitamin D supplements, providing 600 kcal/day and 24 g protein/day as well as 400 IU vitamin D3 and 500 mg calcium) resulted in a reduction in the number of falls (10% vs. 24%, p = 0.02) [120] **(Level of Evidence 1++)**, a significant improvement in self-reported functional limitations (mean difference −0.72, 95% CI -1.15 to −0.28) [121], and was neutral in financial cost [122] **(Level of Evidence 1++).** On the other hand, increase in QoL did not differ between IG and CG receiving standard care [122] **(Level of Evidence 1++).** In the study by Persson et al., which included older patients at risk of malnutrition (85 ± 6 years), treatment with complete or incomplete liquid supplements (providing an average intake of 60 kcals and 11.25 g protein per day) and dietary advice for four months resulted in an improvement of Katz's activities of daily living index (p < 0.001; p = 0.05 between groups), but not in QoL assessed by the SF-36 [119] **(Level of Evidence 1+).** On the other hand, Casals et al. reported significantly improved QoL scores (assessed by SF-12, with a difference between IG and CG of 13.72, p < 0.001) after six months of individualized nutritional support [118].

In younger malnourished patients (50.6 ± 16.1 years) with benign gastrointestinal or liver disease who received ONS during their hospital stay and for three months post discharge, QoL assessed by the 36-Item Short Form Health Survey questionnaire was significantly improved in the IG patients (n = 60) compared to the CG patients (n = 54) (mean improvement at three months was 0.128, 95% CI 0.095 to 0.161 in the IG vs. 0.067, 95% CI 0.031 to 0.103 in the CG) [123] **(Level of Evidence 1+).** HGS and peak expiratory flow increased after three months only in the intervention patients (grip strength improved from 26.1 ± 11.3 to 31.5 ± 10.1 kg, p < 0.0001; and peak flow from 329.2 ± 124.0 to 388.9 ± 108.4 l/min, p = 0.004) [124] **(Level of Evidence 1+).** HGS was also significantly improved in the IG of malnourished patients after three months of ONS (twice a day (one drink providing 350 kcal, 20 g protein, 1.5 g calcium-βHMB), 160 IU vitamin D and other essential micronutrients)) in the NOURISH study **(Level of Evidence 1++)** [39].

A study which used multimodal nutritional approach (dietary counselling with a nutrition plan, telephone follow ups and free samples) in older malnourished patients showed a significant improvement in the 30 s chair rise test in the IG (7.2 ± 4.3 vs. 5.3 ± 4.1), p = 0.010). The improvements in physical function were significantly higher in the IG (Δ 4.2 ± 4.4 vs. Δ 2.2 ± 2.5), p = 0.008) but clinically relevant in both groups. Regarding QoL, the Q-5D-3L VAS-score was higher in IG at the end of the study compared to the CG (IG: 61.6 ± 16.2 vs. CG: 53.3 ± 19.3, p = 0.011) with a significantly higher increase in the IG (Δ 14.3 ± 15.5 vs. Δ 5.6 ± 17.2, p = 0.002). However, the calculated Q-5D-3L scores which reflect the overall multidimensional aspect of QoL did not differ between groups **(Level of Evidence 1+)** [125].

3.22. Recommendation 22

In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention shall be considered to lower mortality.

Grade of recommendation A − Strong consensus 96% agreement.

Commentary

The effect of nutritional intervention with ONS on mortality has not been frequently studied in sufficiently sized patient cohorts. One of the largest RCTs to date (NOURISH study; n = 652 patients aged 65 years or more with medical conditions) on in- and post hospital (=continued) nutritional support reported lower 90-day mortality in the IG receiving ONS twice a day (one drink providing 350 kcal, 20 g protein, 1.5 g calcium-βHMB), 160 IU vitamin D and other essential micronutrients) for three months compared to the CG patients who received a placebo (4.8% in the IG vs. 9.7% in the CG, p = 0.018) [9] **(Level of evidence 1++)**. In the study by Feldblum et al., the IG patients (>65 years) who received individualized nutritional support from a dietitian during hospitalization and for six month after discharge (three home visits after discharge) exhibited a significantly lower mortality rate (3.8%) than the CG (vs. 11.6%, p = 0.03) at month 6 [116]. The PICNIC study of Bonilla-Palomas et al. initiated nutritional intervention in patients with heart failure at admission to hospital and continued for six months. The intervention consisted of counselling with diet optimization and ONS in case nutritional goals were not reached. At twelve months, the primary composite endpoint (all-cause mortality and readmission due to deterioration of heart failure) occurred in 27.1% of the IG compared to 60.7% of CG patients (HR 0.45, 95% CI 0.19–0.62, p = 0.0004). **(Level of evidence 1+)**. Both mortality (HR 0.37, 95% CI 0.19–0.72, p = 0.003) and readmission rates were lower in the IG patients (10.2 vs. 36.1%, p = 0.001) [126]. The benefits of the nutritional intervention persisted at 24 months, as the primary endpoint occurred more frequently in of the CG patients (73.8%) compared to in 47.5% of IG patients (HR 0.45, 95% CI 0.28–0.72; p = 0.001). Thirty-nine % of the IG had died compared to 59% of the CG (HR 0.53, 95% CI 0.31 to 0.89; p = 0.017) **(Level of evidence 1+)** [127]. These effects did not differ comparing patients with hypoalbuminemia and with normalbuminemia [128] **(Level of Evidence 1+)**.

Also, a recently published systematic review and meta-analysis [115] including a total of 2438 patients concluded that mortality was significantly lowered in patients with nutritional support which was continued after hospital discharge (OR 0.63, 95% CI 0.48 to 0.84, p = 0.001, I^2 = 1%; 13 trials). However, trial quality was deemed moderate, highlighting the need for further large-scale studies **(Level of evidence 1++)**. Another meta-analysis by the same author group including 29 studies on nutritional support in hospital as well as continued nutritional support after hospital discharge (n = 7) also showed a 30% reduction in mortality in patients from the IGs (OR 0.72 95% CI 0.57 to 0.91, p = 0.006) **(Level of evidence 1++)** [78].

Only one study studied the impact of nutritional support on long-term mortality (> one year). A secondary analysis of the three-month RCT by Neelemaat revealed no differences in mortality at year one and four between groups **(Level of evidence: 1+)** [129].

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation 22 is limited to the subgroup of polymorbid older patients. For further information regarding the nutritional care of older patients, please refer to the existing ESPEN guidelines on EN and PN for geriatric patients [75].

The present recommendations highlight the need for ongoing review or monitoring nutritional support against patient specific goals post discharge (to establish whether continuation of medical nutrition therapy is needed) and the need for good quality communication of medical nutrition therapy regimens (whether oral, EN or PN) and goals of treatment in discharge documentation.

3.23. Recommendation 23

In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention should be considered for more than two months in order to lower mortality/impact clinical course.

Grade of recommendation B − Strong consensus 100% agreement.

Commentary

The ideal duration of post discharge nutritional intervention varies in all likelihood according to patients' age, underlying disease, initial nutritional status, type of nutritional support and endpoint of interest. However, in most RCTs on intervention with ONS, the sip feeds were given for at least three months [9,120–124], whereas individualized nutritional support (which might include ONS where necessary) was usually carried out for longer periods (e.g. four months in the study by Persson et al. [119], or six months in the studies of Feldblum et al. [116], Casals et al. [118], Bonilla-Palomas et al. [126], and Yang et al. [130]. A longer duration of nutritional support might explain differences in clinical outcome. While readmission rates as an indicator of clinical course e.g. were not reduced after three months in one of the largest trials to date **(level of evidence: 1++)** [9] in geriatric patients (**level of evidence: 1+**) [131] or in older patients (**level of evidence: 1-**) [132], it was significantly reduced after six months of nutritional intervention in several trials (**level of evidence: 1-)** [116] (**level of evidence: 1+**) [130] (**level of evidence: 1++**) [126] but not all (**level of evidence: 1+**) [125]. A recent meta-analysis also showed that interventions which lasted >60 days had a stronger effect on mortality (OR 0.53 95% CI 0.38 to 0.75) than trials with shorter durations of the intervention (OR 0.85 95% CI 0.64 to 1.13, p for subgroup difference: 0.04.) Among the predictors for the success of nutritional support were high protein supplementation (OR 0.57 vs. 0.93, I^2 = 86.3%, p for heterogeneity = 0.007) and long-term nutritional interventions (OR 0.53 vs. 0.85, I^2 = 76.2%, p for heterogeneity = 0.040). However, there was no effect on readmission rates in the meta-analysis, although only one study with data on readmission was included in which nutritional support was carried out for six months (**level of evidence: 1++**) [78].

In all likelihood, a longer duration of nutritional treatment is also necessary to improve QoL in older adults [133]. Neelemaat et al. argue that while they were able to show an effect on functional limitations in their older intervention patients after three

months, the length of nutritional support might not have been sufficient to show an effect on QoL (**level of evidence: 1**+) [122] which is similar to the results in the trial of Munk et al. (**level of evidence: 1**+) [125].

Question 10. Does the monitoring of physical functions, when it is possible, compared to monitoring of nutritional parameters (e.g. body weight, energy and protein intakes), improve other outcomes in polymorbid medical inpatients receiving nutritional support?

3.24. Recommendation 24

While nutritional and functional parameters should be monitored to assess responses to nutritional support, functional indices may be more appropriate in assessing other clinical outcomes (i.e., survival, QoL) in polymorbid medical inpatients and should be used for this purpose.

Grade of recommendation B − Strong consensus 100% agreement.

Commentary

Limited evidence exists to answer this clinical question precisely. Most trials assessing the impact of nutritional support in polymorbid inpatient used nutritional and functional status as outcome rather than as monitoring tools of the efficacy of nutrition intervention in improving other outcomes.

A secondary analysis from the recent large EFFORT trial (described before) supports the use of functional parameters to monitor nutritional support but also to guide the initiation of it. Kaegi-Braun et al. illustrates in 1809 polymorbid medical inpatients at nutritional risk that individualized nutritional support was most effective in reducing mortality in patients with low HGS (adjusted OR 0.29, 95% CI, 0.10 to 0.82 in patients in the $\leq$10th percentile compared with OR 0.98, 95% CI, 0.66 to 1.48 in patients in the >10th percentile; P for interaction = 0.026). This result demonstrates the value of a low HGS in predicting response to nutritional support, which may be a useful tool in clinical practice. Furthermore, an incremental decrease of HGS by 10 kg resulted in more than doubling 30-d mortality in females and a 50% increase in 30-d mortality in males, reflecting the prognostic potential of HGS [134] (**Level of evidence 1**++).

In a cohort study from 2021 by Ballesteros-Pomar et al., 200 polymorbid medical inpatients were included. They determined the impact of low muscle mass and strength on clinical outcome and found that a higher HGS, but not muscle mass, was related to better QoL (total QoL: Beta = −0.323, p = 0.001 and QoL visual analogue scale (VAS): Beta = 0.360, p < 0.001), less readmissions (OR = 0.95, p = 0.026) and lower mortality (OR = 0.85, p = 0.014) after adjusting for age, sex, and comorbidity [135] (**Level of evidence 2**++). However, another prospective observational study failed to show a significant association between HGS and 100-day mortality [136] (**Level of evidence 2-**).

In a study from 1995, Mendehall et al. [137] studied 271 polymorbid medical inpatients with severe alcoholic hepatitis and randomly assigned to oxandrolone therapy plus a high-energy, high-protein supplement (active treatment) or placebo plus a low-energy, low protein supplement (standard treatment). During treatment, energy and protein intake increased significantly in the active treatment group vs. standard treatment (2312 kcal vs. 1495 kcal (p < 0.001) and 89 g vs. 57 g protein (p < 0.001), respectively), leading to a significantly better mid-arm muscle area (change 4.5 vs. 0.3, p = 0.02), creatinine-height index (change 18.4 vs. 2.6, p = 0.03) and % ideal body weight (change 8.1 vs. 2.3, p = 0.04). Interestingly, active treatment did not improve HGS better than standard treatment. However, when assessing the impact of nutrition intervention on 6-month mortality, Mendehall et al. reported that creatinine-height index, total lymphocyte count and HGS are the stronger predictors. This suggests that although nutrition therapy improves nutritional status and outcome (i.e., they are tools to assess the response to therapy), functional parameters are more robust prognosticators of outcome **(Level of evidence: 1-).**

Norman et al. [124] studied 80 malnourished polymorbid patients with gastrointestinal benign disease. After discharge from the hospital, patients were randomized into two groups: one group received for three months dietary counseling plus a standard ONS (IG) whereas the other group received only dietary counseling (CG group). At baseline, no difference was observed in nutritional (i.e., SGA, body composition) and functional parameters (i.e., peak flow, HGS) as well as in QoL (SF-36) between the two groups. At the end of the study, both body weight and body cell mass improved significantly in both groups. However, HGS (change from 26.1 to 31.5 kg, p < 0.0001) and peak flow (change from 329.2 to 388.9 l/min, p = 0.004) improved only in the IG. Also, all SF-36 subscales (n = 8) significantly improved in IG patients, whereas only three (physical functioning, bodily pain and vitality) improved in CG patients. Of interest, the change in HGS correlated with the change in two SF-36 physical scales (i.e., physical functioning and role physical). By applying the reasoning used for the trial by Mendehall et al., it appears that Norman et al. confirm that functional parameters may be superior to nutritional parameters in assessing other clinical outcomes in polymorbid medical inpatients receiving nutritional support **(Level of evidence: 1-).** Supporting our interpretation of the available literature, Koretz et al. [138] analyzed 99 RCTs of nutritional support vs. no nutritional support which reported at least one clinical outcome and at least one nutritional outcome. The authors' assumption was that if changes in nutritional markers predict clinical outcome, changes in both outcomes should go in the same direction. Therefore, the 99 clinical trials were assessed for concordance. The results showed that the rates of concordance were quite low and never >75%. The discordance was usually a result of the nutritional outcome being stronger than the clinical outcome. Koretz et al. concluded that based on their analysis, changes in nutritional markers do not predict clinical outcomes. More recently, Jeejeebhoy et al. [139] prospectively studied 733 patients with complete nutritional intervention data to assess which nutrition indicator better predicts LOS and readmission within 30 days after discharge. After having controlled for age, sex, and diagnosis, only SGA C and reduced food intake during the first week of hospitalization resulted as independent predictors for LOS. SGA C and HGS but not food intake were independent predictors of 30-day readmission. This study appears to suggest that nutritional parameters may serve well as monitoring tools to predict other clinical outcomes.

Question 11. Does meeting more than 75% of energy and/or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid medical inpatients receiving nutritional support?

3.25. Recommendation 25

In polymorbid medical inpatients with reduced food intake and hampered nutritional status, at least 75% of calculated energy and protein requirements shall be achieved in order to reduce the risk of adverse outcomes and mortality.

Grade of recommendation A − Strong consensus 100% agreement.

Commentary

In polymorbid medical inpatients reduced food intake is more the rule than the exception [140] and is often an important part of

the complex symptomatology that forces the patient to the hospital. Reduced food intake has several commonly occurring determinants, including anorexia, dysphagia and oral and dental problems. There are numerous studies indicating that reduced food intake is associated with increased mortality and with complications like infections in medical patients. For example, reports from the large database of the "NutritionDay" initiative demonstrate that reduced food intake during the day of food intake assessment is related to increased in-hospital mortality [141,142]. Likewise, a study on approximately 1100 recently hospital-admitted patients with mixed diagnoses showed that 16% had a food intake below 70% of calculated energy requirement [143]. This energy intake was cross-sectionally associated with an increased risk of infections; adjusted odds ratio being 2.26, 95% CI 1.24 to 4.11.

The EFFORT trial has demonstrated that reaching at least 75% of estimated energy and protein goals versus lower achievements of goals led to significant lower risk of adverse events and mortality (adjusted OR 0.79, 95% CI 0.64 to 0.97 and 0.65, 95% CI 0.47 to 0.91 [8] (**Level of evidence 1++**). Whether the impact would be more pronounced if the IG had achieved 100% of the calculated targets cannot be answered by the data. Achieving 100% of the targets should be strived for, but is usually not realistic when patients are hospitalized and have either an exacerbation of one of their conditions or a current complication. Supporting this finding in a meta-analysis from 2019, Gomes et al. [35] stratified trials by adherence to nutrition protocol and found that in trials with high adherence there was a more pronounced survival benefit (OR 0.67, 95% CI 0.54 to 0.84) compared to trials with low adherence (OR 0.88, 95% CI 0.44 to 1.76). There was also a significant higher energy intake and weight change in the subgroup of high adherence (**Level of evidence 1++).**

In a good quality prospective observational study [144] (**Level of evidence 2++),** of close to 500 polymorbid patients admitted either to a medical service or to a surgical service with mixed diagnoses, 21% had an average nutrient intake of less than 50% of calculated energy needs. Only patients with a hospital stay of more than four days were included in this study. Although baseline characteristics according to demography and diseases were quite similar, patients with reduced food intake had a higher in-hospital mortality as well as 90-day mortality with relative risks of 8.0, 95% CI 2.8 to 22.6 and 2.9, 95% CI 1.4 to 6.1, respectively.

Similar results were observed in a supportive study conducted in the critically ill population [145]. 28-day mortality was registered in a sequential series of 886 mechanically ventilated critically ill patients with both medical and surgical diagnoses, where nutrition was provided either by the enteral (73%) or enteral combined with parenteral routes (26%). The energy target was guided by IC and protein target calculated as 1.2–1.5 g/kg body weight/day. The group of patients who reached their target for both energy and protein needs had a 28-day mortality that was half that of those patients who did not achieve their target. A non-ICU trial Li et al. found nutritional intake to be higher in patients with LOS of less than twelve days compared to patients with higher LOS [21] (**Level of evidence 2-**).

However, a small sample size (n = 40) pilot RCT could not find a difference in readmissions within 30 days between the IG that reached 75% of their nutritional goals and the CG that did not [146] (**Level of evidence 1-**).

A further question is what the optimal amount of nutrition is, or what is the least dose of nutrition needed to achieve potential beneficial effects. Within nutrition support treatment plan the aim is to archive 100% of calculated needs but it has to be taken into account that an acute disease triggers inflammation and several catabolic processes in the body, which will hamper the body's capability to handle energy and protein for growth. Therefore, there is now growing evidence that 75% of calculated needs could be a goal to achieve for energy and protein intake during the hospital stay and when the disease is still in an acute catabolic phase. But also within these populations there are differences in treatment response mainly explained by severity of acute phase [147]. Consequently the question is raising if there is a need for more precise nutritional goals or nutritional therapy.

3.26. Recommendation 26

In polymorbid medical inpatients who are malnourished or at high risk of malnutrition, able to safely receive nutrition orally, and cannot tolerate or wish not to receive ONS, food fortification can be considered an effective way in order to reach relevant energy and protein targets and in improving nutritional intake.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary

There is now growing evidence that reaching 75% of energy and protein goals has a profound impact on clinical outcome as described before. To reach these goals different approaches can be used. A Danish RCT [148] tested the hypothesis that protein fortification of a novel energy dense menu supplementary to the standard hospital food service could increase the food based nutrition intake of energy and protein beyond 75% of calculated requirements **(Level of evidence 1+).** The target population was newly-admitted polymorbid medical inpatients classified as at nutritional risk by NRS 2002. The RCT was well-conducted but too small for providing any evidence on clinical outcome measures. Altogether 81 patients fulfilled the study protocol. The novel menu consisted of protein fortified small energy dense dishes that could be ordered by telephone from the hospital kitchen by the patients from 7 h to 22 h. This intervention significantly improved the energy and protein intakes and also the number of patients that reached the protein target (calculated as 18% of energy intake), i.e. 66% reached the target compared to 30% in the CG. HGS and LOS were also reported but there were no differences to be observed, as expected when the study was not powered for such end-points.

Another supportive study is a Dutch RCT [77], which used protein-enriched familiar foods and drinks (intervention products) to improve protein intake in older hospitalized polymorbid patients. More patients in the IG than in the CG (standard energy and protein rich hospital menu) reached a protein intake of 1.2 g/kg/day (79.1% vs. 47.5%, respectively). Both studies demonstrate that there are effective alternative besides ONS to improve energy and protein intake in hospitalized polymorbid patients.

Another important aspect is that provision of nutritional support via ONS is often discontinued or not well tolerated by hospitalized patients. Taste and texture preferences, limited taste variety and the fact that ONS are not always perceived as food, especially by older adults, often limit the patients' compliance [149,150]. According to a meta-analysis by Mills et al., provision of energy or protein in the form of fortified foods or supplements in food items in a population of patients in acute and rehabilitation state resulted in energy intake increased by 250–450 kcal/day and protein intake increased by 12–16 g/day. According to these results, fortification and supplementation of common food items could be considered a cost-effective, well tolerated and effective way of improving nutrient intake in older inpatients [151]. In another systematic review and meta-analysis on the effect of food fortification in older adults by Morilla-Herrera et al., positive and cost-effective results were reported in terms of dietary energy and protein intake compared to the usual care, but the need of higher quality studies was stressed out [152]. Moreover, studies on the effect on food fortification vs. ONS in hospitalized patients could also be of interest.

Question 12. Do organizational changes in nutritional support (e.g. intervention of a steering committee, implementation of protected mealtimes, different budget allocation) versus no changes improve outcomes of polymorbid medical inpatients?

3.27. Recommendation 27

Organizational changes in nutrition support provision like enriched menus should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition to improve intake and nutritional outcome.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

The organization of nutritional support in hospitals requires a multi-disciplinary approach involving finance, catering, nursing and therapy services. Some general studies have suggested that changes to the organization of nutritional support for in-patients may improve outcomes. These include the use of nutritional healthcare assistants [153], targeted education for dietitians and the MDT to improve early use of ONS [154], food fortification [155], introduction of a nutrition screening tool [156] and technological innovations used at an organizational level to facilitate timely referral to the Nutrition Support Team (NST) [157].

Despite these interesting studies in non-polymorbid patients, a systematic review of non-randomized studies showed that improvements are not consistently demonstrated [158]. Therefore, it is important to consider the specific impact of organizational changes on polymorbid medical inpatients. A single-blinded RCT [148] demonstrated how the use of a protein fortified menu was effective in increasing the protein intake of patients. The IG was able to choose from a protein enriched menu in addition to the standard hospital menu. The CG received the standard hospital menu. There was no significant difference in energy intake, LOS or HGS between groups. However, mean protein intake was significantly increased in the IG; with 27/41 compared to 12/40 in the CG meeting ≥75% protein requirements ($p = 0.001$). **(Level of Evidence 1+).**

A pilot, controlled trial in older patients ($n = 122$) on a subacute ward compared a modified hospital menu, including higher energy and protein choices, to the standard hospital menu [159]. Patients were allocated to IG or CG depending on their room, with the rooms on one side of the ward receiving the intervention and the other side receiving the control. Measures were taken at baseline and after 14 days. Data were missing for 41.1% of patients on day 14. In those with complete data, there was no difference in patients' weight, HGS, functional independence measure or LOS. However, energy (1725 kcal/day vs. 1863 kcal/day, $p = 0.21$) and protein (76 g/day vs. 80 g/day, $p = 0.59$) intake were higher in the IG. This increase was statistically significant when adjusted for weight ($p = 0.03$ for protein, $p = 0.003$ for energy intake) **(Level of evidence 1-)**.

A further, prospective controlled trial [160] involving 298 polymorbid geriatric inpatients, demonstrated the use of an early multi-disciplinary intervention protocol including activities such as nutrition and dysphagia screening, patient positioning and individualizing time of meals. This was compared to standard care in the management of older patients at high risk of protein energy malnutrition across two sites. A significant weight gain (mean + 0.9 kg) was observed in the IG, whereas a weight loss (mean −0.8 kg) was observed in the CG, during admission. Mean LOS was approximately 32 days in both groups. In addition, the IG developed fewer hospital acquired infections (33/140 compared to 58/158, $p = 0.01$). There was no statistically significant difference in the development of pressure ulcers or LOS **(Level of Evidence 2+).**

3.28. Recommendation 28

Organizational changes, particularly the establishment of a NST and the use of multidisciplinary nutrition protocols, should be implemented in polymorbid medical inpatients at risk for malnutrition.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

Several observational studies have considered the effect of introducing broad organizational changes. A cohort study involving 207 adult acute medical patients reported the impact of multiple nutrition improvement initiatives on a one-day record of intake of estimated energy and protein requirements (>75% of requirements) [161]. Initiatives included a magnetic traffic light symbol above the patients' bed to identify nutritional risk, tailored education for nursing, medical and food service staff, and menu changes to include a full and hot breakfast option. Breakfast service was moved to an earlier time to avoid interruptions from ward rounds and clinical interventions. The number of patients achieving adequate energy and protein intake increased significantly from pre-intervention to post-interventional. It is suggested that this increase in intake was primarily a consequence of introducing the hot breakfast option **(Level of Evidence 2+).**

Young et al., reported the implementation of nutrition improvement initiatives over a seven-year period on three medical wards [162]. The primary outcome was energy and protein intake observed on a single day between day three and seven of the patients' admission. Phased initiatives included the introduction of assisted mealtimes, an assistant in nursing to assist with nutrition administration/feeding assistance and additional education for nurses, dietitians and the wider MDT. Results showed a significant difference in energy intake between cohorts (cohort 1: 1212 kcal/day (SD 442), cohort 2: 1291 kcal/day (SD 538), cohort 3: 1431 kcal/day (SD 625), $p = 0.04$). Protein intake increased significantly in each successive cohort (+48 g/day (SD 19), +50 g/day (SD 21) and+57 g/day (SD 26) respectively, $p = 0.02$). These three studies suggest that a combination of organizational changes may be sustained over a period of time and culminate in improved dietary intake **(Level of Evidence 2+).**

In another mealtime assistant study, trained volunteers assisted patients for one year [163]. Volunteers received a half-day training, and provided mealtime assistance at weekday lunchtimes to patients who were identified to need help by a nurse. The authors reported their intervention to potentially release time for nursing staff but, however, found no positive effect on dietary intake **(Level of Evidence 1+)**.

In terms of artificial nutritional support, a cohort study [164] demonstrated the impact of an NST on the management of patients requiring, or referred for, PN. After a structured training program for nurses led by the NST, catheter-related sepsis rates decreased in PN patients from 71% pre-NST to 29% in their first year ($p = 0.05$). Additionally, 55 episodes of PN (41% of referrals) were avoided by appropriate NST assessment and rapid instigation of enteral feeding **(Level of Evidence 2+)**.

Where a controlled trial found no difference in the energy or protein intake of older female patients with the implementation of mealtime volunteers, volunteers were as effective as ward nursing staff in providing appropriate feeding assistance. This suggests that mealtime volunteers may be successfully implemented to release nursing staff to carry out other clinical tasks [161] **(Level of Evidence 1+).**

Thus, the evidence shows that organizational changes in nutritional support provision can improve energy and protein intake and reduce the risk of adverse outcomes in polymorbid medical

inpatients. The use of conceptual frameworks to implement changes has been successful in some studies [161,162].

Question 13. Does underlying disease have an impact on expected outcome from nutritional support?

3.29. Recommendation 29

The severity of acute-phase response should be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary

There is growing evidence that type of underlying disease, severity of disease and extend of the acute-phase reaction have an impact on the effect of nutrition therapy [165]. Thereby, inflammation is a key factor with several important metabolic effects on a cellular level (e.g., increase in insulin resistance leading to an inhibition of nutrition entering cells) and on different organs such as the brain (e.g., causing disease-related anorexia and reduced food intake), the intestines and on muscle (e.g., causing catabolism and sarcopenia). Interestingly, recent data also suggest that inflammation modulates the response to nutritional treatment. A double-blind randomized trial of nutritional supplementation published [166] by Gariballa et al., in 2006, including 445 polymorbid patients, concluded that the acute-phase response was strongly associated with poor nutritional status and worse clinical outcomes, particularly in older patients (**Level of evidence: 1**++). There are also studies showing that patients with high inflammation do not show a positive response to nutritional interventions while patients with lower levels of inflammation did. A secondary analysis of the multicentre randomized-controlled EFFORT trial suggested that patients with CRP levels of ≥100 mg/l no longer responded to nutritional therapy, while patients with lower levels had a significant mortality benefit from nutritional support [147] (**Level of evidence: 1**++). A similar association was also found for cancer patients, with a significantly extenuated response to nutrition in patients with high inflammation [167]. These findings may also explain differences in results of nutritional trials, depending on the clinical setting with several nutritional studies in the ICU setting or in patients with advanced cancer not showing significant benefits form nutrition in regard to clinical outcomes [165,168]. Clearly, there is need for additional research to confirm the relationship between acute-phase response, expected outcome and response to nutritional support to understand the optimal timing and composition of nutritional therapy in an individual patient, based on the acuity of illness and the metabolic stress.

3.30. Recommendation 30

Underlying disease modifies the effect of nutritional therapy and should be considered when initiating nutritional support.

Grade of recommendation B – Strong consensus 92% agreement.

Commentary

There is strong evidence from large RCTs that polymorbid patients at risk for malnutrition benefit from nutritional support [36]. In a population-based cohort study of more than 110,000 patients, effect of nutritional support remained robust in subgroup analyses which stratified for main diagnoses and comorbidities, among others [169] (**Level of evidence: 2-**). However, among medical patients, the effect of nutritional support may also depend on underlying disease. Characterisation of the polymorbid patient may therefore help to provide optimal nutritional care. Still, understanding the interplay of different chronic and acute diseases is challenging and needs further research. Mudge et al. identified diagnosis of infection or cancer to be associated with inadequate energy intake in patients aged 65 years or older [170] (**Level of evidence: 2**++). A recent study by Bargetzi et al. found that kidney disease predicted response to nutritional treatment with lower estimated glomerular filtration rates [eGFR] showing stronger clinical benefit [89] (**Level of evidence: 1**++). Similarly, patients with chronic heart failure have shown strong benefit from nutritional support. A survival benefit in chronic heart failure patients receiving nutritional support was found in a Spanish trial by Bonilla-Palomas et al. with 120 patients [126] (**Level of evidence: 1**++) and in secondary analysis of 645 patients from a randomized trial by Hersberger et al. [107] (**Level of evidence: 1**++). Similar results were also found within the NOURISH study with a significant survival benefit associated with nutritional support [9] (**Level of evidence: 1**++). Other conditions which may increase the effects of nutritional support are cancer [171], COPD [39] among others. However it remains unclear how to implement these findings into clinical routine.

Question 14. Are there risks of polypharmacy and drug–nutrient interaction in polymorbid medical inpatients?

3.31. Recommendation 31

In polymorbid medical inpatients there is an important possibility of drug–drug or drug–nutrient interactions that needs to be taken into account, therefore, a pharmacist-assisted management plan for any interactions should be established.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary

Polymorbid medical inpatients will often require the prescription of multiple medicines in order to manage their comorbidities. Whilst the use of multiple medicines is often essential, it can present a number of risks that include potential 'drug–drug' and/or 'drug-nutrient' interactions. Indeed, as the number of medicines required increases so does the risk of these interactions as well as the risk of potential effects on nutritional status. For example, a systematic review of polypharmacy defined as ≥5 medicines in subjects ≥65 years of age was significantly associated with malnutrition [172], and polypharmacy when defined as >10 medicines was associated with an increased risk of malnutrition after three years in those >75 years [173]. Polypharmacy has been associated with sarcopenia [174], which could result in insufficiency of some electrolytes or micronutrients [175]. A recent meta-analysis from 2023, which included 29 studies, demonstrated that sarcopenia is associated with a higher prevalence of polypharmacy (OR: 1.65 [1.23, 2.20], $p < 0.01$) and higher number of medications (mean difference: 1.39, 95% CI 0.59 to 2.19, $I^2 = 95\%$, $p < 0.01$) compared with individuals without sarcopenia [176]. Side effects of medicines affecting body systems are described by Yoshimura et al. [177]. Such adverse effects from medicines on body systems could affect the status of specific types of nutrients. Doses of medicines may need to be adjusted or other changes to the clinical management and monitoring of patients may be necessary, with examples including patients with comorbidities in addition to human immunodeficiency virus infection [178,179] or psoriasis [180]. It is, however, important that care is taken to not only consider interactions that may be more familiar. For example, many healthcare professionals are familiar with the physical binding of drugs such as tetracyclines to the divalent and trivalent cations found in milk or antacid preparations [181] or in many of the ONS and enteral formulas, which limits absorption from the gastrointestinal tract.

Fewer are likely to be familiar with the potential for physical binding of ceftriaxone to calcium salts when each is given intravenously [182] or that hydration status, which is for example commonly impaired in acute medical admissions [183], can affect drug enrichment [184]. A holistic approach to assessment of hydration status of older people rather than the use of some individual tests may be necessary [185]. It is also important that care is taken to not only account for dietary intake but also oral fluid intake when considering potential drug–nutrient interactions. This is because whilst drugs such as simvastatin have no specific requirement to be taken with or without food it has the potential to be toxic when taken concurrently with grapefruit juice [186]. A description of pharmacokinetic interactions between food and drugs is available [187]. Advice on the complexities of all these potential interactions in polymorbid medical inpatients may be obtained from a pharmacist or a pharmacologist. We suggest that a review of medication is undertaken to identify unnecessary medications or medications that have side-effects which may compromise nutritional intake.

In summary, while some of the recommendations for screening, assessment and provision of nutritional support in polymorbid medical inpatients may not differ significantly from those recommendations applicable to single-disease patients, we have identified certain aspects of these patients' care that require particular attention, such as the identification of drug–drug or drug–nutrient interactions and the importance of continuing nutritional support after hospital discharge.

One of the strengths of this study was the conduct of the literature searches for all the clinical questions by a single author, which allowed the use of a systematic methodology to identify potentially relevant publications. This is particularly important for the present guidelines because, when compared to disease-specific guidelines, the methodology used for the identification of potentially relevant studies was more complex, as many of the published studies did not report data on the presence of multiple comorbidities or did not use typical key terms for this purpose. Additionally, there are no MeSH terms dedicated to multiple chronic conditions [3]. Consequently, we have not used search terms to define polymorbidity during the literature searches; instead we used different strategies to identify studies conducted in polymorbid populations, including the contact of authors to obtain further information on the presence of multiple comorbidities. In this context, we would encourage all authors of future trials to report data on polymorbidity.

Furthermore, due to the complex nature of the needs of polymorbid medical inpatients, we would encourage access to dietetic expertise to assess, manage and monitor nutritional status and nutritional intervention, whenever possible. Community-based approaches are also encouraged for the non-hospitalized polymorbid patients at nutritional risk, allowing for prevention (of the deterioration of their nutritional status) and an early intervention.

Question 15. Are there nutritional biomarkers that predict the response to nutritional treatment?

3.32. Recommendation 32

Specific nutritional biomarkers can be used to predict the response to nutritional support in polymorbid medical inpatients and therefore may help to personalize nutritional treatments.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary

Finding specific nutritional biomarkers to predict the response to nutritional treatment is an emerging field in clinical research. Several studies and secondary analyses of trials within the polymorbid medical inpatient population have found that markers of inflammation, muscle strength, kidney function among others may help to further individualize treatment [165]. This concept of "personalized" nutrition is based on the observation that not all patients show the same response to nutritional interventions. For example, it has been known for long that patients with cachexia may show less response compared to patients with less severe stages or phenotypes of malnutrition [165,188]. There are several other factors and conditions which may predict whether or not a patient benefits from nutritional therapy including illness-specific factors (comorbidities, inflammation, acute vs. chronic course) or patient-specific factors (age, gender and genetic vulnerability).

While there are several biomarkers that have been proposed historically based on pathophysiological considerations (e.g., transthyretin, albumin, retinal-binding globulin) [189], only few have really been subject to rigorous scientific evaluation. Markers of inflammation (i.e. C-reactive protein [CRP]) have been shown to correlate with disease-related anorexia, reduced food intake and muscle catabolism, and at the same predict lack of response to nutritional treatment [147,190,191]. In a secondary analysis of EFFORT, unlike patients with lower CRP concentrations ($\leq$100 mg/L), patients with high inflammation (defined as CRP level >100 mg/L) did not respond to nutritional support [147] **(Level of evidence 1++).** Similarly, markers of chronic kidney dysfunction (i.e., creatinine) are associated with renal cachexia and weight loss, but patients with reduced kidney function show a particularly stronger response to nutritional treatment [8] **(Level of evidence 1++)**. Albumin and prealbumin levels also have a strong prognostic value, but little correlation with nutritional response [192,193] **(both Level of evidence 1++).**There are several studies looking at biomarkers of muscle strength and/or function with some suggesting that low muscle strength measured by HGS is a predictor for response [134] **(Level of evidence 1++)** while others found sarcopenia to be a predictor of non-response in mixed populations [165,188].

There are also efforts to find certain metabolites as biomarkers to predict treatment response. In a secondary analysis of the EFFORT trial from 2022, Struja et al. used an untargeted proteomics approach to find predictive and prognostic metabolites. They concluded, due to high heterogeneity and small sample size, that so far the metabolites had only little prognostic and therapeutic potential for phenotyping the risk of malnutrition and response to nutritional therapy [194] **(Level of evidence 1++)**. Until now there are no studies using a targeted proteomics approach.

Currently, no specific blood biomarkers of treatment response are used in routine clinical care apart from physiological nutritional markers such as weight and weight-loss, appetite among others although data from large RCTs suggest that their use might be advantageous. Thus, there is need for additional validation of results before wide-spread use in clinical routine.

4. Conclusions

This guideline provides 32 practical and non-disease specific recommendations to guide clinicians treating polymorbid patients. Recent high-quality RCTS have provided increasing evidence that nutritional support can reduce morbidity and other complications, which is reflected by several A and B recommendations. The practical recommendations cover the most relevant aspects of nutrition support (screening, assessment, nutritional requirements, monitoring and procedure of intervention) and provide a glimpse into the future, where individualization of nutritional therapy will become increasingly important. Nevertheless this work also allowed gaps in the literature (areas with little or no evidence) to be identified which require further research.

Funding

This work was supported by the ESPEN society as well as by the Swiss National Science Foundation (SNSF Professorship, PP00 P3_150531/1) and the Research Council of the Kantonsspital Aarau, Switzerland (1410.000.044).

Disclaimer

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Conflict of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict-of-interest forms are stored at the ESPEN guideline office and can be reviewed with legitimate interest upon request to the ESPEN executive.

Acknowledgements

We thank the ESPEN committees (namely Stephan Bischoff and Anna Schweinlin) for the continuous support during the whole process of updating current guideline.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.06.023.

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3.1.3 ESPEN practical guideline: nutritional support for polymorbid medical inpatients [92]

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CW, FG, SB and PS designed the research. CW drafted the practical algorithms. CW wrote the paper. PS, CW, FG, and SB had primary responsibility for final content, including introduction and discussion. PS and SB were responsible for resources, supervision, and funding acquisition. All authors read, revised, and approved the final version of the manuscript.

Clinical Nutrition 43 (2024) 674–691

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN practical guideline: Nutritional support for polymorbid medical inpatients

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ARTICLE INFO

Article history:
Received 3 January 2024
Accepted 9 January 2024

Keywords:
Guideline
Polymorbid
Multimorbidity
Nutritional support
Hospitalized patients

SUMMARY

Background: Disease-related malnutrition in polymorbid medical inpatients is a highly prevalent syndrome associated with significantly increased morbidity, disability, short- and long-term mortality, impaired recovery from illness, and healthcare costs.
Aim: As there are uncertainties in applying disease-specific guidelines to patients with multiple conditions, our aim was to provide evidence-based recommendations on nutritional support for the polymorbid patient population hospitalized in medical wards.
Methods: The 2023 update adheres to the standard operating procedures for ESPEN guidelines. We undertook a systematic literature search for 15 clinical questions in three different databases (Medline, Embase and the Cochrane Library), as well as in secondary sources (e.g., published guidelines), until July 12th, 2022. Retrieved abstracts were screened to identify relevant studies that were used to develop recommendations (including SIGN grading), which was followed by submission to Delphi voting. Here, the practical version of the guideline is presented which has been shortened and equipped with flow charts for patients care.
Results: 32 recommendations (7× A, 11× B, 10× O and 4× GPP), which encompass different aspects of nutritional support were included from the scientific guideline including indication, route of feeding, energy and protein requirements, micronutrient requirements, disease-specific nutrients, timing, monitoring and procedure of intervention. Here, the practical version of the guideline is presented which has been shortened and equipped with flow charts for patients care.
Conclusions: Recent high-quality trials have provided increasing evidence that nutritional support can reduce morbidity and other complications associated with malnutrition in polymorbid patients. The timely screening of patients for risk of malnutrition at hospital admission followed by individualized nutritional support interventions for at-risk patients should be part of routine clinical care and multimodal treatment in hospitals worldwide. Use of this updated practical guideline offers an evidence-based nutritional approach to polymorbid medical inpatients and may improve their outcomes.

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https://doi.org/10.1016/j.clnu.2024.01.008
0261-5614/

Abbreviations

BI	Barthel Index
βHMB	β-hydroxy β-methylbutyrate
CG	Control Group
DRM	Disease-Related Malnutrition
EN	Enteral Nutrition
GLIM	Global Leadership Initiative on Malnutrition
HGS	Handgrip strength
IC	Indirect Calorimetry
IG	Intervention Group
LOS	Length Of hospital Stay
MDT	multidisciplinary team
MNA(-SF)	Mini Nutritional Assessment (Short Form)
MUST	Malnutrition Universal Screening Tool
NRS 2002	Nutritional Risk Screening 2002
NST	Nutrition Support Team
ONS	Oral Nutritional Supplement(s)
PICO	Population of interest, Interventions, Comparisons, Outcomes
PN	Parenteral Nutrition
QoL	Quality Of Life
REE	Resting Energy Expenditure
RCT	Randomized Controlled Trial
SF-12	1 Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
SGA	Subjective Global Assessment
SIGN	Scottish Intercollegiate Guidelines Network
SNAQ	Short Nutritional Assessment Questionnaire
TEE	Total Energy Expenditure
WG	Working Group

1. Introduction

As life expectancy increases and individuals acquire a variety of chronic illnesses, polymorbidity is becoming one of the greatest challenges facing many health services worldwide. Although there is no universally accepted definition of polymorbidity, some authors define it as being the co-occurrence of at least two chronic health conditions in the same person [1,2]. Lefevre et al. stated, "*we know, for example, how to educate a diabetic patient, a chronic bronchitis patient, and a hypertensive patient, but we do not know, in practical terms, how to educate a patient with all three diseases*" [3]. In this context, the current single-disease healthcare approach has been challenged [4]. Yet, recent large randomized controlled trials (RCT) have provided important new evidence showing that nutritional support can reduce morbidity and other complications in polymorbid patients. Therefore, there is a need for an up-to-date, evidence-based consensus on how to provide nutritional support for the polymorbid medical inpatient population and to strengthen recommendations that now have a solid evidence base for clinician decision making [5,6].

This guideline provides 32 practical and non-disease specific recommendations to guide clinicians treating polymorbid patients (flowchart overview, see Supplementary Fig. 1 and Table 1). Recent high-quality randomized controlled trials have provided increasing evidence that nutritional support can reduce morbidity and other complications, which is reflected by several A and B recommendation grades. The practical recommendations cover the most relevant aspects of nutrition support (screening, assessment, nutritional requirements, monitoring, and procedure of intervention) and provide a glimpse into the future, where individualization of nutritional therapy will become increasingly important. Nevertheless, this work also allowed gaps in the literature (areas with little or no evidence) to be identified which require further research.

2. Materials and methods

2.1. General methodology

The present practical guideline consists of 32 recommendations, it is based on the ESPEN guideline on nutritional support for polymorbid medical inpatients [7]. The original guideline was shortened by focusing the commentaries on the evidence and literature on which the recommendations are based on. The recommendations were not changed, but the presentation of the content was transformed into a graphical presentation. The original guideline was developed according to the standard operating procedure for ESPEN guidelines and consensus papers [8].

A comprehensive literature search was performed in July 2022. The search strategies used are presented the original guideline [9]. Existing evidence was graded according to the SIGN (Scottish Intercollegiate Guidelines Network) grading system. Recommendations were developed and graded into four classes (A/B/0/GPP) [10].

All recommendations were agreed in a multistage consensus process, which resulted in a percentage of agreement (%). The guideline process was funded both by ESPEN. For further details on methodology, see the full version of the ESPEN guideline [9] and the ESPEN standard operating procedure [8].

2.2. Pragmatic definition of polymorbidity for the current project

This guideline is based on clinical trials that investigate the effects of nutritional support on different outcomes. Because these population-based trials usually report an average number of comorbidities or number of drugs/medications, a pragmatic definition of the polymorbid medical inpatient population was established and does not differ from the original guideline:

- at least two co-occurring chronic diseases present in at least 50 % of the study population (in a few of the studies it is stated that x% of the study population suffers from disease A, y% of the study population suffers from disease B, and so on)

or, alternatively.

- a Charlson comorbidity index in the study population >1.5
- a mean number of diseases or drugs (medications) > 1.5

Full list of inclusion and exclusion criteria can be found in Table 2.

Table 1
Overview of covered topics and recommendations.

Topics	Recommendations
Screening for malnutrition risk and personalizing nutritional support	Recommendation 1 In polymorbid medical inpatients, a quick and simple nutritional screening method using a validated tool should be applied to identify malnutrition risk. Grade of recommendation B, Strong consensus 97 % agreement Recommendation 2 In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to allow an early adequate nutritional therapy and to define quality outcome measures. B, 97 % Recommendation 3 The severity of acute-phase response should be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention. B, 100 % Recommendation 4 Specific nutritional biomarkers can be used to predict the response to nutritional support in polymorbid medical inpatients and therefore may help to personalize nutritional treatments. 0, 100 %
Nutritional support plan	**Definition of nutritional targets** **Energy/caloric target** Recommendation 5 Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula, although the accuracy of prediction equations in this population is low. 0, 100 % Recommendation 6 In the absence of IC, total energy expenditure (TEE) for polymorbid older patients (aged ≥65 years) can be estimated at approximately 27 kcal/kg actual body weight/day. REE can be estimated at 18–20 kcal/kg actual body weight/day with the addition of activity or stress factors to estimate TEE. 0, 100 % Recommendation 7 In the absence of IC, resting energy expenditure (REE) for severely underweight patients can be estimated at 30 kcal/kg actual body weight. 0, 96 % Recommendation 8 This target of 30 kcal/kg actual body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome. GPP, 100 % **Protein target** Recommendation 9 Polymorbid medical inpatients requiring nutritional support shall receive 1.1.5 g protein/kg of body weight per day as a cost-effective and highly efficient measure to prevent body weight loss, to reduce complications, to improve functional outcome and quality of life. A, 100 % Recommendation 10 For polymorbid medical inpatients at nutritional risk with impaired kidney function (eGFR <30 ml/min/1.73m2) who are not on kidney replacement therapy, a low amount of protein of 0.8 g protein/kg body weight/day should be targeted. B, 96 % **Micronutrient target** Recommendation 11 In polymorbid medical inpatients exclusively fed orally, an adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured. GPP, 100 % Recommendation 12 In polymorbid medical inpatients exclusively fed orally, documented or suspected micronutrient deficiencies should be repleted. GPP, 96 % **Other specific targets** Recommendation 13 In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and βHMB can be added to oral/enteral feeds to accelerate the healing of pressure ulcers. 0, 92 % Recommendation 14 In polymorbid medical older inpatients requiring EN, EN formulas enriched in a mixture of soluble and insoluble fibers can be used to improve bowel function. 0, 96 % Recommendation 15 We cannot recommend the use of other disease-specific nutritional supplementation in polymorbid medical inpatients. 0, 100 %
Initiation of nutritional support	Recommendation 16 In polymorbid medical inpatients with reduced food intake and hampered nutritional status, at least 75 % of calculated energy and protein requirements shall be achieved in order to reduce the risk of adverse outcomes and mortality. A, 100 % Recommendation 17 Early nutritional support (i.e. provided in less than 48 h post hospital admission) compared to later nutritional support shall be performed in polymorbid medical inpatients, as mortality and adverse events are lower and lean body mass loss could be decreased and self-sufficiency could be improved. A, 100 % Recommendation 18 Underlying disease modifies the effect of nutritional therapy and should be considered when initiating nutritional support. B, 92 % **Oral Nutrition** Recommendation 19 In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely receive oral nutrition, individualized provision of nutritional support via oral nutritional supplements (ONS) to reach energy and protein requirements shall be offered to improve their nutritional status, QoL and overall survival. A, 100 % Recommendation 20 In malnourished polymorbid medical inpatients or those at high risk of malnutrition, high protein nutrient specific ONS should be administered, when they may help maintain functional status and muscle mass, reduce mortality and improve QoL. B, 96 % Recommendation 21 In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely receive nutrition orally, ONS shall be offered as a cost-effective way of intervention towards improved outcomes. A, 100 % Recommendation 22 In polymorbid medical inpatients who are malnourished or at high risk of malnutrition, able to safely receive nutrition orally, and cannot tolerate or wish not to receive ONS, food fortification can be

Table 1 (*continued*)

Topics	Recommendations
	considered an effective way in order to reach relevant energy and protein targets and in improving nutritional intake. 0, 100 % **Enteral and parenteral nutrition** Recommendation 23 In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN before PN can be administered to ensure reaching nutritional goals. 0, 100 % Recommendation 24 In polymorbid medical inpatients whose nutritional requirements cannot be met orally, the use of EN may be superior to PN because of a lower risk of infectious, non-infectious complications and maintenance of gut integrity. 0, 100 %
Monitoring and continuation post-discharge	**Monitoring** Recommendation 25 While nutritional and functional parameters should be monitored to assess responses to nutritional support, functional indices may be more appropriate in assessing other clinical outcomes (i.e., survival, quality of life) in polymorbid medical inpatients and should be used for this purpose. B, 100 % Recommendation 26 In polymorbid medical inpatients there is an important possibility of drug–drug or drug–nutrient interactions that needs to be taken into account, therefore, a pharmacist-assisted management plan for any interactions should be established. GPP, 100 % **Continuation of nutritional support** Recommendation 27 In malnourished polymorbid medical inpatients or those at risk of malnutrition, nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status. A, 100 % Recommendation 28 In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and quality of life. B, 100 % Recommendation 29 In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention shall be considered to lower mortality. A, 96 % Recommendation 30 In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention should be considered for more than two months in order to lower mortality/impact clinical course. B, 100 % **Organizational changes** Recommendation 31 Organizational changes in nutrition support provision like enriched menus should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition to improve intake and nutritional outcome. B, 100 % Recommendation 32 Organizational changes, particularly the establishment

(*continued on next page*)

Table 1 (*continued*)

Topics	Recommendations
	of a nutrition support team and the use of multidisciplinary nutrition protocols, should be implemented in polymorbid medical inpatients at risk for malnutrition. B, 100 %

ONS, oral nutritional supplements; EN, enteral nutrition; PN, parenteral nutrition; IC, indirect calorimetry; TEE, total energy expenditure; REE, resting energy expenditure; eGFR, estimated glomerular filtration rate; BCAA, branched chain amino acids, βHMB, beta-hydroxy-beta-methylbutyrat.

3. Results

3.1. Screening for malnutrition risk (Fig. 1, Fig. 2)

1) **In polymorbid medical inpatients, a quick and simple nutritional screening method using a validated tool should be applied to identify malnutrition risk.**

(R1, Grade B, Strong consensus 97 %)
Commentary

Polymorbid medical inpatients are at high risk of malnutrition. Several prospective cohort studies showed a prevalence of approximately 40–50 % in a hospitalized population of tertiary centers [11,12]. In a prospective observational cohort study, Lengfelder et al. were able to show higher odds for malnourished patients having a LOS of ≥3 days (2.38, 95 % CI, 1.45 to 3.88; $p < 0.001$) and for readmission within 30 days (2.28, 95 % CI, 1.26 to 4.12; $p < 0.006$) [13]. The same effect was shown by Li et al. in patients with community acquired pneumonia [14]. The latter also showed a significant increase in the prevalence of nutritional risk measured by the Nutritional Risk Screening 2002 (NRS 2002) within two weeks after admission (40.61 % vs. 48.93 %; $p = 0.036$).

Scoring systems for determining nutritional risk, such as NRS 2002 and the Mini Nutritional Assessment Short-Form (MNA-SF) link nutritional risk assessment to treatment by predicting that nutritional interventions will have a positive influence on variable outcomes [15–18]. Both of these tools are rapid, easily undertaken and show a high degree of content validity and reliability, thereby making them suitable in polymorbid medical inpatients including those patients with cognitive dysfunction [19,20].

2) **In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to allow an early adequate nutritional therapy and to define quality outcome measures.**

(R2, Grade B, Strong consensus 97 %)
Commentary

If patients screen positive, diagnosis should be established according to GLIM criteria – the Global Leadership Initiative on Malnutrition (GLIM) proposes a two-step approach for the malnutrition diagnosis, which includes a validated screening and second, a detailed assessment with phenotypic and etiologic criteria for diagnosis and grading the severity of malnutrition [21]. This guideline did not focus specifically on the assessment and diagnosis with GLIM criteria in polymorbid medical inpatients but generally on assessments to identify pathogenic factors which should be used to develop a treatment plan.

In a controlled trial, Rypkema et al. demonstrated that a standardized, early nutritional intervention in older polymorbid medical inpatients at nutritional risk, determined by the MNA-SF, is effective and does not significantly increase hospital costs. The

Table 2
Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Patients characteristics	- Human adults aged ≥18 years	- Non human, ≤18 years, pregnant women
	- Patients hospitalized in acute care wards	- Patients admitted to critical/intensive care units - Surgical patients - Patients living on long-term care facilities - Outpatients - Patients receiving end of life care
	- Polymorbid inpatient population as defined by a) at least two co-occurring chronic diseases are present in at least 50 % of the study population Or b) mean number of diseases or drugs/medication or the Charlson comorbidity index in the study population as being more than 1.5 In case of uncertainties about the way comorbidities are reported, the trials' authors are contacted in to obtain more information; if contact is not possible, the WG makes a consensus decision about the inclusion/exclusion of the studies.	- Healthy population - Less than 50 % of the study population has two co-occurring diseases
Outcomes	Nutritional outcomes (e.g. weight, energy and protein intake) Clinical outcomes (e.g. mortality, infections) Patient-centered outcomes (e.g. quality of life) Healthcare resources use	
Language and year	English; no restriction on publication year	

intervention resulted in both a more pronounced weight gain (0.92 ± 0.27 kg in the IG (IG) vs. −0.76 ± 0.28 kg in the CG, $p < 0.001$) and a significant lower rate of nosocomial infections (23.6 % vs. 36.7 %, $p = 0.01$) [22].

In a prospective, non-randomized cohort study, Jie et al. found nutritional support was beneficial for polymorbid medical inpatients at nutritional risk as defined by the NRS 2002 [12]. The overall complication rate was significantly lower in the group with nutritional therapy than in the no-support group (20.3 % vs. 28.1 %, $p = 0.009$), primarily because of the lower rate of infectious complications (10.5 % vs. 18.9 %, $p < 0.001$). These effects were robust after multivariate adjustment.

3.1.1. Individualizing nutritional support

3) **The severity of acute-phase response should be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention.**

(R29, Grade B, Strong consensus 100 %)
Commentary

Inflammation is a key factor with several important metabolic effects on a cellular level (e.g., increase in insulin resistance leading to an inhibition of nutrition entering cells) and on different organs such as the brain (e.g., causing disease-related anorexia and reduced food intake), the intestines and on muscle (e.g., causing catabolism and sarcopenia) [23]. A double-blind randomized trial of nutritional supplementation published [24] by Gariballa et al., in 2006, including 445 polymorbid patients, concluded that the acute-phase response was strongly associated with poor nutritional status and worse clinical outcomes, particularly in older patients. Interestingly, recent data also suggest that inflammation modulates the response to nutritional treatment. A secondary analysis of EFFORT suggested that patients with CRP levels of ≥100 mg/L no longer responded to nutritional therapy, while patients with lower levels had a significant mortality benefit from nutritional support [25]. A similar association was also found for cancer patients, with a significantly extenuated response to nutrition in patients with high inflammation [26]. These findings may also explain differences in results of nutritional trials, depending on the clinical setting with several nutritional studies in the ICU setting or in patients with advanced cancer not showing significant benefits form nutrition in regard to clinical outcomes [23,27].

4) **Specific nutritional biomarkers can be used to predict the response to nutritional support in polymorbid medical inpatients and therefore may help to personalize nutritional treatments.**

(R32, Grade 0, Strong consensus 100 %)
Commentary

Finding specific nutritional biomarkers to predict the response to nutritional treatment is an emerging field in clinical research as not all patients show the same benefit from nutritional interventions [23] (e.g. patients with cachexia may show less response [23,28]).

Markers of inflammation have been shown to correlate with several malnutrition parameters and predict lack of response to nutritional treatment [25,29,30]. In a secondary analysis of EFFORT, unlike patients with lower CRP concentrations (≤100 mg/L), patients with high inflammation (CRP level >100 mg/L) did not respond to nutritional support [25]. Similarly, markers of chronic kidney dysfunction are associated with renal cachexia and weight loss, but patients with reduced kidney function show a particularly stronger response to nutritional treatment [5]. Albumin and prealbumin levels also have a strong prognostic value, but little correlation with nutritional response [31,32]. There are several studies looking at biomarkers of muscle strength and/or function with some suggesting that low muscle strength measured by HGS is a predictor for response [33] while others found sarcopenia to be a predictor of non-response in mixed populations [23,28].

Struja et al. used an untargeted proteomics approach to find predictive and prognostic metabolites – so far the metabolites had only little potential for phenotyping the malnutrition risk or treatment response [34]. Currently, no specific blood biomarkers of treatment response are used in routine clinical care.

4. Nutritional support plan

4.1. Definition of nutritional targets (Fig. 3)

4.1.1. Caloric target

5) **Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula, although the accuracy of prediction equations in this population is low.**

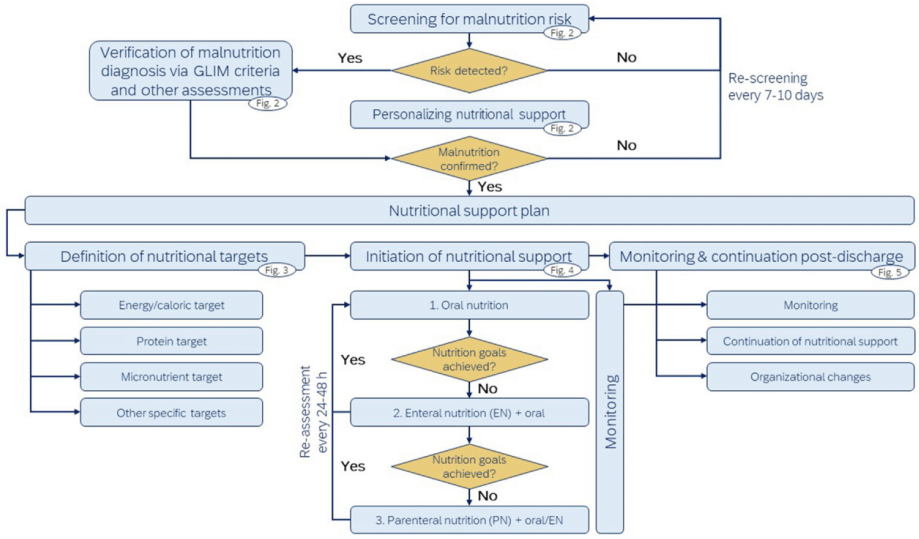


Fig. 1. Nutritional support for polymorbid medical inpatients. EN, enteral nutrition; GLIM, Global Leadership Initiative on Malnutrition; PN, parenteral nutrition.

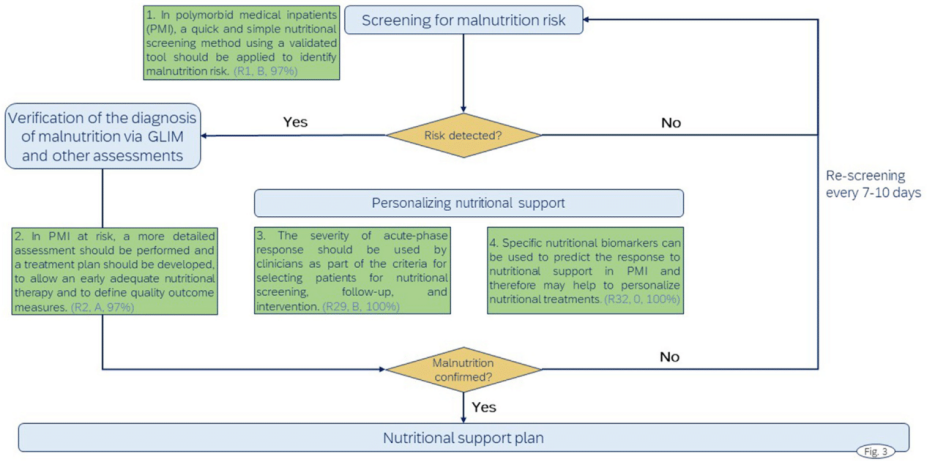


Fig. 2. Screening for malnutrition risk. GLIM, Global Leadership Initiative on Malnutrition; PMI, polymorbid medical inpatients.

(R8, Grade 0, Strong consensus 100 %)

Commentary

The estimation of energy requirements requires the determination of an individual's total energy expenditure (TEE) i.e., the sum of resting energy expenditure (REE), diet-induced thermogenesis and the energy expended during physical activity. The gold standard to measure REE is IC and for TEE the gold standard is doubly labelled water. However, these methods are rarely available in the clinical setting and require considerable expertise [35]. Practitioners therefore tend to rely on either published prediction equations (e.g. Harris-Benedict [36] or Ireton-Jones [37]) or weight-based formulae (e.g. 25–30 kcal/kg body weight/day).

In a study designed to evaluate the accuracy of prediction equations against IC in hospitalized patients demonstrated that no single prediction equation was accurate (within 90–110 % of measured REE). Another recent study conducted in 23 malnourished polymorbid, older hospitalized patients confirmed these results: the average REE predicted by the Harris–Benedict formula exceeded the REE measured by IC (after an overnight fast) on admission and at discharge by 29 % and 11 %, respectively,

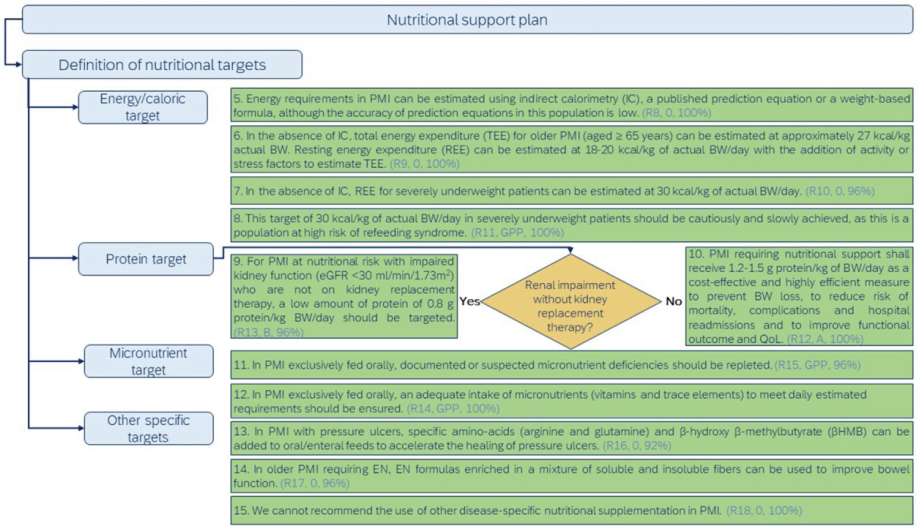


Fig. 3. Definition nutritional targets. β-HMB, β-hydroxy β-methylbutyrate; BW, body weight; eGFR, estimated glomerular filtration rate; EN, enteral nutrition; IC, indirect calorimetry; PMI, polymorbid medical inpatients; PN, parenteral nutrition; REE, resting energy expenditure; TEE, total energy expenditure.

suggesting that the Harris–Benedict formula is not accurate in this patient population [38].

Clinicians should be aware of the limitations of using precise numbers on weight-based formulae (or prediction equations) since in all studies there is considerable variation around the effect estimate. They should therefore only be used as a starting point when estimating requirements. In fact, this highlights the need for input from a suitable and experienced healthcare professional to adequately assess the nutritional needs of the patient, e.g., a dietitian.

6) **In the absence of IC, TEE for polymorbid older patients (aged ≥65 years) can be estimated at approximately 27 kcal/kg actual body weight/day. REE can be estimated at 18–20 kcal/kg actual body weight/day with the addition of activity or stress factors to estimate TEE.**

(R9, Grade 0, Strong consensus 100 %)

Commentary

In a review designed to determine the energy requirements of frail older people [39], including polymorbid patients, 33 studies (2450 subjects) were identified where REE was measured by IC in subjects aged 65 years or more and the results were compared with healthy older individuals. Only studies that measured REE by IC after a fast and at rest were considered eligible for inclusion in the review. The mean age was 73.0 ± 6.6 years, with no significant difference in BMI between the healthy and sick cohorts (25.6 ± 1.5 kg/m^2 and 25.2 ± 2.5 kg/m^2 respectively) and no differences in fat mass or fat-free mass. The weighted mean for the whole group was 20.4 kcal/kg actual body weight whereas the weighted mean for the polymorbid hospitalized older group was lower at 18.5 kcal/kg body weight. The mean TEE in sick older individuals was 27 ± 1.8 kcal/kg body weight and the weighted physical activity level in these patients was 1.36 ± 0.03 reflecting the relative physical inactivity of this population. The results of this review should be interpreted with caution since relatively few data were available in the sick older individuals (n = 248) compared with the healthy older individuals (n = 1970).

7) **In the absence of IC, REE for severely underweight patients can be estimated at 30 kcal/kg actual body weight.**

(R10, Grade 0, Strong consensus 96 %)

8) **This target of 30 kcal/kg actual body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.**

(R11, Grade GPP, Strong consensus 100 %)

Commentary

In a study designed to determine the energy requirements of severely underweight hospitalized patients energy expenditure was measured by IC in 14 patients [40]. Mean BMI was 15.8 ± 1.8 kg/m^2 and mean age was 66.5 ± 13.9 years. In this study mean REE by IC was 1300 ± 160 kcal/day equating to 31.4 kcal/kg body weight. These results should be interpreted with caution since the sample size was very small. Furthermore, patients received continuous EN or PN during IC and thus measured energy expenditure included not only REE but also diet-induced thermogenesis.

The target of approximately 30 kcal/kg body weight in severely underweight patients may need to be achieved with caution, as this is a population at high risk of refeeding syndrome. The diagnostic criteria and the factors proposed for screening of refeeding syndrome have been proposed elsewhere [41].

4.1.2. Protein target

9) **For polymorbid medical inpatients at nutritional risk with impaired kidney function (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73m^2) who are not on kidney**

replacement therapy, a low amount of protein of 0.8 g protein/kg body weight/day should be targeted.

(R13, Grade B, Strong consensus 96 %)
Commentary

In polymorbid medical inpatients with impaired kidney function, protein requirements should be lower [42]. Within EFFORT [43], protein targets of 1.2–1.5 g were lowered to 0.8 g/kg body weight/day for patients with eGFR <30 ml/min/1.73 m^2 according to earlier guidelines [7,44]. However, the degree of kidney impairment was a strong predictor for response to nutritional support and patients with eGFR of 15–29 L/min/1.73 m^2 receiving 0.8 g protein and those with 30–59 ml/min/1.73 m^2 receiving 1.2–1.5 g protein/kg body weight/day showed the strongest benefits on 30-day mortality (OR 0.37, 95 % CI 0.14 to 0.95 and 0.39, 95 % CI 0.21 to 0.75, respectively) [45]. This finding supports the concept of adjusting protein goals in polymorbid patients with renal conditions and impaired kidney function for eGFR and using targets from 0.8 g/kg body weight if eGFR is < 30 ml/min/1.73 m^2 and at 1.2–1.5 g with eGFR if ≥ 30 ml/min/1.73 m^2. Based on our search, there is a lack of trials comparing higher vs. lower protein targets in the polymorbid patient population with impaired kidney function. A recent critical review supported by the European Renal Nutrition Group of the European Renal Association (ERN-ERA) and ESPEN also recommends that renal status be prioritized in patients with advanced CKD (stages 4 and 5) [46] - however, they also conclude that patients with CKD need a personalized approach to prior renal or nutritional goals.

10) **Polymorbid medical inpatients requiring nutritional support shall receive 1.2–1.5 g protein/kg of body weight per day as a cost-effective and highly efficient measure to prevent body weight loss, to reduce risk of mortality, complications and hospital readmissions and to improve functional outcome and QoL.**

(R12, Grade A, Strong consensus 100 %)
Commentary

Protein targets of at least 1.0 g/kg body weight/day have been recommended in the past [7], e.g. supported by a high-quality RCT with 132 polymorbid patients. More recent and larger RCTs, such as the EFFORT trial including 2088 polymorbid patients, support a higher daily protein target of 1.2–1.5 g/kg body weight [43,47,48]. Compared to the usual care CG, odds for adverse outcomes and 30-day mortality were significantly lower in patients receiving individualized nutrition with these protein targets (OR 0.79, 95 % CI 0.64 to 0.97 and OR 0.65, 95 % CI 0.47 to 0.91 respectively), while functional status via BI, and QoL significantly increased - an intervention that was also cost-effective [48].

To reach high protein targets of 1.2–1.5 g/kg body weight, several strategies were used in recent trials and combined to respect patients individual preferences including ONS, protein-rich hospital menu, food fortification, and high-protein deserts and snacks [43,49,50].

Regarding combination of nutrition with exercise, one RCT of 47 malnourished polymorbid patients participating in a rehabilitation program on a geriatric ward, compared whey supplementation vs. no whey supplementation and demonstrated positive effects on daily protein intake (1.48 vs. 1.05 g/kg body weight) and muscle strength [49].

4.1.3. Micronutrient target

11) **In polymorbid medical inpatients exclusively fed orally, documented or suspected micronutrient deficiencies should be repleted.**

(R15, Grade GPP, Strong consensus 96 %)
Commentary

The need for micronutrient supplementation is often based on clinical assessment and in some cases estimated daily micronutrient requirements may temporarily exceed recommended daily intakes in order to account for depleted stores and/or increased utilization (particularly in patients who are exclusively fed orally) [51]. A study by Kilonzo et al. [52] on self-reported morbidity from infections in free-living patients (rather than inpatients) aged >65 years, randomized to receive either a daily vitamin and mineral supplement or placebo, found fewer QALYs per person in the supplemented group. This result is counter-intuitive; however, incomplete supplements not designed to replete micronutrient stores were used despite almost one third of the participants being judged at risk of micronutrient deficiency on recruitment. Daily micronutrient supplementation in free living individuals ≥60 years old did not improve incidence and severity of acute respiratory tract infections [53], although since the subjects were well-nourished they perhaps did not benefit from the supplementation. Another study of frail subjects in the community ≥65 years found a reduction in frailty with increased dietary intake but not with supplementation of only micronutrients [54]. However, the potential influence of increased micronutrient intake associated with the higher dietary intake in this study is unclear and the micronutrients-only group received estimated daily needs rather than repletion [55].

12) **In polymorbid medical inpatients exclusively fed orally, an adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured.**

(R14, Grade GPP, Strong consensus 100 %)
Commentary

Polymorbid medical inpatients may be at risk of micronutrient deficiency due to decreased intake or greater utilization, which can compromise health and recovery from illness. Some studies suggest beneficial outcomes from supplementation of micronutrients like James et al. [56] or Schuetz et al. [5], although the specific role of micronutrient supplementation is still unclear. Just as micronutrients underprovision could compromise polymorbid medical inpatients so too could overprovision.

General micronutrient supplementation (provision of multivitamins rather than combined multivitamin and multi-trace element) appears to be common, and often based on financial cost of the supplement. However, if a subject may have general micronutrient depletion or generally increased micronutrient requirements then there is likely to be a need to provide trace elements as well as vitamins. Therefore, supplementation should aim to deliver a complete range of both multivitamins and multi-trace elements rather than multivitamins alone. Complete micronutrient supplementation to meet reference nutrient intakes or otherwise estimated daily requirements could be particularly important in polymorbid medical inpatients due to the potential for any deficiencies to affect multiple and already compromised organ systems [57]. ESPEN provides practical advice on micronutrient status affecting disease and vice versa, micronutrient provision and monitoring, and potential micronutrient deficiencies resulting from medicine administration such as vitamin B12 or iron with proton pump inhibitors, or thiamine with diuretic therapy [58]. No studies were identified that reported the supplementation of multivitamins (with or without trace elements) compared to no supplements in polymorbid medical inpatients exclusively fed orally.

4.1.4. Other specific targets

13) **In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and βHMB can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.**

(R16, Grade 0, Strong consensus 92 %)
Commentary

Pressure ulcers are responsible for protein loss, hypermetabolism and hypercatabolism, and are often associated with malnutrition. This includes nutrient deficiencies that are critical to the different phases of wound healing (conditionally essential amino acids and antioxidant micronutrients). A RCT from Singapore that included 26 polymorbid patients hospitalized for more than two weeks [59] showed a marginal albeit significant effect of an arginine/glutamine/βHMB mixture on the healing of pressure ulcers (greatest improvement of viable tissues at two weeks in the IG, by 43 % vs. 26 %, $p = 0.02$). The amino acid mixture (14 g arginine, 14 g glutamine and 2.4 g calcium βHMB per day) was not part of a nutritional formula, but all patients were fed per recommendations for hypermetabolic and hypercatabolic patients (30–35 kcal and 1.2.0 g protein/kg body weight/day according to the stage of the ulcer). In another RCT from Hong Kong, 87 polymorbid malnourished older adults with pressure ulcers were randomized to receive or not the same mix of arginine/glutamine/βHMB for four weeks, besides an adapted nutritional support (at least 30 kcal and 1.2 g protein/kg body weight/day) [60]. A statistically significant reduction in pressure ulcer size ($p = 0.048$) and depth ($p = 0.002$) was observed in the IG while the Pressure Ulcer Scale for Healing (PUSH score) showed a significant improvement in the CG ($p < 0.001$).

Other positive studies have been published using an oral nutritional supplement enriched in arginine, zinc and antioxidants in patients outside the scope of these guidelines [61,62].

14) **In polymorbid medical older inpatients requiring EN, EN formulas enriched in a mixture of soluble and insoluble fibers can be used to improve bowel function.**

(R17, Grade 0, Strong consensus 96 %)
Commentary

Diarrhea and constipation are the most frequent complications of EN in hospitalized patients. A Belgian study of 145 older patients receiving enteral feeding [63] found positive effects of a formula enriched with 30 g fiber including 33 % insoluble (cellulose and hemicellulose A) and 67 % soluble (pectin, hemicellulose B, inulin) fiber (IG) vs. the CG, which received the same EN with no fiber. The frequency of stools was lower (4.1 ± 2.6 per week versus 6.3 ± 4.7 per week; $p < 0.001$) and the stool consistency higher in the IG (31 % had solid form stools in the IG vs. 21 % in the CG, and 2 % had liquid-watery stool in the IG vs. 13 % in the CG, $p < 0.001$); however, patients in the CG received more laxatives during the study period than patients in the fiber group. A global 4-week mortality of 24 % underlines the severity of the patients' conditions.

The effects on bowel function associated with the absence of detrimental metabolic effect argue for a recommendation for a first intention use of EN formulae enriched with a mixture of soluble and insoluble fibers (supposed to match the multiple sources of fibers in normal food). The same recommendation has been made in ESPEN's clinical nutrition and hydration guidelines in geriatrics [57].

15) **We cannot recommend the use of other disease-specific nutritional supplementation in polymorbid medical inpatients.**

(R18, Grade 0, Strong consensus 100 %)

Many specialized ONS/EN feeds have been developed for specific diseases that usually involve chronic/acute inflammation, specific micronutrient deficiency or specific metabolic disorders [64]. However, most studies were not conducted in identified hospitalized polymorbid patients, even though some of these patients may well be polymorbid, and the number of useable studies identified is extremely low. The scarcity of quality intervention studies in populations adequately described as polymorbid does not allow to recommend the use of other disease-specific nutrients. One of such prospective studies with negative findings was conducted in Japan in 50 patients with exacerbation of COPD [65]. They were randomized to receive either ONS with 1.1 g of eicosapentaenoic acid (EPA) or a comparable one without n-3 fatty acid during their hospitalization, both groups receiving a total of 30–35 kcal/kg/day. At discharge (after 12–13 days of supplementation in both groups), there was a non-significant increase in lean body mass index and skeletal muscle mass index in the EPA group compared with the CG (lean body mass index: +0.35 vs. +0.19 kg/m^2, $p = 0.60$, and skeletal muscle mass index: +0.2 vs. −0.3 kg/m^2, $p = 0.17$, respectively). The changes in skeletal muscle mass index were significantly correlated with the LOS in the EPA group, but not in the CG ($r = 0.53$, $p = 0.008$, and $r = -0.32$, $p = 0.31$, respectively).

4.2. Initiation of nutritional support (Fig. 4)

16) **In polymorbid medical inpatients with reduced food intake and hampered nutritional status, at least 75 % of calculated energy and protein requirements shall be achieved in order to reduce the risk of adverse outcomes and mortality.**

(R25, Grade A, Strong consensus 100 %)
Commentary

In polymorbid medical inpatients reduced food intake is associated with increased mortality and complications [66–69]. The EFFORT trial has demonstrated that reaching ≥75 % of estimated nutrition goals versus lower achievements led to significant lower risk of adverse events and mortality [5]. Supporting this finding in a meta-analysis from 2019, Gomes et al. [70] stratified trials by adherence to nutrition protocol and found that high adherence led to a more pronounced survival benefit. Whether the impact would be more pronounced if the IG had achieved 100 % cannot be answered by the data. Achieving 100 % of the targets should be strived for but is usually not realistic when patients are hospitalized and have either an exacerbation of one of their conditions or a current complication.

A prospective observational study [71], reported that patients with reduced food intake had a higher in-hospital mortality as well as 90-day mortality. Similar results were observed in a supportive study conducted in the critically ill population [72]. In a trial Li et al. found nutritional intake to be higher in patients with LOS of less than twelve days compared to patients with higher LOS [14]. However, a small sample size ($n = 40$) pilot RCT could not find a difference in readmissions within 30 days between the IG that reached 75 % of their nutritional goals and the CG that did not [73].

17) **Early nutritional support (i.e., provided in less than 48 h post hospital admission) compared to later nutritional support shall be performed in polymorbid medical inpatients, as mortality and adverse events are lower and lean body mass loss could be decreased and self-sufficiency could be improved.**

(R17, Grade A, Strong consensus 100 %)
Commentary

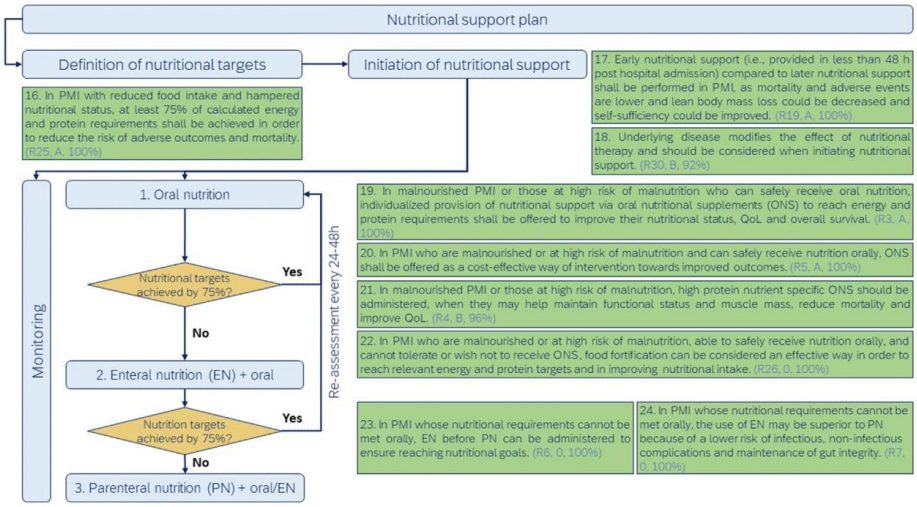


Fig. 4. Initiation of nutritional support. EN, enteral nutrition; ONS, oral nutritional supplements; PMI, polymorbid medical inpatients; PN, parenteral nutrition; QoL, quality of life.

The large EFFORT trial [5] addressed this question as the IG got their therapy initiated within 48 h. By 30 days, patients in the IG experienced 21 % less adverse clinical outcomes and 35 % lower mortality (adjusted OR 0.65 [0.47 to 0·91], p = 0.011).

A prospective RCT from Hegerová et al. [74] demonstrated that early nutrition support ONS (600 kcal, 20 g/day protein) added to the standard diet and exercise lead to no decrease in lean body mass compared to CG - an effect that persisted 3 months after discharge. Zheng et al. [75] compared early EN with "family managed nutrition" in a RCT of patients with acute stroke and dysphagia. Early nutrition support led to a significant lower infections rate and to a better National Institutes of Health Stroke Scale (NIHSS) score.

Using a nationwide inpatient database with 432,620 eligible patients hospitalized for acute heart failure after propensity score matching, Kaneko et al. showed that delayed initiation of feeding was associated with higher in-hospital mortality, longer LOS and higher incidence of pneumonia and sepsis when compared to earlier initiation of feeding [76].

Two studies addressed budget impact analysis applied to Colombian [77] and Mexican [78] population. Both found early nutritional support to be cost-effective (savings of 1351 $/patient in

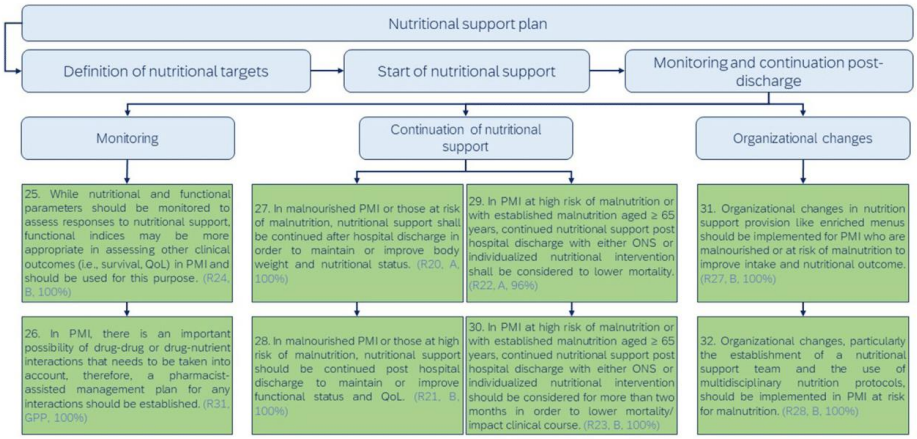


Fig. 5. Monitoring and continuation post-discharge. ONS, oral nutritional supplements; PMI, polymorbid medical inpatients; QoL, quality of life.

Colombia and 2505 $/patient in Mexico, mainly due to lower complications and readmissions.

18) **Underlying disease modifies the effect of nutritional therapy and should be considered when initiating nutritional support.**

(R30, Grade B, Strong consensus 92 %)
Commentary

There is strong evidence from large RCTs that polymorbid patients at risk for malnutrition benefit from nutritional support [79]. In a population-based cohort study of more than 110,000 patients, effect of nutritional support remained robust in subgroup analyses which stratified for main diagnoses and comorbidities, among others [80]. However, among medical patients, the effect of nutritional support may also depend on underlying disease. Mudge et al. identified diagnosis of infection or cancer to be associated with inadequate energy intake in patients aged 65 years or older [81]. A recent study by Bargetzi et al. found that kidney disease predicted response to nutritional treatment with lower eGFR showing stronger clinical benefit [45]. Similarly, patients with chronic heart failure have shown strong benefit from nutritional support. A survival benefit in chronic heart failure patients receiving nutritional support was found in a Spanish trial by Bonilla-Palomas et al. with 120 patients [82] and in secondary analysis of 645 patients from a randomized trial by Hersberger et al. [83]. Similar results were also found within the NOURISH study with a significant survival benefit associated with nutritional support [6]. Other conditions which may increase the effects of nutritional support are cancer [84], COPD [85] among others. However, it remains unclear how to implement these findings into clinical routine.

4.3. Oral nutrition

19) **In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely receive oral nutrition, individualized provision of nutritional support via oral nutritional supplements (ONS) to reach energy and protein requirements shall be offered to improve their nutritional status, QoL and overall survival.**

(R3, Grade A, Strong consensus 100 %)
Commentary

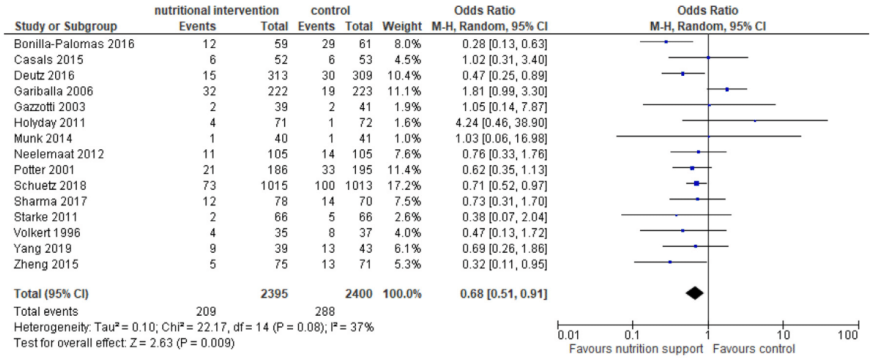
Provision of ONS has been found to impact clinical outcome. Schuetz et al., in the EFFORT trial, reported a lower risk of adverse clinical outcome in the IG compared to controls (adjusted OR 0.79, 95 % CI 0.64 to 0.97, p = 0.023) and a lower risk of mortality (adjusted OR 0.65, 95 % CI 0.47 to 0.91, p = 0.011), with no statistically significant difference in side effects between both groups [86]. Similarly, improved survival, lower non-elective hospitalizations, improvements in functional status in medical inpatients receiving nutritional support was reported in the meta-analysis by Gomes et al. [70]. Gressies et al. confirmed these findings in 2022 by an updating and re-analyzing Gomes et al. for the polymorbid patient cohort only. The analysis again showed a significant reduction in mortality risk (OR 0.68; 95 % CI 0.51–0.91) (Fig. 6) and hospital readmissions (OR 0.64; 95 % CI 0.45–0.90) [87]. Hegerová el al. conducted a prospective RCT in 200 medical inpatients and found that the provision of ONS (with physiotherapy) increased the energy and protein intake without negatively affecting the hospital food consumption [74]. This supplementation resulted in significant preservation of muscle mass and increased independence (Barthel Index).

In EFFORT the positive effects of individualized nutritional support provided during hospitalization which were observed at 30 days, were not sustained at six months after discharge when nutritional support was discontinued [47].

20) **In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely receive nutrition orally, ONS shall be offered as a cost-effective way of intervention towards improved outcomes.**

(R5, Grade A, Strong consensus 100 %)
Commentary

Early detection and intervention against DRM has been shown to improve nutritional status and reduce complications during hospital stay and non-elective readmissions [6,88]. According to a retrospective cost-effectiveness analysis by Philipson et al., the provision of ONS resulted in a reduction in LOS of 2.3 days that subsequently decreased annual hospital costs by 4734 and reduced the readmission rate by 6.7 % [89]. The greatest benefit was seen among the most severely ill patients, underscoring the importance of providing nutritional support to those who need it most [90].



A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95% CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95% CIs.

Fig. 6. Forest plot comparing nutritional intervention versus control for mortality in polymorbid medical inpatients [87].

The cost analysis of the EFFORT trial showed that nutritional support for polymorbid medical inpatients is a highly cost-effective intervention to reduce risks for ICU admissions and hospital-associated complications, while improving patient survival [91]. Confirming results were also reported in an economic analysis of Schuetz et al. [92] and a meta-analysis of RCTs on hospitalized patients at high risk of developing pressure ulcers, by Tuffaha et al. [93].

In line with these findings the economic evaluation of the NOURISH study concluded that the high protein βHMB ONS intervention was cost effective and positive in terms of survival [94] . Moreover, Ballesteros-Pomar et al. analysis proved the intervention to be cost effective, improved survival and marginally reduced cost of treatment [95].

21) **In malnourished polymorbid medical inpatients or those at high risk of malnutrition, high protein nutrient specific ONS should be administered, when they may help maintain functional status and muscle mass, reduce mortality and improve QoL.**

(R4, Grade B, Strong consensus 96 %)
Commentary

Several nutrient specific ONS have been tested for their effectiveness in improving outcomes in hospitalized patients. According to the NOURISH study, a multicenter RCT which included 652 malnourished inpatients, a high protein Hydroxy β-Methylbutyrate (βHMB) ONS may not yield a difference when compared with placebo on readmission rates, but may help with the maintenance of muscle mass during hospital stay and result in a significant decrease in post-discharge mortality (90-day mortality was 4.8 % in the IG vs. 9.7 % in the CG; RR 0.49, 95 % CI 0.27 to 0.90, p = 0.018) [6]. The effects of this ONS were also positive in a subgroup of patients with chronic obstructive pulmonary disease (COPD). Moreover, COPD patients receiving the high protein βHMB ONS showed an increase in handgrip strength (HGS) from discharge to 30 days (1.56 kg vs. −0.34 kg, p = 0.0413) and increased body weight (0.66 kg vs. −0.01 kg, p < 0.05) [96]. Improved functionality measured by HGS was also observed in other subgroup analyses from the NOURISH study, including patients with cardiovascular and pulmonary disease [85].

In addition, provision of ONS containing 995 kcal from macronutrients and covering 100 % of the RDA for healthy older adults in vitamins and minerals led to a lower incidence of depressive symptoms (p = 0.021) in older medical inpatients, with no other effect on their cognitive performance but with a significant positive effect on their self-reported QoL [97,98].

22) **In polymorbid medical inpatients who are malnourished or at high risk of malnutrition, able to safely receive nutrition orally, and cannot tolerate or wish not to receive ONS, food fortification can be considered an effective way in order to reach relevant energy and protein targets and in improving nutritional intake.**

(R26, Grade 0, Strong consensus 100 %)
Commentary

To reach nutritional goals different approaches can be used, especially because provision of nutritional support via ONS is often discontinued or not well tolerated by hospitalized patients [99,100] A Danish RCT [101] tested protein fortification of a novel energy dense menu supplementary to the standard hospital food service and could increase the food based nutrition intake of energy and protein beyond 75 % of calculated requirements. HGS and LOS were also reported but there were no differences to be observed, as expected when the study was not powered for such endpoints.

Another supportive study is a Dutch RCT [50] used protein-enriched familiar foods and drinks to improve protein intake in older hospitalized polymorbid patients. According to Mills et al.'s meta-analysis provision of energy or protein in the form of fortified foods or supplements in food items could be considered a cost-effective, well tolerated and effective way of improving nutrient intake in older inpatients [102]. A result that was confirmed in another meta-analysis by Morilla-Herrera et al. [103], but also the need of higher quality studies was stressed.

4.4. Enteral and parenteral nutrition

23) **In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN before parenteral nutrition (PN) can be administered to ensure reaching nutritional goals.**

(R6, Grade 0 − Strong consensus 100 %)
Commentary

Reaching energy goals in medical inpatients is important to prevent weight loss and the loss of muscle mass that may lead to poorer functional outcomes. However, in the acute care setting many obstacles may prevent patients from meeting their nutritional requirements orally. These obstacles include loss of appetite due to acute illness, delayed gastric emptying causing both nausea and early satiety, inability to swallow, and vomiting, among others. In these situations, the use of EN or PN can help increase nutritional intake until oral intake is sufficient [42,104]. Several randomized studies have compared the effect of nutritional support on outcomes of medical inpatients. A 2019 systematic review and meta-analysis on nutritional support in medical inpatients found significantly improved clinical outcomes in those receiving adequate nutritional support. The review included 27 RCTs from several countries comprising 6803 medical inpatients, and reported a 27 % reduction in mortality and non-elective hospital readmissions [70]. The review also found significantly higher energy and protein intake, as well as beneficial effects on weight when comparing nutritional support (including counseling and oral and enteral feeding) to CG patients.

24) **In polymorbid medical inpatients whose nutritional requirements cannot be met orally, the use of EN may be superior to PN because of a lower risk of infectious, non-infectious complications and maintenance of gut integrity.**

(R24, Grade 0, Strong consensus 100 %)
Commentary

Several trials found that the addition of either EN or PN to oral nutrition improves outcomes [105–107], but high-quality randomized studies comparing EN and PN head-to-head in the polymorbid medical inpatient setting are scarce. Observational evidence consists of one large, prospective, non-randomized study including patients at nutritional risk, that investigated the outcomes of patients receiving either EN or PN to patients without nutritional support [12]. Overall, the study found a significantly lower risk of overall complications and infectious complications associated with nutritional support (adjusted OR 0.54, 95 % CI 0.38 to 0.77), p < 0.001 and adjusted OR 0.42, 95 % CI 0.27 to 0.64, p < 0.001, respectively). When comparing patients receiving PN and EN within the nutritional support group, those receiving EN had significantly lower overall complication rates, as well as rates of infectious and non-infectious complications, compared to patients

without nutritional support (p = 0.001). However, no difference in the complication rates was found between patients with PN and patients with no nutritional support (p = 0.29).

Still, when also considering high-quality evidence from critical care [108] and in patients with pancreatitis [109] as well as observational evidence from polymorbid medical inpatients, there are several arguments for the use of EN as a first line therapy as compared to PN due to lower risks for infectious and non-infectious complications. An important physiological rational is also the prevention of intestinal mucosal atrophy by EN compared to PN [110].

4.5. Monitoring and continuation post-discharge (Fig. 5)

4.5.1. Monitoring

25) **While nutritional and functional parameters should be monitored to assess responses to nutritional support, functional indices may be more appropriate in assessing other clinical outcomes (i.e., survival, QoL) in polymorbid medical inpatients and should be used for this purpose.**

(R24, Grade B, Strong consensus 100 %)

Commentary

Limited evidence exists to answer this clinical question as most trials use nutritional and functional status as outcome rather than as monitoring tools. A secondary analysis from EFFORT supports the use of functional parameters to monitor nutritional support but also to guide initiation of it. Kaegi-Braun et al. illustrates that individualized nutritional support was most effective in reducing mortality in patients with low HGS. Furthermore, an incremental decrease of HGS by 10 kg resulted in doubling 30-d mortality in females and 50 % increase in 30-d mortality in males, reflecting the prognostic potential of HGS [33].

A cohort study by Ballesteros-Pomar et al. found that a higher HGS, but not muscle mass, was related to better QoL, less readmissions and lower mortality after adjusting for age, sex, and comorbidity [111]. However, another prospective observational study failed to show a significant association between HGS and 100-day mortality [112].

A study from 1995 [113] suggests that although nutrition therapy improves nutritional status and outcome, functional parameters are more robust prognosticators of outcome. Norman et al. [114] demonstrated that post-discharge dietary counseling plus ONS (IG) and dietary counseling (CG) improved body weight and body cell mass. However, HGS and peak flow improved only in the IG. By applying the reasoning used for the trial by Mendehall et al., it appears that Norman et al. confirm that functional parameters may be superior to nutritional parameters.

26) **In polymorbid medical inpatients there is an important possibility of drug–drug or drug-nutrient interactions that needs to be taken into account, therefore, a pharmacist-assisted management plan for any interactions should be established.**

(R31, Grade GPP, Strong consensus 100 %)

Commentary

Polymorbid medical inpatients often require multiple medicines to manage their comorbidities. Whilst this may be an essential approach, it carries several risks including potential 'drug–drug' and/or 'drug-nutrient' interactions and their associated consequences [115]. In a systematic review polypharmacy was significantly associated with malnutrition [116,117] and with sarcopenia [118], which could result in insufficiency of some electrolytes or micronutrients [119]. A recent meta-analysis from 2023, which included 29 studies, also demonstrated that sarcopenia is associated with a higher prevalence of polypharmacy and higher number of medications compared with individuals without sarcopenia [120]. Some interactions will be familiar including physical binding of drugs such as tetracyclines to the divalent and trivalent cations from milk or antacid preparations [121] or in many of the ONS and enteral formulas, which limits absorption from the gastrointestinal tract. Other interactions that may be less familiar include the potential for physical binding of ceftriaxone to calcium salts when both are given intravenously [122] or the effect of hydration status, which is commonly impaired in acute medical admissions [123], on drug enrichment [124]. Whilst some drugs have no specific requirement to be taken with or without food there can still be toxic potential if specific examples such as simvastatin are taken concurrently with grapefruit juice [125]. A description of pharmacokinetic interactions between food and drugs is available [126]. Advice on the complexities of all these potential interactions in polymorbid medical inpatients may be obtained from a pharmacist or pharmacologist.

5. Continuation of nutritional support

27) **In malnourished polymorbid medical inpatients or those at risk of malnutrition, nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status.**

(R20, Grade A, Strong consensus 100 %)

Commentary

For the present question, only interventions initiated in the hospital (and continued after discharge) were included. Many polymorbid patients leave the hospital malnourished, which increases the risk for functional decline, loss of independence, greater morbidity and risk of unplanned readmissions [127]. A recent meta-analysis also demonstrated that caloric intake but also protein intake was significantly higher in patients receiving nutritional support after hospital discharge [128], which is also confirmed by systematic reviews [129,130].

One study by Feldblum et al. which directly compared 6-month individualized nutritional support in hospital followed by three home visits after discharge showed that continued nutritional support in malnourished patients resulted in a significantly higher change in mean MNA score, compared to the CG [131]. Similarly, in a prospective RCT of 80 patients aged 75 years or more admitted for acute disease and at risk for malnutrition, a 60-day intervention with ONS resulted in maintained body weight and improved MNA scores, whereas CG patients continued to lose weight [132].

Similar results were obtained in other RCTs e.g. by Casals et al. [133] or Persson et al. [134] Confirming this, a sub-analysis of the NOURISH study showed an increase in nutrient intake in IG patients without decrease in dietary intake [55].

28) **In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and QoL.**

(R21, Grade B, Strong consensus 100 %)

Commentary

Enhancing functional status post-discharge is crucial in preventing extended recovery, readmissions, or loss of autonomy. In one RCT conducted in malnourished adults, 3-month specialist ONS intervention resulted in a reduction in the number of falls [135], a significant improvement in functional limitations [136], and was neutral in financial cost [137]. In a study by Persson et al. treatment with liquid supplements and dietary advice for four months

resulted in an improvement of Katz's activities of daily living index, but not in QoL assessed by the SF-36 [134]. On the other hand, Casals et al. reported significantly improved QoL scores after six months of individualized nutritional support [138].

In malnourished patients who received ONS during their hospital stay and for three months post discharge, QoL assessed by the SF-36 was significantly improved in the IG patients compared to the CG patients [139]. HGS and peak expiratory flow increased after three months only in the intervention patients [114]. HGS was also significantly improved in the IG of malnourished patients after three months of nutrient adapted ONS in the NOURISH study [140].

A study which used multimodal nutritional approach showed a significant improvement in the 30 s chair rise test in the IG. The improvements in physical function were significantly higher in the IG but clinically relevant in both groups [141].

29) **In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention shall be considered to lower mortality.**

(R22, Grade A, Strong consensus 96 %)
Commentary

One of the largest RCTs to date (NOURISH; n = 652) on in- and post hospital (=continued) nutritional support reported lower 90-day mortality in the IG receiving nutrient-adapted ONS twice a day for three months compared to the CG patients who received a placebo (4.8 % in the IG vs. 9.7 % in the CG, p = 0.018) [6]. A finding that is supported by Feldblum et al.'s study [131]. The PICNIC study of Bonilla-Palomas et al. initiated nutritional intervention in patients with heart failure at admission to hospital and continued for six months. At twelve months, the primary composite endpoint occurred in 27.1 % of the IG compared to 60.7 % of CG patients (HR 0.45, 95 % CI 0.19–0.62, p = 0.0004). Both mortality (HR 0.37, 95 % CI 0.19–0.72, p = 0.003) and readmission rates were lower in the IG patients (10.2 vs. 36.1 %, p = 0.001) [82]. The benefits of the nutritional intervention persisted at 24 months [142,143].

Also two recent systematic reviews and meta-analyses [128,144] concluded that mortality was significantly lowered in patients with nutritional support which was continued after hospital discharge (OR 0.63, 95 % CI 0.48 to 0.84, p = 0.001) and (OR 0.72 95 % CI 0.57 to 0.91, p = 0.006).

Only one study studied the impact of three-month nutritional support on long-term mortality and revealed no differences in mortality at year one and four between groups [145].

30) **In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention should be considered for more than two months in order to lower mortality/impact clinical course.**

(R23, Grade B, Strong consensus 100 %)
Commentary

The ideal duration of post discharge nutritional intervention varies. However, most RCTs on interventions with ONS spanned three months [6,114,135–137,139], while individualized nutritional support was usually provided for longer periods (four month [134], or six months [82,131,138,146]). While readmission rates were not reduced after three months in one of the largest trials [6] in geriatric patients [147] or in older patients [148], it was significantly reduced after six months of nutritional intervention in several trials [82,131,146] but not all [141]. A recent meta-analysis also showed that interventions which lasted >60 days had a stronger effect on mortality (OR 0.53 95 % CI 0.38 to 0.75) than trials with shorter durations of the intervention (OR 0.85 95 % CI 0.64 to 1.13, p for subgroup difference: 0.04) [144].

A longer duration of nutritional treatment is also necessary to improve QoL in older adults [149]. Neelemaat et al. argue that while they were able to show an effect on functional limitations after three months, the length of nutritional support might not have been sufficient to show an effect on QoL [137] which is similar to the results in the trial of Munk et al. [141].

6. Organizational changes

31) **Organizational changes in nutrition support provision like enriched menus should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition to improve intake and nutritional outcome.**

(R27, Grade B, Strong consensus 100 %)
Commentary

The organization of nutritional support in hospitals requires a multi-disciplinary approach involving catering, nursing, finance, and therapy services. Changes to the organization for inpatients may improve outcomes: these include the use of nutritional healthcare assistants [150], targeted education for dietitians and the multidisciplinary team (MDT) to improve early use of ONS [151], food fortification [152], introduction of nutritional screening [153] and technological innovations used to facilitate timely referral to the Nutrition Support Team (NST) [154]. Despite these general studies, a systematic review of non-randomized studies showed that improvements are not consistently demonstrated [155]. Therefore, it is important to consider the specific impact of organizational changes on polymorbid medical inpatients. A single-blinded RCT [101,156] demonstrated that the use of a protein fortified menu was effective in increasing protein intake of IG but however did not change energy intake, LOS or HGS. The CG received the standard hospital menu.

A pilot, controlled trial compared a modified hospital menu, including higher energy and protein choices, to the standard hospital menu [157]. There was no difference in patients' weight, HGS, functional independence or LOS. However, energy and protein intake were higher in the IG.

A further, prospective controlled trial [22] demonstrated that applying an early multi-disciplinary intervention protocol led to a significant weight gain in IG, without a change in LOS or the development of pressure ulcers. In addition, the IG developed fewer hospital acquired infections.

32) **Organizational changes, particularly the establishment of a NST and the use of multidisciplinary nutrition protocols, should be implemented in polymorbid medical inpatients at risk for malnutrition.**

(R28, Grade B, Strong consensus 100 %)
Commentary

A cohort study reported the impact of multiple nutrition improvement initiatives on a one-day record of intake of estimated energy and protein requirements (>75 % of requirements) [158]. The number of patients achieving adequate energy and protein intake increased significantly from pre-intervention to post-interventional. It is suggested that this increase in intake was primarily a consequence of introducing the hot breakfast option. Dietary intake also improved via nutrition improvement initiatives

over seven years by Young et al. on three medical wards [159]. Phased initiatives included the introduction of assisted mealtimes, nursing assistant to help with nutrition administration/feeding assistance and additional education for nurses, dietitians and the wider MDT.

In another mealtime study, trained volunteers assisted patients for one year [160]. The authors reported that although their intervention released time for nursing staff, they found no positive effect on dietary intake, which is a similar finding to Roberts et al. [158].

A cohort study [161] demonstrated the impact of an NST on the management of patients requiring PN. After a structured training program for nurses led by the NST, catheter-related sepsis rates decreased in PN patients from 71 % pre-NST to 29 % in their first year ($p = 0.05$).

Funding

This work was supported by the ESPEN society as well as by the SNF Swiss National Science Foundation (SNSF Professorship, PP00 P3_150531/1) and the Research Council of the Kantonsspital Aarau, Switzerland (1410.000.044).

Disclaimer

This guideline has been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using this guideline shall do so only after consultation with a health professional and shall not mistake this guideline as professional medical advice. This guideline must not substitute seeking professional medical and health advice from a health professional.

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Conflicts of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict-of-interest forms are stored at the ESPEN guideline office and can be reviewed with legitimate interest upon request to the ESPEN executive.

Acknowledgements

We thank the ESPEN committees (namely Stephan Bischoff and Anna Schweinlin) for the continuous support during the whole process of updating current guideline.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.01.008.

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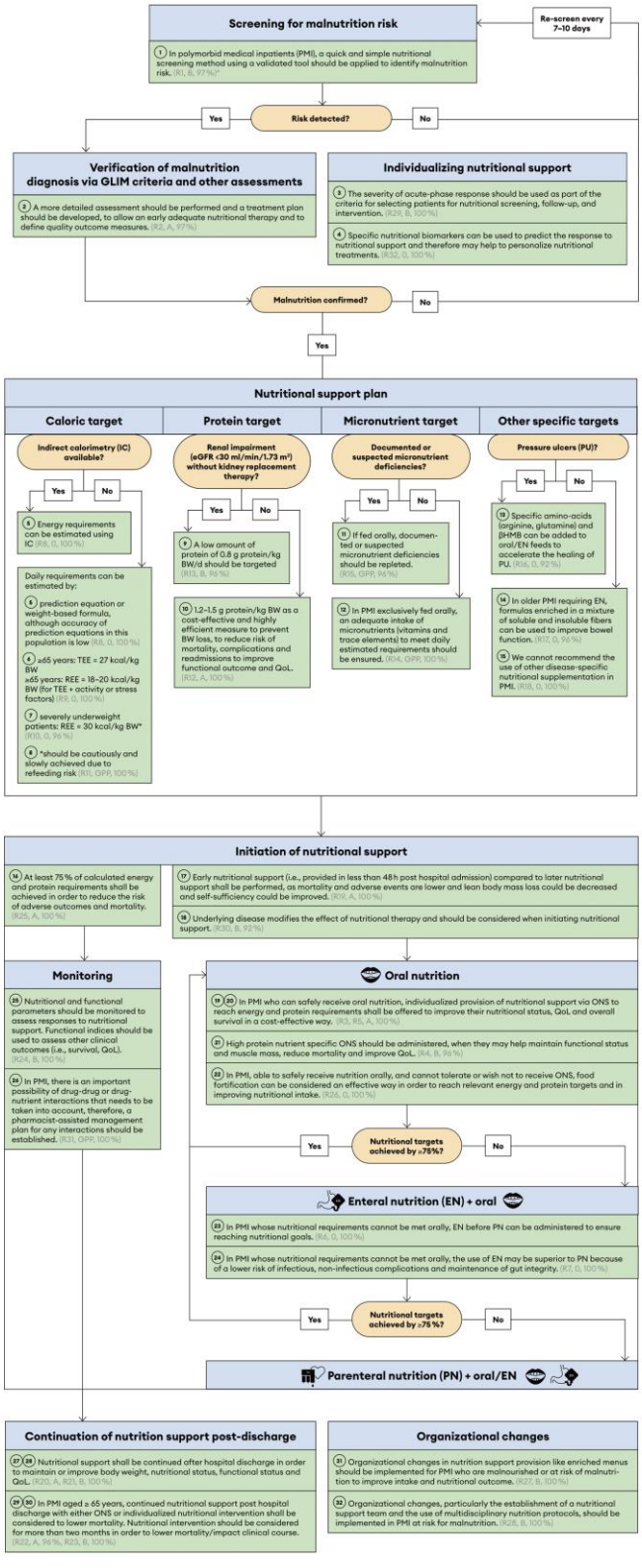
3.1.4 ESPEN practical guideline: evidence-based algorithm on nutritional support in polymorbid medical inpatients [92]

ESPEN guideline on nutritional support for polymorbid medical inpatients

Carla Wunderle, Filomena Gomes, Philipp Schuetz on behalf of the entire working group



Abbreviations:

- PMI: polymorbid medical inpatient
- GLIM: Global Leadership Initiative on Malnutrition
- IC: indirect calorimetry
- eGFR: estimated glomerular filtration rate
- TEE: total energy expenditure
- REE: resting energy expenditure
- BW: body weight
- QoL: quality of life
- βHMB: β-hydroxy β-methylbutyrate
- ONS: Oral Nutritional Supplement(s)
- EN: enteral nutrition
- PN: parenteral nutrition

***ESPEN Guideline Codes:**

- R: number of the recommendation in the original guideline
- B: Grade of recommendation ascending GPP, 0, B, A
- 97%: Percentage agreement with the recommendation

3.2.1 Nutritional issues concerning general medical ward patients: feeding patients recovering from critical illness [93]

Author contributions:

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CW: Conceptualization, literature search, writing - original draft preparation, writing – review and editing and visualization. PS: Conceptualization, investigation, writing – review and editing, project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

REVIEW

Nutritional issues concerning general medical ward patients: feeding patients recovering from critical illness

Carla Gressies[a] *and Philipp Schuetz*[a,b]

Purpose of review
ICU survivors often spend long periods of time in general wards following transfer from ICU in which they are still nutritionally compromised. This brief review will focus on the feeding of patients recovering from critical illness, as no formal recommendations or guidelines on nutrition management are available for this specific situation.

Recent findings
While feeding should start in the ICU, it is important to continue and adapt nutritional plans on the ward to support individuals recovering from critical illness. This process is highly complex – suboptimal feeding may contribute significantly to higher morbidity and mortality, and seriously hinder recovery from illness. Recently, consensus diagnostic criteria for malnutrition have been defined and large-scale trials have advanced our understanding of the pathophysiological pathways underlying malnutrition. They have also helped further develop treatment algorithms. However, we must continue to identify specific clinical parameters and blood biomarkers to further personalize therapy for malnourished patients. Better understanding of such factors may help us adapt nutritional plans more efficiently.

Summary
Adequate nutrition is a vigorous component of treatment in the post-ICU period and can enhance recovery and improve clinical outcome. To better personalize nutritional treatment because not every patient benefits from support in the same manner, it is important to further investigate biomarkers with a possible prognostic value.

Keywords
disease-related malnutrition, individualized nutrition therapy, nutritional treatment algorithm, post-ICU in-hospital nutrition support, recovering from critical illness

INTRODUCTION

Although ICU patients are at risk for malnutrition, optimal feeding strategies are still under debate [1]. Recommendations for medical nutrition therapy in critical illness vary between guidelines of the DGEM (German Society for Nutritional Medicine), the ESPEN (European Society of Enteral and Parenteral Nutrition), the ASPEN (American Society of Enteral and Parenteral Nutrition), and numerous other associations. Implementation of guidelines in clinical practice remains challenging. Nutritional feeding protocols must be continued and adapted once patients survive the acute phase of illness and transition to the medical ward for recovering phase [2]. Subsequently, patients may transition to a rehabilitation phase, which can also last for months [3]. Although nutrition therapy in the early ICU period has been researched intensively, data focusing on the recovery period is limited [4]. This brief review will focus on the feeding of patients recovering from critical illness, as no formal recommendations or guidelines on nutrition management are available for this specific situation. Figure 1 provides an

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Curr Opin Clin Nutr Metab Care 2023, 26:138–145
DOI:10.1097/MCO.0000000000000894

KEY POINTS

- There is a lack of research for the post-ICU phase.
- There are no formal guidelines about nutrition support in this period, although it is proven that nutrition therapy is able to improve recovery of patients.
- Nutrition support significantly influences survival, readmissions, adverse outcome and other functional outcome.
- Barriers for oral intake and other physiological abnormality in the post-ICU period need to be considered within the treatment team.
- There are promising biomarkers like CRP that could guide the initiation of nutritional support and will help to further personalize and improve nutritional treatment.

overview of the characteristics and difficulties of the various phases.

As disease-related malnutrition is associated with impaired recovery from illness, it is important to identify patients at risk, assess their nutritional status, and initiate nutritional support, if necessary [5▪]. In the post-ICU period, there is a metabolic shift toward anabolism and substrate tolerance normalizes. Energy requirements can still be 1.2–1.5-times the calculated amount [3] as common equations to estimate the energy expenditure failed to predict the actual amount [6]. Overall, oral ingestion is the most common mode of providing nutrition at that time. However, calorie and protein intake more frequently remains below predicted targets [4,7]. Additionally, some serum trace elements like chromium and zinc are frequently be below reference values after ICU discharge [8]. A current review suggests that after extubation, ICU survivors consume less

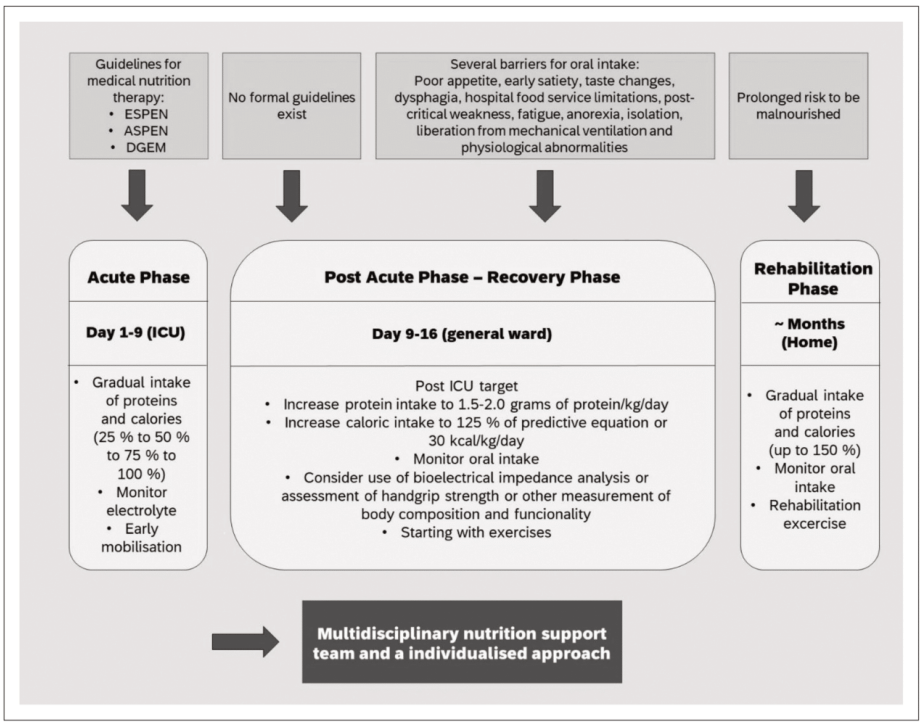

FIGURE 1. Phases from critical illness in the ICU to recovery and rehabilitation, and their nutritional characteristics. ASPEN, American Society for Parenteral and Enteral Nutrition; DGEM, Deutsche Gesellschaft für Ernaehrungsmedizin (German Society for Nutritional Medicine); ESPEN, European Society for Clinical Nutrition and Metabolism.

than 60% of the required calories [9]. The most frequently mentioned barriers to eating were poor appetite, early satiety, and change in the sense of taste. Therefore, acceptable strategies to enhance nutrition intake in post-ICU patients during the recovery stages of critical illness are needed [10].

MALNUTRITION: PATHOGENESIS, SCREENING, AND DIAGNOSTIC CRITERIA

Malnutrition is associated with detrimental metabolic consequences such as catabolism and muscle wasting [5▪]. These effects are of particular importance in ICU survivors who are nutritionally compromised and suffer from muscle loss and fatigue [11]. It is well known that malnutrition in this population is associated with high mortality and morbidity, elevated risk for infection, and increased hospital length-of-stay (LOS) [5▪]. However, it is important to evaluate effective and well tolerated strategies to counteract these effects and understanding the optimal use of nutritional support to effectively prevent and treat malnutrition is complex and constitutes a major area of current research.

Agreeing on criteria for the diagnosis of malnutrition has remained challenging for years, as it is not one specific well defined illness, but a syndrome with several potential mechanisms. Recently, global experts have proposed specific variables for a consensus definition of malnutrition and recommended that malnutrition be diagnosed in a two-step approach [12]. The first step consists of nutritional screening to identify patients at risk of malnutrition. Today, various easy-to-use malnutrition screening tools like the Nutrition Risk Screening (NRS) 2002 facilitate the estimation of malnutrition risk in patients admitted to hospital [13]. For further insights, there is a recent study that compared all common instruments regarding accuracy of predictions regarding mortality and response to nutritional support [14].

The second step is to apply more specific criteria to assess and grade the severity of malnutrition. The Global Leadership Initiative on Malnutrition (GLIM) has proposed three phenotypic criteria (unintentional weight loss, low BMI, and reduced muscle mass), and two aetiological criteria (reduced food intake or assimilation, and inflammation or disease burden) which should be assessed by a nutritional specialist [15,16]. A minimum of one phenotypic criterion and one aetiologic criterion must be present to diagnose malnutrition. This allows the classification of malnutrition into four aetiology-related diagnosis categories – from chronic disease with no inflammation to acute disease with severe inflammation. Phenotypic metrics are used to classify severity into Stage 1 (moderate) and Stage 2 (severe) malnutrition. Although several studies have validated the GLIM criteria regarding their ability to identify patients at higher medical risk, further large-scale studies are needed to understand whether these criteria can also be applied for surgical patients, and if they help predict response to nutritional interventions. One recent analysis of data from the EFFORT trial found GLIM criteria to have a high prognostic value regarding mortality and other clinical outcomes. However, patients at nutritional risk (as judged by the NRS score) but not meeting GLIM criteria for being malnourished also had benefit from nutritional therapy. The study thus suggested that GLIM have an excellent prognostic value to identify patients at high risk for mortality and adverse outcome, but GLIM may be less helpful to predict treatment response [17]. These results suggest that additional more specific parameters are needed in order to select patients for nutritional support. A systematic review and meta-analysis from 2022 concluded that diagnosing malnutrition with the GLIM criteria has the potential to be the gold standard with an interesting finding that the accuracy of later studies of the GLIM criteria was better than that in the earlier studies, suggesting that experience has improved the use of the criteria [18]. However, there is still lack of evidence that this new approach will generate added value to clinical practice and will be better in identifying patients with malnutrition benefitting from nutrition therapy compared with the current approach.

Further initiatives similar to GLIM regarding consensus criteria for the diagnosis of malnutrition also exist. The Academy of Nutrition and Dietetics (AND) and the American Society for Parenteral and Enteral Nutrition (ASPEN) published a standardized set of diagnostic characteristics and an aetiology-based malnutrition definition [19]. One study from 2022 compared the AND-ASPEN and GLIM malnutrition diagnostic criteria, and found high degrees of validity and reliability when identifying malnutrition in a hospital setting [20]. Clearly, further studies are needed to clarify and validate the best approach to diagnose malnutrition in clinical care settings.

FEEDING STRATEGY AND NUTRITIONAL SUPPORT IN THE RECOVERY PHASE TO IMPROVE CLINICAL OUTCOME

As mentioned above, no formal guidelines for feeding patients recovering from illness currently exist – despite the fact that nutrition rehabilitation may be

vital in this phase [4]. Guidelines for nutritional support of polymorbid medical inpatients [21] may be consulted, as many ICU survivors are polymorbid as well. A pragmatic treatment algorithm for malnutrition in the inpatient setting is shown in Fig. 2. It was based on a consensus conference [22] and a subsequent validation trial [23], and can be adapted for the stage of recovery.

As feeding is already initiated for most patients in the ICU, it is important to reassess their special nutritional needs following transfer to the medical ward. This process requires the multidisciplinary cooperation of all involved personal to ensure optimal continued care [2].

This nutritional assessment includes: consideration of medication side effects and specific medical illnesses that cause loss of appetite, difficulties in feeding, barriers for oral nutrition (because of prior ventilation, etc.), or malabsorption and the defining of individualized nutritional goals for each patient [21,22] – including aims for total energy, protein, fluid, micronutrient, and vitamin intake. Energy-intake goals can be estimated using indirect calorimetry, a highly sensitive, accurate, and minimally invasive method for measurements of an individual's energy expenditure. Especially for ICU survivors, there is a need to further validate this method because the patient's cooperation during measurement may be challenging (i.e. because of anxiety, delirium, consequences of ventilation, and more) [24,25]. Alternatively, validated formulas such as the adapted Harris–Benedict equation [26], or more simple weight-based formulae (e.g. 25–30 kcal/kg body weight/day) are helpful in estimating caloric needs [5▪], although they failed to predict the measured energy expenditure in a recent analysis performed in ICU survivors. In this observational study, the Harris–Benedict equation overestimated the total energy expenditure while the Penn–State equation underestimated it [6]. A recent review of Hill *et al.* [3] suggests to multiply the calculated energy requirements with 1.2–1.5. Until now, it is unclear whether the measurement or exact determination of the energy requirements will result in better outcome. The EFFORT trial (Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial) reported that protein intake of 1.2–1.5 g/kg body weight/day improves clinical outcomes in medical, and older adult patients [23,27]. This trial was conducted in non-critically ill polymorbid medical inpatients. Sufficient protein intake is also important to prevent further loss of muscle mass and function [28], and post-ICU requirements can reach 2 g/kg body weight/day [29]. Once set, a nutritional plan to achieve these goals must be established within the entire treating team. Oral feeding should be prioritized – including optimization of diet according to patient preferences [22] – and then adapted for possible oral barriers [10]. Escalation to enteral and parenteral nutrition should be considered if goals are not achieved.

An interim analysis of a retrospective review suggested an association between prolonged enteral nutrition in the post-ICU setting and a reduction in 30-day readmissions [30]. This finding, however, needs confirmation in prospective randomized interventional trials. During the critically ill period, supplements like leucine and its metabolite β-hydroxy-β-methylbutyrate (HMB) have also been shown to positively impact long-term outcome and recovery [31].

There are several barriers to oral intake in the post-ICU period like poor appetite, early satiety, changes in taste, dysphagia, hospital food service limitations, postcritical weakness, fatigue, anorexia, isolation, liberation from mechanical ventilation, and physiological abnormalities [3,4,32]. A recent review summarized and categorized the various difficulties into: changes of appetite and taste, gastrointestinal disturbances, swallow function, physical function, psychosocial, clinician factors, transitional care, feeding tube removal, nursing care, and systemic problems [4].

One interesting physiological abnormality was recently investigated by Whitehead *et al.* They assessed 26 patients regarding delayed gastric emptying and impaired glucose absorption and discovered rapid recovery of both symptoms following transfer from ICU [32]. The same group of researchers found no difference in gastric emptying between ICU survivor and healthy volunteers 3 months after ICU discharge [33] and could now show that the recovery is much faster. If confirmed in a larger population, these factors will promote a more intensive nutritional strategy to improve outcomes, including functional recovery following discharge from ICU.

Worth mentioning is the current prospective, multicentre, unblinded, parallel-group, phase II randomized controlled trial (RCT) conducted in 23 hospitals in Australia and New Zealand by Ridley *et al.* They focus among other outcomes on daily energy during critical care but specifically also in the post-ICU what will deliver great insights in that neglected period during acute illness [34].

A single-site, double-blind, randomized, controlled trial showed that protein supplementation in hospitalized elderly with sarcopenia improved physical performance, and reduced rehabilitation

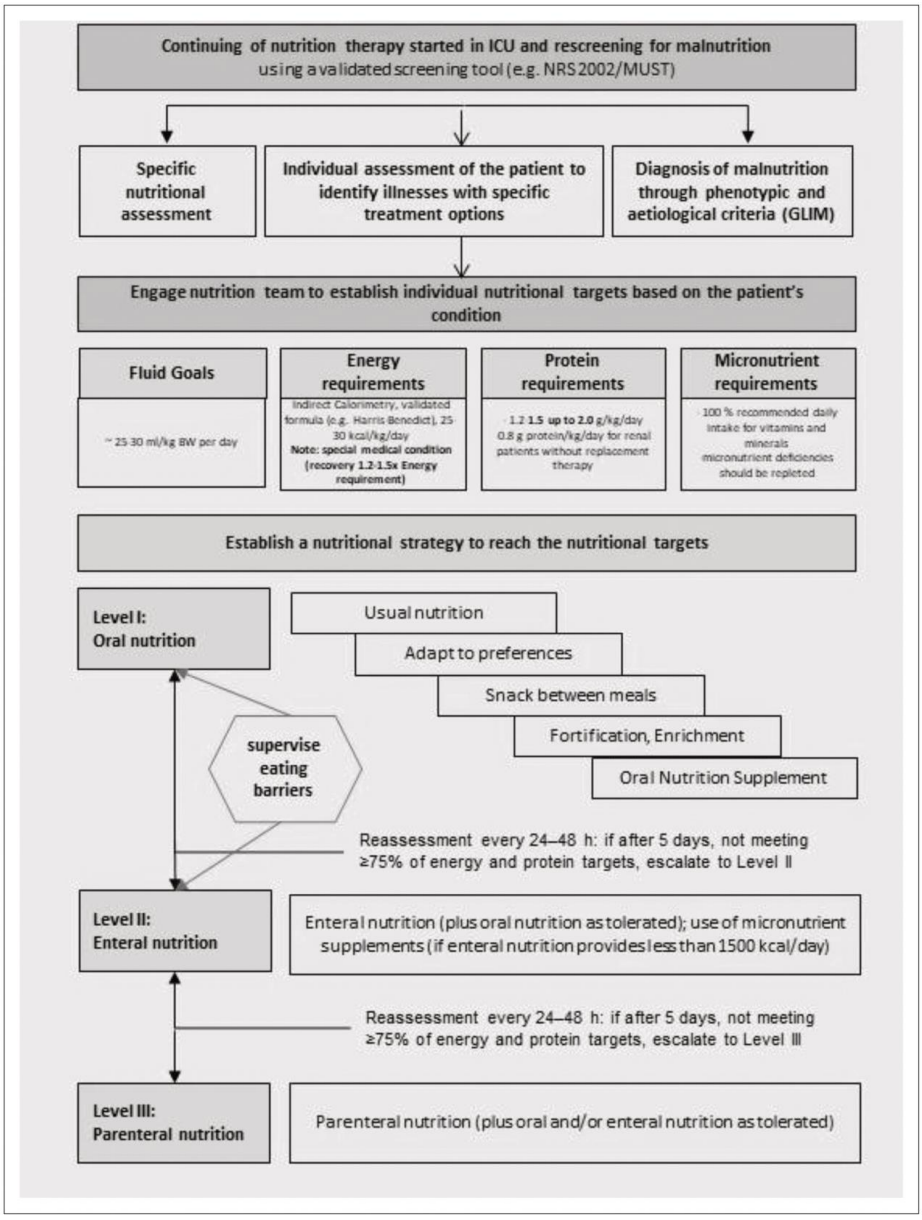

FIGURE 2. Treatment algorithm for malnutrition on a general ward in the recovery phase. GLIM, Global Leadership Initiative on Malnutrition; MUST, Malnutrition Universal Screening Tool; NRS 2002, Nutritional Risk Screening 2002.

time and hospital LOS. The intervention group received a whey protein-based nutritional formula enriched with leucine and vitamin D until discharge, whereas the control group were given an iso-caloric control formula twice daily, in addition to the standard hospital diet. Supplementation with the experimental formula ($n = 64$) resulted in greater increase in mean gait speed than placebo [0.061 m/s/month (95% CI 0.043–0.080) compared with placebo −0.001 m/s/month (95% CI 0.008–0.006)]. A similar significant effect was found for muscle mass, all key secondary outcomes, as well as functional and cognitive endpoints. Supplementation also resulted in improved rehabilitation intensity profiles faster discharge to home, shorter rehabilitation, and less time in hospital as a whole [mean length of stay (±SD) 41.8 ± 6.4 days vs. control 52.2 ± 5.2 days] [35]. Although patients were not specifically post-ICU, all were elderly with a median intake of seven medications. These findings highlight the potential of an anabolic signal provided by certain components, and a possible treatment strategy for patients suffering from muscle loss during the post-ICU phase. Further research, however, is required [28].

As this study demonstrates, disease-related malnutrition is an (at least partly) influenceable risk factor for adverse clinical outcomes. In fact, the field of nutritional care for medical inpatients has advanced significantly in recent years. A 2019 systematic review and meta-analysis including 27 trials constituting 6803 patients reported that nutritional support during hospitalization is associated with a 25% reduction in mortality and non-elective hospital readmissions [36]. Furthermore, trial subgroups receiving high-protein diets and long-term nutritional support showed the most significant decrease in mortality; highlighting the key importance of nutritional care [37▪]. EFFORT – the largest trial of it, performed with over 2000 patients in eight Swiss hospital – compared individualized nutritional support to energy and protein goals vs. standard hospital food. The primary endpoints were: severe complications, a composite of mortality, admission to ICU, cardiovascular and gastrointestinal complications, functional decline, and hospital readmission. In this trial, nutritional support intervention was highly effective in lowering the risk for mortality, with only 37 cases of 'number needed to treat' (NNT) [23]. A similar effect regarding mortality (NNT = 20) was also found in the placebo-controlled, 652-patient NOURISH trial, which studied the clinical outcome of providing protein-rich oral supplements to malnourished, medical inpatients in the United States [27].

MALNUTRITION BIOMARKERS AND PREDICTORS FOR 'PERSONALIZED NUTRITION'?

To improve nutritional care of patients, one must not only ask if nutritional support reduces long-term malnutrition-associated risks but also what the underlying mechanisms are, and how to identify parameters to tailor nutritional support to the specific needs of patients. Published studies in the field of 'personalized nutrition' using biomarkers, proteomics, and metabolomics are promising [38,39▪].

Recently, inflammation has been identified as a main driver of malnutrition via several mechanisms, which negatively influence appetite and food intake. In addition, multiple cytokines affecting brain circuits control food intake, delay gastric emptying, and influence skeletal muscle catabolism. Inflammation markers are also helpful because of their highly prognostic responses to nutritional support. A secondary analysis of EFFORT comparing the success of individualized nutritional support vs. standard hospital food in reaching energy and protein goals discovered another interesting threshold: nutritional support did not reduce mortality in patients with C-reactive protein (CRP) greater than 100 mg/l as compared with patients with CRP concentrations 100 mg/l or less [39▪]. These effects were independent of infection and severity of disease, and suggest that individuals affected by severe inflammation may require different nutritional approaches than patients with lower levels of inflammation. The ideal strategy in cases with high inflammation is not yet clear, but could include nutrients with anti-inflammatory properties [40]. This finding may explain in part why results of many trials on the critically ill have been inconclusive and could help guide the initiation of more intensive nutrition therapy post-ICU. Further, it needs to be determined if CRP is a good marker to assess inflammation and possible treatment response in the population of ICU survivors as a recent secondary analysis of the EPaNIC trial shows that a rise of CRP was not related to cytokine responses and thus did not reflect more systemic inflammation [41].

Another similar study analysing kidney function at time of hospital admission, found significant association between worsening kidney function and benefits from improved nutrition [42]. This data suggests that worsening kidney function could also help to identify acutely ill patients who require special nutritional attention.

Another interesting and promising biomarker is the stress response cytokine growth-differentiation factor-15 (GDF15) [43▪], which elevates during aging and acute illness [44], and leads to illness-induced

anorexia, emesis, and aversive reactions to food [45]. A recent study of critically ill patients investigated the potential of low GDF15 to identify individuals who could benefit from early parenteral nutrition, tolerate enteral nutrition, and resume spontaneous oral intake. Although high GDF15 was strongly associated with severity of illness and poor prognosis, it did not identify patients who may benefit from – or be harmed by – early parenteral nutrition, and the association with enteral feeding (in) tolerance was weak [43▪]. However, as GDF15 is associated with poorer outcome and remains elevated during recovery and convalescence following acute illness compared with age-matched controls [44], it may be useful to investigate its prognostic value for response to nutrition support – not only in critical care but also in the recovery phase or in cases of acute illness not requiring ICU.

Other markers, however, have not improved the identification of patients most likely to benefit from treatment. In the past, circulating albumin levels at hospital admission were used as biochemical markers for nutritional assessment. One recent study has suggested that although low-admission albumin in hospitalized patients at nutritional risk has prognostic implications and indicates higher risk of mortality, it is not helpful in selecting patients for nutritional intervention [46]. These results are in line with a recent consensus paper and a meta-analysis concluding that albumin levels should be used to evaluate severity of disease but not to assess nutritional status or diagnose malnutrition [12,47,48]. This may be because albumin serum concentrations are affected by many nonnutritional factors – mostly reflecting acute disease or inflammation – but not by available plasma proteins or nutritional status [48,49]. The visceral protein albumin is a negative acute-phase protein whose levels are inversely correlated with CRP. Normalization of albumin may, therefore, not result from nutritional changes or albumin therapy but rather from the resolution of inflammation [50]. Therefore albumin is no longer recommended to use in ICU patients as a biomarker for nutritional status as its plasma concentration is rapidly and markedly decreased by inflammatory conditions [51].

Finally, no convincing data exists to demonstrate that the addition of proteonomic or metabolomic data improves patient phenotyping for malnutrition and response to treatment [52]. Further tools to measure gut microbiota or nutrigenetics could also be applied to advance personalized nutrition, but studies investigating their benefit for patient management are lacking here as well.

CONCLUSION

Although feeding should start in the ICU, it is important to continue and adapt nutritional plans on the ward to support individuals recovering from critical illness and improve clinical outcomes. Because not every patient may show the same benefit from nutritional support, it is important to better personalize nutritional treatment in the future by use of specific biomarkers that could help to predict treatment response in the post-ICU period.

Acknowledgements

P.S. is supported by grantsof the Swiss National Science Foundation (SNSF Professorship, PP00P3_150531) and the Research Committee of the Kantonsspital Aarau (1410.000.058 and 1410.000.044). P.S.'s institution has previously received unrestricted grant money from Nestle Health Science and Abbott Nutrition. All other authors report no conflicts of interest within the last 36 months.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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3.2.2. Inflammation and response to nutrition interventions [94]

Author contributions:

CW, Carla Wunderle; FS, Franziska Stumpf; PS, Philipp Schuetz,

CW: Conceptualization, literature search, writing - original draft preparation, writing – review and editing and visualization. FS: preparation of first draft of figures, review and editing and visualization. PS: Conceptualization, investigation, writing – review and editing, project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

DOI: 10.1002/jpen.2534

REVIEW

Inflammation and response to nutrition interventions

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Funding information
Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung, Grant/Award Numbers: SNSF Professorship, PP00P3_150531; Forschungsrat des Kantonsspitals Aarau, Grant/Award Numbers: 1410.000.058, 1410.000.044

Abstract

The complex interplay between nutrition and inflammation has become a major focus of research in recent years across different clinical settings and patient populations. Inflammation has been identified as a key driver for disease-related malnutrition promoting anorexia, reduced food intake, muscle loss, and on a cellular level, insulin resistance, which together stimulate catabolism. However, these effects may well be bidirectional, and there is strong evidence showing that nutrition influences inflammation. Several single nutrients and dietary patterns with either proinflammatory or anti-inflammatory properties have been studied, such as the long-chain ω-3 fatty acids eicosapentaenoic acid or docosahexaenoic acid. The Mediterranean diet combines several such nutrients and has been shown to improve medical outcomes in the outpatient setting. In addition, there is increasing evidence suggesting that inflammation affects the metabolism and modulates the response to nutrition support interventions. In fact, recent studies from the medical inpatient setting suggest that inflammation, mirrored by high levels of C-reactive protein, diminishes the positive effects of nutrition support. This may explain the lack of positive effects of some nutrition trials in severely ill patients, whereas similar approaches to nutritional support have shown positive results in less severely ill patients. The use of biomarkers, such as C-reactive protein, may help to identify patients with a lower response to nutrition, in whom other treatment options need to be used. There is need for additional research to understand how to best address the malnourished patient with inflammation by specifically lowering inflammation through anti-inflammatory medical treatments and/or nutrition interventions.

KEYWORDS
clinical outcome, disease-related malnutrition, inflammation, personalized nutrition, treatment response

INTERPLAY BETWEEN NUTRITION AND INFLAMMATION

Inflammation has been classified into acute or chronic inflammation, which differ from duration of the process as well as various immune factors.[1] Although chronic inflammation has been studied extensively and has been shown to be associated with cardiovascular disease and other illnesses,[2–4] acute inflammation is predominant in acute illness, lasting normally from minutes to a few days. Acute inflammation has a complex regulation and is mediated by innate immunity and the increase of several acute-period proteins, including C-reactive protein (CRP) (Figure 1).[1] In inflammatory response, leukocytes and

This review was invited by the ASPEN Physicians Engagement Committee.

mast cells are present, which lead to a "respiratory burst" as a result of an enhanced uptake of oxygen and, therefore, enhance the production and release of reactive oxygen species (ROS). Free radicals can also further induce inflammation[5,6] if not resolved within antioxidative capacities. In healthy body condition, there is a balance between ROS/free radical and endogenous antioxidant defense mechanisms. A disturbed balance, however, can lead to oxidative stress and associated damage. This oxidative stress state can cause injury to all vital cellular components, such as DNA, proteins, and membrane lipids, and it may lead to cell death (Figure 2). Additionally, it plays a major role in the development of illnesses, including cardiovascular diseases, diabetes, degenerative diseases, cancer, anemia, and ischemia.[1,7]

In addition to anti-inflammatory strategies, such as the use of glucocorticoids, there is important evidence suggesting that the inflammatory response can be modulated by nutrition. In fact, specific ingredients have been shown to have proinflammatory or anti-inflammatory properties. The most studied nutrition components in this regard with strong anti-inflammatory properties are specific polyunsaturated fatty acids (PUFAs), for instance the long-chain ω-3 FAs eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid. On the other hand, certain long-chain ω-6 FAs like the arachidonic acid (AA) have shown proinflammatory effects.[8] These nutrients are substrates for immunomodulatory mediators, such as prostaglandins, thromboxanes, and leukotrienes, which mediate either an anti-inflammatory or a proinflammatory effect depending on the starting substrate. Moreover, because of the use of the same enzymes in both pathways, ω-3 FAs have the potential to competitively reduce the metabolism of ω-6 FAs to proinflammatory mediators.[9] Yet the effect of ω-3 FA supplementation on important clinical outcomes, such as mortality, has not been conclusively demonstrated in randomized controlled clinical trials.[10,11] Next to specific long-chain FAs, there are various bioactive substances, such as polyphenols, that influence inflammation in different ways, for example, by interfering with immune cell regulation, proinflammatory cytokines' synthesis, and gene expression. They can also inactivate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and modulate mitogen-activated protein kinase and AA pathways and influence inflammation this way.[12]

In recognition of the complex interactions of different nutrients within a particular diet, the focus has shifted towards research on the effects of dietary patterns instead of single nutrients.[13] Two of the most extensively investigated dietary pattern in terms of its anti-inflammatory effects in the outpatient setting is the Mediterranean diet and a fiber-rich diet. Next to high intake of plant-based nutrients and nonprocessed food, both are often associated with a high intake of polyphenols and complex carbohydrates, which may have anti-inflammatory effects, including their turnover of nondigestible

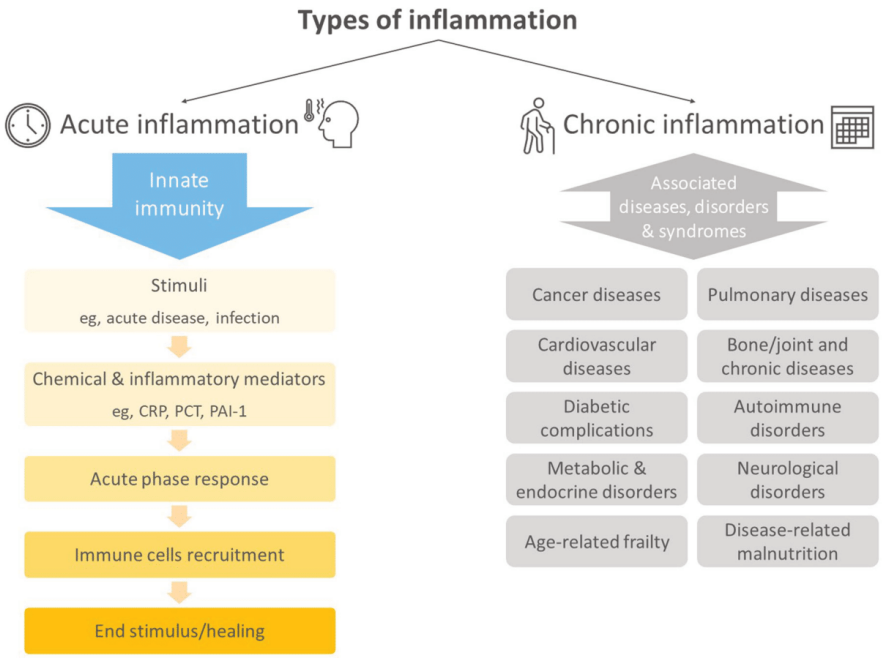

FIGURE 1 Different types of inflammation: the cascade of acute inflammation and selected associations of chronic inflammation with diseases. CRP, C-reactive protein; PAI-1, plasminogen-activator-inhibitor type 1; PCT, procalcitonin.

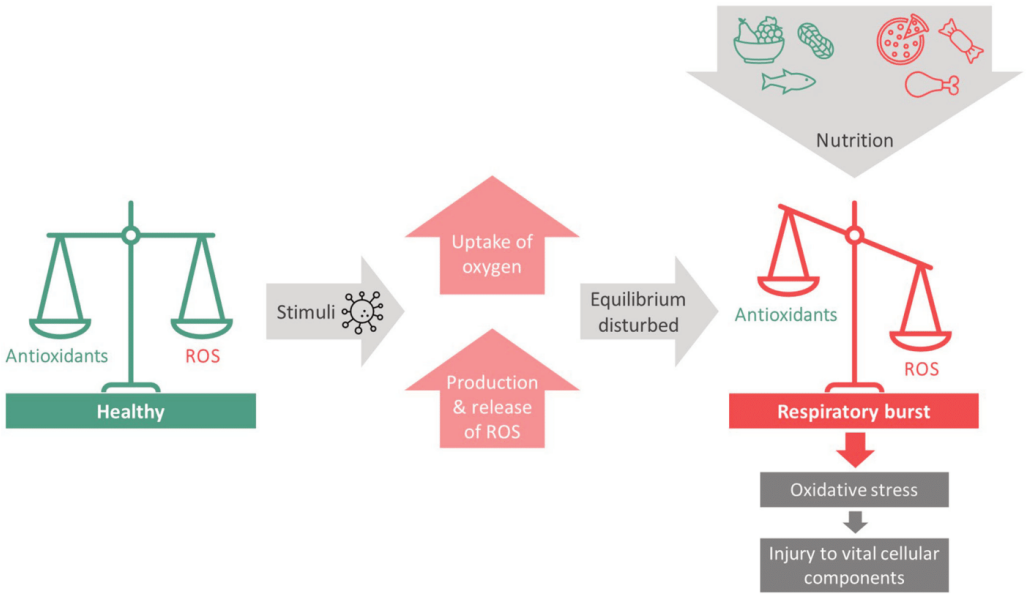

FIGURE 2 Oxidative stress, inflammation, and the influence of immunomodulatory nutrients. ROS, reactive oxygen species.

carbohydrates into immuno-regulators substances like short-chain FAs by the gut microbiota.[14,15] Importantly, most of the studies focused on long-term nutrition interventions and outpatients with chronic inflammation and did not investigate acute inflammation in acute medicine patients.[16] There are, however, several medical options to reduce the systemic inflammatory response, including corticosteroids and anti–interleukin (IL) 6 inhibitors, which have been used successful in hyperinflammation during COVID-19.[17] Nevertheless, within this review, we will focus mainly on anti-inflammatory effects of nutrition. Although there are convincing data showing that nutrition has a strong effect on inflammation, we are now starting to understand how inflammation affects the way the body responds to diet, which will be the focus of this review.

DISEASE-RELATED MALNUTRITION

Disease-related malnutrition (DRM) is a multifactorial complex syndrome that is negatively affected by disease-related systemic inflammatory response,[18] contributes to high morbidity and mortality,[19,20] and seriously interferes with recovery from acute illness.[21] In industrialized countries, malnutrition is mainly disease-related and its relevance is reflected by its prevalence. Data from Europe and the United States demonstrate that about 30% of patients have malnutrition or are at risk at hospital admission.[18,22,23]

The European Society of Clinical Nutrition and Metabolism (ESPEN) proposes three etiological groups of malnutrition: DRM with inflammation, DRM without inflammation, and malnutrition/undernutrition without disease.[24] To diagnose malnutrition, the Global Leadership Initiative on Malnutrition (GLIM) proposes a 2-step approach consisting of a nutrition risk screening followed by a more detailed assessment. If a nutrition risk is detected, a nutrition assessment for diagnosis should be performed, including etiological (reduced food intake or assimilation, and disease burden/inflammation) and phenotypic (nonvolitional weight loss, low body mass index [BMI], and reduced muscle mass) criteria. According to GLIM, the diagnosis of malnutrition is made if one etiological and one phenotypic criterion apply for the patient.[25] The ESPEN classification and also the GLIM criteria include inflammation as an etiological factor, revealing its relevance in DRM. They also suggest that DRM with or without inflammation are different malnutrition phenotypes. However, the question whether these phenotypes also need a different therapeutic approach has not been conclusively answered today.

WHY IS OUR PATIENT BECOMING MALNOURISHED?

The pathogenesis of DRM is complex and often results from different factors, including starvation, acute or chronic disease (eg, polypharmacy, disease-related inflammatory mechanisms, and compromised intake or assimilation of nutrients), immobility-associated muscle wasting, and older age or social isolation. Focusing on inflammation,

which has been suggested to be the main driver of DRM, there are several effects on the metabolism. There are measurable elevated levels of proinflammatory cytokines like tumor necrosis factor α (TNF-α), CRP, IL-1β, and IL-6. The release of those is mainly caused by activation of the hypothalamic–pituitary axis, a systemic response to a stressor like disease or other noxious stimuli. Affecting brain circuits, proinflammatory cytokines control food intake, delay gastric emptying, and increase skeletal muscle catabolism.[18,26] Further modulation of the hypothalamic-pituitary-adrenal axis provokes the release of stress hormones, including cortisol and catecholamines, and suppresses other hormones regulating sex, thyroid, and other peripheral functions.[27] In malnutrition, the deiodination of thyroxine (T_4) to triiodothyronine (T_3) was shown to be down-regulated—a process called "low T_3 syndrome," which is an adaptive metabolic mechanism to reduce energy expenditure and prevent catabolism.[28] Catecholamines and cortisol increase glycogenolysis and hepatic gluconeogenesis excessively while simultaneously inducing peripheral insulin resistance and inhibiting glucose from entering peripheral tissues, such as the skeletal muscles.[27]

HAVE WE MADE PROGRESS IN TREATING MALNUTRITION?

There has been intensive research on how to detect and diagnose malnutrition.[25] These findings have led to an improvement in early detection and thus the start of therapy. Although the possible benefits of nutrition therapy in malnourished patients have long been unclear,[29,30] recently there has been growing evidence in favor of nutrition therapy in the medical inpatient setting, also due to large high-quality randomized controlled trials (RCTs).[19,20] In a recent meta-analysis, Gomes et al found that nutrition therapy significantly reduces the risk for mortality by 25%. Also, nutrition interventions during the hospital stay reduced the risk of complications and hospital readmission, improved functional outcome, and prevented body weight loss in medical inpatients. Compared with studies published before 2014, which were predominantly heterogeneous and of small sample size, studies published after 2014 had an even more pronounced beneficial effect on mortality (odds ratio [OR]: 0.47, 95% CI: 0.28–0.79), which indicates an improvement in nutrition treatment.[31] Further stratifications demonstrated that trials using high-protein nutrition interventions and whose intervention lasted longer than 60 days were the most effective. Among the trials, nutrition strategies used were dietary counselling, food modifications and optimization, supplement prescriptions, oral nutritional supplements, individualized nutrition plans, or nutrition care from healthcare assistants. There were no studies included using enteral or parental feeding strategies.[32] These investigations provided important evidence that nutrition support is a highly effective therapy in medical inpatients with improvements in clinical outcomes.

Interestingly, these positive results were not consistent across different patient populations. A Cochrane review from 2017 also including critically ill and surgical patients (and higher-risk parenteral and enteral nutrition trials) has only found few significant beneficial effects on clinical outcome and some controversial effects.[29] Herein, a highly vulnerable population are patients treated in intensive care units (ICUs). These patients are severely ill and often are unable to feed volitionally by mouth for periods up to weeks.[21] The catabolic response is much more pronounced than that evoked by fasting in healthy persons, since the energy deficit in acutely ill patients is often superimposed on immobilization and pronounced inflammatory and endocrine stress response.[33] Even after ICU discharge, the majority of patients remain nutritionally compromised and oral intake of food continues to be hampered by various barriers like low appetite, taste changes, impaired swallow function, gastrointestinal disturbances, or psychosocial factors.[34] A comparison of five large ICU trials (eg, EPaNIC trial with 4640 patients[35] comparing early or full nutrition support to standard care and more [Table 1]) showed that every nutrition intervention improved energy and protein intake. Nutrition interventions included a combination of oral, enteral, and parenteral nutrition. Interestingly, reaching higher energy and protein goals did not translate into improved clinical outcome and mortality, length of ICU stay, or need for mechanical ventilation in these trials. The findings of these recent adequately powered RCTs limit the number of nutrition interventions that can be confidently recommended for critical care patients. There is need for research on the mechanisms underlying benefit or harm from nutrition support and additionally to identify biomarkers of the anabolic recovery period to guide the initiation of more intense feeding. A validated scoring system to predict treatment response would potentially further help selecting patients and improving nutrition treatment.

WHY DO WE SEE DIFFERENCES IN TREATMENT RESPONSE?

An important research question in nutrition research is why there are such differences in treatment response among different patient populations. Although recent research has focused more on the detection and diagnosis of malnutrition, it will be important to now focus on understanding whether different malnutrition phenotypes exist that respond differently to different types of nutrition interventions. Herein, the severity of inflammation may be an important consideration. A hypermetabolic, burned, and highly inflamed patient unable to eat volitionally, who is treated in the receiving ICU, is obviously a different patient with different nutrition needs compared with an older geriatric patient with low appetite, who is not eating enough. Although there is already a consensus that nutrition protocols should be individualized regarding nutrition targets for inpatients (mainly based on their BMI and severity of illness) in critical care and hospital ward settings, current research suggests that tailoring nutrition to the specific medical and metabolic condition could further improve the effectiveness of nutrition intervention. Herein, a better understanding of the underlying pathophysiology is key to developing effective new interventions.[18]

TABLE 1 Comparison of mortality and length of ICU stay in five randomized controlled trials during critical illness.

	EDEN trial	Early PN trial	EPaNIC trial	SPN trial	TICACOS
Full name	Trophic vs full-energy enteral nutrition in mechanically ventilated patients with acute lung injury	Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition	Early parenteral nutrition completing enteral nutrition in adult critically ill patients	Impact of supplemental PN on infection rate, duration of mechanical ventilation, and rehabilitation in ICU patients	Tight calorie control study
Number of patients	1000	1372	4640	305	130
Length of stay in ICU	Unaffected	Unaffected	Longer with early PN	Unaffected	Longer with REE
Mortality in ICU	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected

Abbreviations: ICU, intensive care unit; PN, parenteral nutrition; REE, resting energy expenditure.

PERSONALIZED NUTRITION AND THE USE OF BIOMARKERS

The concept of personalized nutrition is based on the observation that not all patients show the same response to nutrition interventions.[18] Even in a homogenous cohort, clinically relevant differences can be seen regarding treatment response.[19] The EFFORT trial (Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial) investigated the effect of individualized nutrition support to reach energy and protein targets in polymorbid medical inpatients at nutrition risk. This large non-ICU nutrition trial with >2000 patients was conducted in eight Swiss hospitals. Although the overall effect of nutrition support on mortality (adjusted OR: 0.65, 95% CI: 0.47–0.91; $P = 0.011$) and adverse events (adjusted OR: 0.79, 95% CI: 0.64–0.97; $P = 0.023$) was positive, there were some noteworthy differences within certain subgroups.

Focusing on different illness-related factors, Bargetzi et al investigated the effects of nutrition support on mortality in subgroups of patients stratified according to kidney function at the time of hospital admission (estimated glomerular filtration rates [eGFRs] <15, 15–29, 30–59, 60–89, and ≥90 ml/min/1.73 m^2) in the EFFORT cohort.[36] Patients with a chronic kidney disease admitted to the hospital are often at risk for malnutrition or already malnourished and their status can further deteriorate during the hospital stay.[37] Bargetzi et al demonstrated that, within this population, patients with a lowered kidney function (eGFR 15–59 ml/min/1.73 m^2) had a more pronounced survival benefit through nutrition support compared with patients with an eGRF >60 ml/min/1.73 m^2.

Another important analysis focused on inflammation within the EFFORT cohort. The most used inflammatory marker to assess inflammation in the acute phase of illness is CRP. When stratifying the EFFORT cohort according to CRP groups, nutrition support did not reduce mortality in patients with high CRP levels >100 mg/L as compared with patients with CRP concentrations ≤100 mg/L (Figure 3).[38] These effects were independent of infection and severity of disease and suggested that nutrition support is less effective in individuals with severe inflammation. Interestingly, a further analysis within EFFORT showed that the subgroup of patients with different types of cancer had a benefit of nutrition support, which again was not found in cancer patients with high inflammation.[39,40] This finding may explain the heterogeneity of results of nutrition trials, with some trials in the critically ill not showing beneficial results. Yet how to best approach the patient with severe inflammation is not yet clear, but it could include nutrients with anti-inflammatory properties.[41] Further, it needs to be determined if CRP is a good marker to assess inflammation and possible treatment response in the population of ICU survivors, as a recent secondary analysis of the EPaNIC trial shows that a rise of CRP was not related to cytokine responses and thus did not reflect higher systemic inflammation.[42] Furthermore, CRP as an acute-phase protein cannot represent the entire systemic inflammatory response, is influenced by noninfectious factors (eg, cardiovascular diseases, cirrhosis, cancer or systemic lupus erythematosus), and has a high interpersonal variability, and values can fluctuate from day to day.[43] Furthermore, it seems complicated to assess whether high CRP values reflect acute or chronic inflammation. Additional biomarkers, including proinflammatory cytokines (eg, interleukin, TNF), biomarkers of activated neutrophils and monocytes (eg, cluster of differentiation), infectious organisms, and related protein or receptors (eg, toll-like receptors, TNF receptors), would provide a more sophisticated assessment for inflammation.[44] To date, to our knowledge, no study has conclusively examined inflammatory status and response to nutrition therapy with a combination of the above inflammatory biomarkers.

Besides CRP, no other parameter has been considered to select patients for nutrition support. Albumin serves as a negative acute-phase protein and was historically used to assess nutrition status or to evaluate progress of nutrition support.[45] A recent study investigated the question whether selecting patients for nutrition

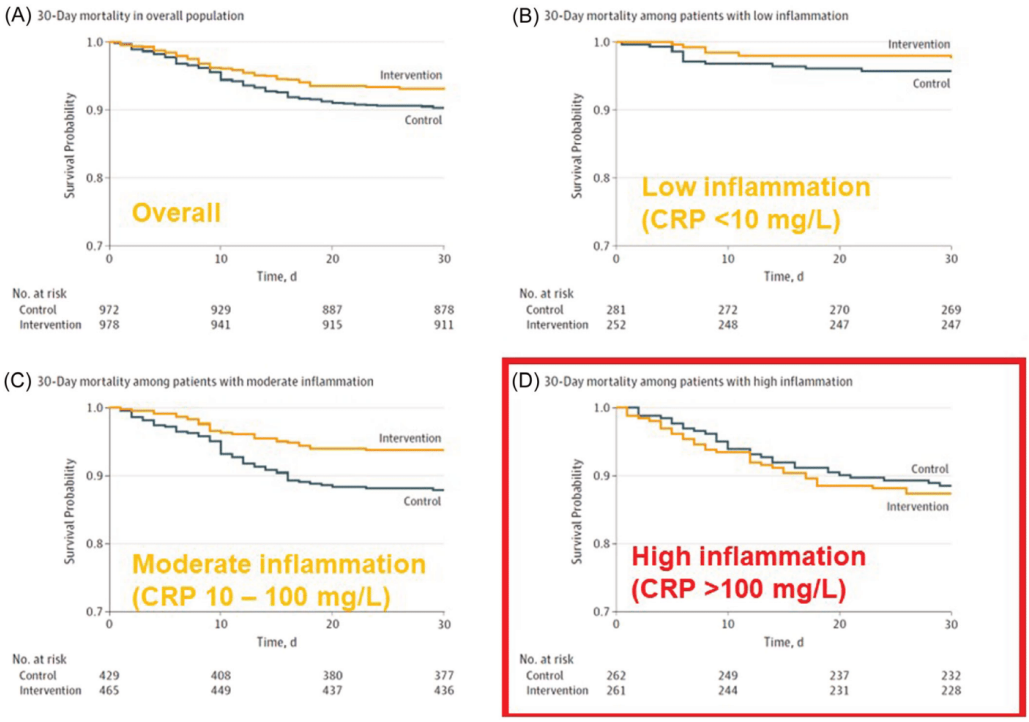

FIGURE 3 Kaplan-Meier estimate for time to death within 30 days according to inflammatory status. *Source*: Adapted from Merker et al.[38] CRP, C-reactive protein.

support by serum albumin level or prealbumin is helpful. Although patients with a low serum albumin level (<30 g/L) had a significantly higher risk to die within 30 days (adjusted hazard ratio [HR]: 1.4, 95% CI: 1.11–1.77; $P = 0.005$), the effects of nutrition support on 30-day mortality were similar for patients with a low serum albumin level compared with patients with normal serum albumin concentrations, with no evidence for a subgroup effect.[46] As albumin has a particular long half-life time, prealbumin with a half-life time of approximately 2 days, may be more accurate for characterization of patients in the acute care setting. A post hoc analysis demonstrated a similar prognostic value of prealbumin (adjusted HR: 1.59, 95% CI: 1.11–2.28; $P = 0.011$) for mortality. However, regarding the predictive value of treatment response, prealbumin also failed to identify patients who benefit from nutrition support.[47]

It is worth noting that there is a wide range of possible biomarkers that have been studied in regard to assessnig malnutrition. Next to common serum visceral proteins like mentioned albumin or prealbumin, also transferrin or retinol-binding protein have been considered. Other laboratory markers that are associated with malnutrition are urinary creatinine, urinary 3-methylhistidine, serum cholesterol, blood lymphocyte count, serum insulin-like growth factor-1 (IGF1), serum leptin and many more. Also, proteonomic and metabolomic markers have been studied.[48,49] Because of their association with malnutrition, these different markers may be considered potential candidates for predicting response to nutrition treatment, but it is important to consider individual limitations of each marker.[50] Besides, hypothesis-generating studies on treatment response are lacking so far.

To summarize, in medical inpatients at nutrition risk, there are some promising biomarkers, which might help to personalize nutrition support in the near future. Clearly, validation studies will be needed, and results are so far rather hypothesis-generating and mostly generated by secondary analyses. A possible potent and well-studied biomarker for treatment response is CRP in non-ICU patients, which represents acute inflammation but has low specificity. Using biomarkers to stratify patients according to their malnutrition phenotype and their treatment response will be key to evolve from traditional treatment to individualized and eventually personalized/precise treatment (Figure 4).

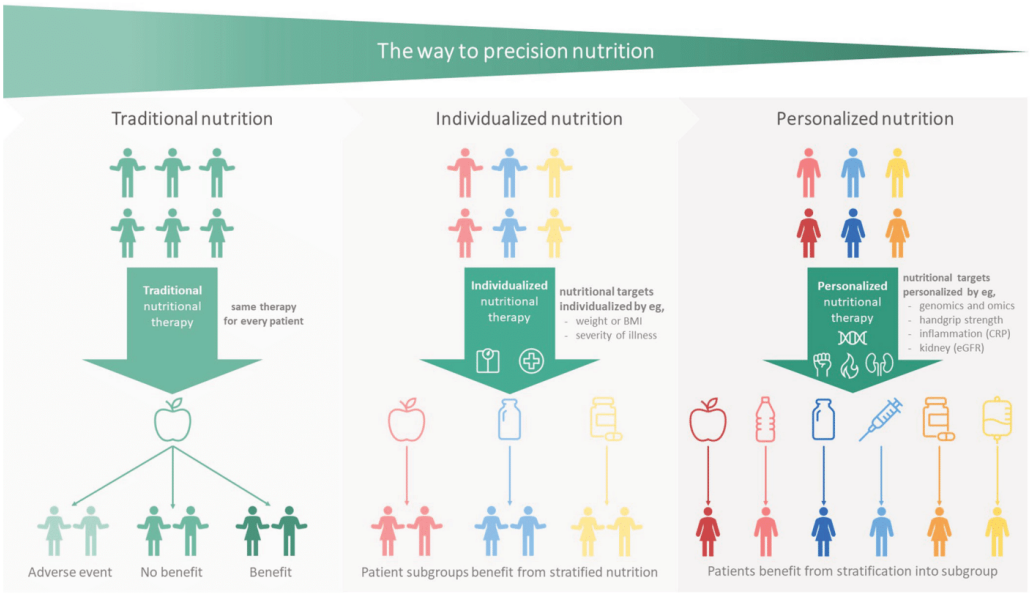

FIGURE 4 The way to precision nutrition. BMI, body mass index; CRP, C-reactive protein, eGFR, estimated glomerular filtration rate.

EFFECTS OF INFLAMMATION ON METABOLISM

As a key driver of malnutrition, inflammation has several effects on the metabolism, which might explain the less pronounced effects of nutrition support in highly inflamed patients observed in previous studies. Several mechanisms may explain these effects. A well-known effect of acute inflammation in medical inpatients is cytokine-induced anorexia. Inflammation also interferes with gastrointestinal motility, leading to gastroparesis and nausea.[51] Further, neuroendocrine response, together with inflammatory response, leads to mobilization of energy storages, triggering the release of FAs by lipolysis, the release and degradation of glucose from glycolysis, glycogenolysis, and gluconeogenesis in the liver and release of amino acids from muscle proteolysis. These metabolic changes cause hyperglycemia, together with peripheral insulin resistance, hindering glucose entering the cells. All this culminates to uncontrolled catabolism, which leads to an increase in the release of ROS and therefore enhanced inflammation.[26]

Nutrition support alone appears to be ineffective in reversing the impaired metabolism because insulin resistance and other previously mentioned mechanisms prevent adequate metabolism of the ingredients. Past trials in the ICU or with patients with advanced cancer support this hypothesis.[33,52]

In addition to elevated ROS levels, other mechanisms may exist. Macroautophagy, also called autophagy, is responsible for clearing potentially toxic protein aggregates and damaged organelles and is the only pathway able to degrade such bulk cytoplasmic material. It has a crucial role in maintaining integrity of cells, organs, or tissues and has a fundamental role in immunity. The cytoplasmic clean-up function of autophagy is by default anti-inflammatory in any type of cells and like this contributes to the inflammatory response to a stressor.[53] There is evidence from some studies in critically ill patients suggesting that [over]nutrition interferes with autophagy, thereby lowering detoxication of cells with negative effects on outcomes.[54] Vanhorebeek et al studied the activation of autophagy in hepatic and skeletal muscle biopsies within a trial focusing on hyperglycemia prevention in prolonged critically ill patients. Morphologically, both liver and skeletal muscle revealed an autophagy-deficiency phenotype. Proteins involved in the key steps of autophagy were induced 1.3- to 6.5-fold by critical illness ($P = 0.01$), but mature autophagic vacuole formation was impaired by 62% ($P = 0.05$) and proteins normally degraded by autophagy accumulated up to 97-fold ($P = 0.03$). Also, specific mitophagy markers were unaltered or down-regulated ($P = 0.05$). Despite obvious attempts of the ill body to activate the autophagic machinery, this pathway appeared incomplete and insufficient as indicated by a reduced number of mature autophagic vacuoles, accumulation of specific substrates, and damaged organelles normally eliminated by autophagy. Autophagy can be influenced—two of the most powerful suppressors of autophagy are nutrients and insulin through the activation of mTOR pathway.[55] Considering

the previously mentioned impaired autophagy in critical illness and the assumed additional suppressive effect of nutrients on autophagy, the role of artificial (enteral and parenteral) and aggressive feeding during critical illness should be further investigated.[54] This finding supports the hypothesis that especially overfeeding might be more harmful in this patient population.

Therefore, there is a need to find biomarkers that indicate when the patient is ready to be fed or to receive more intensive nutrition therapy. In a secondary analysis of the EPaNIC trial, Van Dyck et al aimed to find a "ready-to-feed indicator" for critically ill adults. They investigated the predictive potential of the circulating growth differentiation factor 15 (GDF15), a cellular stress marker that abruptly increases during critical illness. Within the EPaNIC cohort GDF15 was elevated throughout ICU stay, but similarly in early parenteral nutrition and late parenteral nutrition patients, and remained high beyond ICU discharge. It was only weakly related to gastrointestinal tolerance and the potential as "ready-to-feed indicator" appears limited.[56] So far, no other biomarker that indicates the optimal timing for nutrition initiation could have been identified. Thus, the intention to find a suitable marker remains important for the future of personalized nutrition.

COMPLEXITY OF INVESTIGATING INFLAMMATION

Investigating the interplay between nutrition and inflammation is a highly complex task with many confounding factors, and there are many questions to answer. There are several processes within the cellular level and the core that occur beforehand and thus not fully accounted for.[57] Simultaneous analysis of complement factors, cytokines, chemokines, and other mediators would provide a more integrated picture of inflammation and the disease process[58] but will be difficult to transfer into clinical practice. In addition, a difficulty in studying the effect of inflammation on treatment response is that many of the used biomarkers are also biomarkers of disease severity. Therefore, there is overlap, and the individual effects cannot always be determined so far.

CONCLUSIONS

Inflammation is a key driver of DRM leading to anorexia and a compromised metabolism of ingested nutrients in medical inpatients. There is current evidence suggesting that stratifying patients according to their inflammatory state (eg, on the basis of CRP levels) might be useful for predicting the benefit of nutrition support. The approach on how to feed highly inflamed patients is unclear today. There are certain nutrients and dietary patterns that have anti-inflammatory properties, but there are no data showing that these nutrients would be of benefit for the patient with high inflammation today. Within this research area, the complexity of inflammatory processes at different levels (nucleus, cell, and systemic level) must be kept in mind. In the future, biomarkers might help to guide initiation of nutrition therapy and to select patients who would benefit from nutrition support.

AUTHOR CONTRIBUTIONS

Carla Wunderle, Franziska Stumpf, and Philipp Schuetz contributed to the conception and design of the manuscript; and Carla Wunderle drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Dr P. Schuetz is supported by grants of the Swiss National Science Foundation (SNSF Professorship, PP00P3_150531) and the Research Committee of the Kantonsspital Aarau (1410.000.058 and 1410.000.044). Dr P. Schuetz's institution has previously received unrestricted grant money from Nestlé Health Science and Abbott Nutrition. The remaining authors declare no conflict of interest within the last 36 months.

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How to cite this article: Wunderle C, Stumpf F, Schuetz P. Inflammation and response to nutrition interventions. *J Parenter Enteral Nutr*. 2024;48:27-36. doi:10.1002/jpen.2534

3.2.3. Adaptation of nutritional risk screening tools may better predict response to nutritional treatment. A secondary analysis of the randomized controlled trial EFFORT [95]

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CW, JS, DS and PS designed the research. CW and JS conducted the research and analyzed data/performed statistical analysis. CW, JS, DS, MOM, and PS wrote the paper. PS, DS, CW, BM, ZS, and PT had primary responsibility for final content. All authors read and approved the final version of the manuscript.

The American Journal of Clinical Nutrition xxx (xxxx) xxx

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Original Research Article

Adaptation of nutritional risk screening tools may better predict response to nutritional treatment: a secondary analysis of the randomized controlled trial Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT)

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A B S T R A C T

Background: Nutritional screening tools have proven valuable for predicting clinical outcomes but have failed to determine which patients would be most likely to benefit from nourishment interventions. The Nutritional Risk Screening 2002 (NRS) and the Mini Nutritional Assessment (MNA) are 2 of these tools, which are based on both nutritional parameters and parameters reflecting disease severity.

Objectives: We hypothesized that the adaptation of nutritional risk scores, by removing parameters reflecting disease severity, would improve their predictive value regarding response to a nutritional intervention while providing similar prognostic information regarding mortality at short and long terms.

Methods: We reanalyzed data of 2028 patients included in the Swiss-wide multicenter, randomized controlled trial EFFORT (Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial) comparing individualized nutritional support with usual care nutrition in medical inpatients. The primary endpoint was 30-d all-cause mortality.

Results: Although stratifying patients by high compared with low NRS score showed no difference in response to nutritional support, patients with high adapted NRS showed substantial benefit, whereas patients with low adapted NRS showed no survival benefit [adjusted hazard ratio: 0.55 [95% confidence interval (CI): 0.37, 0.80]] compared with 1.17 (95% CI: 0.70, 1.93), a finding that was significant in an interaction analysis [coefficient: 0.48 (95% CI: 0.25, 0.94), $P = 0.031$]. A similar effect regarding treatment response was found when stratifying patients on the basis of MNA compared with the adapted MNA. Regarding the prognostic performance, both original scores were slightly superior in predicting mortality than the adapted scores.

Conclusions: Adapting the NRS and MNA by including nutritional parameters only improves their ability to predict response to a nutrition intervention, but slightly reduces their overall prognostic performance. Scores dependent on disease severity may best be considered prognostic scores, whereas nutritional risk scores not including parameters reflecting disease severity may indeed improve a more personalized treatment approach for nourishment interventions.

The trial was registered at clinicaltrials.gov as NCT02517476.

Keywords: disease-related malnutrition, nutritional support, mortality, nutritional risk screening, treatment response, personalized nutrition, clinical outcome, polymorbid medical inpatient

Abbreviations: CI, confidence interval; CRP, C-reactive protein; EFFORT, Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial; ESPEN, European Society for Clinical Nutrition and Metabolism; HR, hazard ratio; ICU, intensive care unit; MNA, Mini Nutritional Assessment—Long Form; NRS, Nutritional Risk Screening 2002; OR, odds ratio.

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https://doi.org/10.1016/j.ajcnut.2024.01.013
Received 15 November 2023; Received in revised form 18 January 2024; Accepted 22 January 2024; Available online xxxx

Introduction

Disease-related malnutrition affects at least one-third of medical inpatients, and is a condition strongly associated with reduced quality of life, higher mortality, increased complications, and impaired functional status [1–4]. However, current definitions for malnutrition conflate wasting because of disease and wasting because of starvation [5,6] and thus may not accurately predict whether a nourishment intervention will be of benefit. To detect and quantify risk of malnutrition, several screening and assessment tools have been validated. These scores usually combine parameters that reflect nutritional status as well as other risk factors including age and disease severity. Among these scores, the Nutritional Risk Screening 2002 (NRS) [7] and the Mini Nutritional Assessment—Long Form (MNA) [8] are widely used and fast to perform, and are validated screening or assessment tools for predicting the development of malnutrition and clinical outcomes in general. Early screening and initiation of nutritional support are discussed as particularly important because several randomized controlled trials and meta-analyses have demonstrated that nutritional support improves clinical outcomes by reducing mortality and complications [1,9–11]. However, despite these findings, a large body of literature has failed to demonstrate the benefits to nourishment interventions on the basis of standard assessments. For example, a large-scale Cochrane meta-analysis, which included a mixed heterogeneous patient population, showed no significant effect of nutritional intervention [12]. Various other studies have suggested that there are differences in regard to nutritional treatment response. A secondary analysis of the EFFORT (Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial) revealed that patients with high C-reactive protein (CRP) concentrations (>100 mg/L) had less benefit from nutritional therapy compared with patients with moderate or low CRP concentrations (<100 mg/L) in terms of 30-d mortality [13]. Concurring findings were also reported from randomized controlled trials conducted in severely ill patients in the intensive care unit (ICU) setting, when increasing energy and protein intake did not translate into improved clinical outcomes [14–17]. This indicates that disease-related malnutrition may not respond to nutritional interventions in some patient populations, particularly those with high disease severity [18].

Historically, nutritional therapy has been used in patients at risk of adverse outcomes that are associated with malnutrition but may or may not be caused by malnourishment. A better understanding of malnutrition phenotype, reflecting the specific pathophysiology, may allow for better characterization of patients and selection of those who will benefit most from nutrition, contributing to a more personalized approach. Finding biomarkers or scores that help identify patients who benefit from certain nutritional interventions is therefore crucial in the concept of personalized medicine [2]. Although common screening and assessment tools such as the NRS or MNA [8] are well validated to predict risk of developing malnutrition and associated adverse clinical outcomes, these tools have not been validated for selecting patients who can benefit from nutritional support and have shown to lack the predictive value [19].

Herein, we tested the hypothesis that an adaptation of malnutrition screening scores by removing disease severity would improve their predictive value regarding treatment response within a large cohort of patients from the randomized controlled EFFORT. We posit that, because disease severity has been shown to potentially negate the benefit of nourishment [13], the inclusion of markers of disease severity may negate the predictive value, and the removal of markers of disease severity contained within nutrition assessment tools will increase the predictive value of these measures. In addition, we investigated whether adapting the risk scores reduces their prognostic value in terms of predicting clinical outcomes such as mortality.

Methods

Study design and setting

This is a secondary analysis of EFFORT, a prospective multicenter randomized controlled trial that was conducted in 8 Swiss hospitals from April 2014 to February 2018 [1]. EFFORT compared the effect of individualized nutritional support with usual care in medical inpatients at nutritional risk. The main results, the study protocol, as well as different secondary analyses were published previously [1,13,19–26]. The Ethics Committee of Northwestern Switzerland (EKNZ; 2014_001) approved the trial in January 2014 and it was registered at ClinicalTrial.gov (NCT02517476).

Patient population and interventions

Adult inpatients (≥18 y of age) at nutritional risk (NRS total score ≥ 3 points) and with an expected hospital stay of >4 d who were willing to sign an informed consent form participated in the EFFORT. Exclusion criteria were an initial hospitalization in ICUs or surgical wards; unable to ingest oral nutrition; already receiving nutritional support at admission; with a terminal condition; admitted to the hospital because of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, or stem-cell transplantation; after gastric bypass surgery; with contraindications for nutritional support; and previously included in the trial. All patients were randomly assigned (1:1) by an interactive web-response system, clustered by the NRS total score, either to the intervention group with individualized nutritional support or to the control group receiving usual hospital food. The treatment of intervention group patients was initiated within 48 h after hospitalization on the basis of a previously published consensus protocol and in accordance with international guidelines [27,28] to reach energy and protein goals. A trained registered dietitian defined an individual nutrition plan for each patient with calculated energy and protein targets. For energy requirements, the Harris–Benedict equation [29] was used and protein goals were set at 1.2–1.5 g/kg body weight per day, except in patients with kidney failure, where it was 0.8 g/kg body weight per day [30]. The diet plan was initially based on oral nutrition provided by the hospital kitchen and oral nutrition supplements. An escalation to enteral tube feeding or parenteral feeding was recommended if ≥75% of the protein and energy targets could not be reached within 5 d through oral feeding. A reassessment was done every 24–48 h. Patients in the control group obtained usual hospital food without nutritional consultation or supplementation.

Patient group and outcomes

The NRS includes the assessment of the patient's nutritional status (based on weight loss, BMI, and general condition or food intake) and disease severity (stress metabolism). Each risk predictor is scored from 0 to 3 points, and patients receive an extra point if they are aged over 70 y. For this secondary analysis, we recalculated the NRS total scores of all EFFORT participants, excluding 0–3 points that reflect disease severity (referred to as adapted NRS). We then categorized them into 2 groups: *1*) those with a low adapted NRS score (ranging from 0 to 2 points) and *2*) those with a high adapted NRS score (ranging from 3 to 4 points). We compared the adapted NRS to the original NRS scores, which were grouped using the same approach. The study population

was divided into 2 groups on the basis of their NRS scores, with 1 group having low NRS scores (0–4 points) and the other having high NRS scores (5–7 points).

We also assessed the MNA in all study participants on the basis of the parameters prospectively collected upon hospital admission. The hospital stay in which patients were included in the study was not considered for points in question D of the MNA. We adapted the MNA by removing parameters regarding disease severity (referred to as adapted MNA; for details, see the appendix: Supplemental Figure 1). We then divided the population into 2 groups: *1*) 1 with low risk of malnutrition (low-risk adapted MNA; ranging from 13 to 19 points) and *2*) 1 with high risk of malnutrition (high-risk adapted MNA; ranging from 0 to 12 points). Likewise, we divided the population into 2 groups on the basis of the original MNA, with 1 group with low risk of malnutrition (MNA score: 24–30 points) and a second group with high risk of malnutrition (MNA score: 0–23.5 points), similar to the previous investigations [19].

The primary endpoint of this analysis was all-cause mortality within 30 d. The main secondary endpoints were short- and long-term mortality (≤7-y all-cause mortality), rehospitalization, and adverse outcomes (admission to ICU, major complications, decline in functional status within 30 d or falls within 180 d) and reaching caloric and protein targets. Structured follow-up interviews to assess outcomes were conducted by telephone by a blinded study nurse on days 30 and 180 and annually thereafter. Mortality during the follow-up was verified by relatives or the patient's family doctor.

Statistical analysis

All analyses were performed in the intention-to-treat population, including all patients with available NRS scores. Continuous data were expressed as means with SDs or medians with IQRs, whereas categorical and binary variables were expresses as counts and percentages.

For all analyses, we used regression models to investigate the association between the adapted scores and primary and secondary outcomes. Hazard ratios (HRs) and odds ratios (ORs), along with the corresponding 95% confidence intervals (CIs), were reported as measures of association. In addition, we assessed positive and negative predictive values to further characterize their prognostic value. The analyses were adjusted for different predefined confounders: center, age, sex, and randomization group. Kaplan–Meier curves were used to display 3-y mortality according to the different assessment or screening total scores.

To analyze the ability of the adapted scores to predict treatment response, we compared patients receiving nutritional support with those in the control group, stratified for the predefined groups (for adapted NRS: low and high; for adapted MNA: low risk and high risk). In detail, we compared the all-cause 30-d mortality of participants in the nutritional intervention arm of the EFFORT with control group participants on the basis of the classified group. We also used Kaplan–Meier curves to graphically display these results and generated a forest plot. In addition, we conducted interaction analyses using logistic regression models. In addition to the overall cohort, we analyzed the response to treatment in other important subgroups to determine whether the effect was independent of age, predefined main diagnoses, sex, and BMI.

All statistical analyses were performed with STATA 18.0 (Stata Corp). A P value of <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

We used data of all 2028 EFFORT patients for this secondary analysis (Supplemental Figure 2). Table 1 shows baseline characteristics stratified by high or low adapted NRS and adapted MNA. Additional baseline characteristics of the overall cohort (Supplemental Table 1) and stratified according to the randomization group are shown in the Supplemental Material Table 2 and Table 3.

Patients who were stratified in the high adapted NRS were older and had lower body weight and BMI at admission to the hospital. In the high adapted NRS group, the patients had more comorbidities, particularly hypertension and chronic kidney disease, whereas the distribution of the main diagnoses was similar. Patients in the high-risk adapted MNA group had slightly less hypertension, but more malignancies, chronic kidney disease, and congestive heart failure, and had some imbalances in main diagnoses. Like the low-risk adapted NRS group, they had lower BMI and lower weight at admission. The groups were well balanced regarding randomization to the study groups (Supplemental Tables 2 and 3).

Prognostic value of screening instruments regarding mortality and secondary outcomes

First, to quantify the prognostic value of the original and adapted scores, we analyzed the association of the scores with 30-d all-cause mortality (Table 2). We found that a high NRS total score was significantly associated with 30-d mortality in an adjusted model with an HR of 1.56 (95% CI: 1.15, 2.11); $P = 0.004$. The same was not true for the adapted scores—no significant associations of the adapted NRS and the adapted MNA with short-term mortality [adjusted HR: 1.32 (95% CI: 0.97, 1.80); $P = 0.081$ and adjusted HR of 1.10 (95% CI: 0.81, 1.48); $P = 0.551$ for adapted MNA]. Also, the MNA was not significantly associated with 30-d mortality [adjusted HR: 0.89 (95% CI: 0.62, 1.28); $P = 0.532$].

In addition to 30-d all-cause mortality, we also investigated the associations of the different scores with secondary endpoints such as long-term mortality, adverse events, rehospitalization, major complications, and others. For most outcomes, the results were similar between adapted and original scores, with comparable positive and negative prediction values, except for adverse events within 30 d, where again the original NRS showed a stronger association than the adapted score {for adapted NRS [HR: 1.12 (95% CI: 0.91, 1.37); $P = 0.296$] compared with NRS [HR: 1.29 (95% CI: 1.04, 1.60); $P = 0.019$]}. A detailed overview of results is presented in Table 2 for all adjusted analyses, and in the appendix, Supplemental Table 4 for unadjusted analyses. In unadjusted analyses, a high NRS was found to be associated with a 10% decline in functional status [OR: 1.39 (95% CI: 1.05, 1.83); $P = 0.021$]. An association that was also true for MNA [OR: 1.58 (95% CI: 1.09, 2.28); $P = 0.016$] and adapted MNA [OR: 1.49 (95% CI: 1.13, 1.95); $P = 0.004$] but not for adapted NRS [OR: 1.24 (95% CI: 0.94, 1.24); $P = 0.123$].

Figure 1 shows the 3-y survival probability of all adapted and original scores. Here again, the original NRS score had better prognostic accuracy than the adapted NRS score.

Therapeutic response according to screening tools

To understand treatment response, we compared the effect of nutritional support according to the initial trial (intervention compared

TABLE 1
Baseline characteristics stratified by adapted risk total scores[1]

	Adapted NRS		Adapted MNA	
	Low adapted NRS	High adapted NRS	Low risk adapted MNA	High risk adapted MNA
n (%)	834 (41.1%)	1194 (58.9%)	974 (48.0%)	1054 (52.0%)
Sociodemographic factors				
Male sex, *n* (%)	456 (54.7%)	608 (50.9%)	515 (52.9%)	549 (52.1%)
Age, mean (SD) (y)	69.8 (15.4)	74.6 (12.7)	75.4 (12.5)	70.0 (15.0)
Nutritional assessment				
BMI, mean (SD) (kg/m^2)	26.0 (5.0)	24.0 (5.4)	26.4 (5.2)	23.3 (5.0)
Weight at admission, mean (SD) (kg)	74.2 (16.2)	68.5 (16.6)	75.1 (15.4)	67.1 (17.0)
NRS-2002 total score, *n* (%)				
3 points	624 (74.8%)	0 (0.0%)	385 (39.5%)	239 (22.7%)
4 points	205 (24.6%)	570 (47.7%)	350 (35.9%)	425 (40.3%)
5 points	5 (0.6%)	519 (43.5%)	194 (19.9%)	330 (31.3%)
≥6 points	0 (0.0%)	105 (8.8%)	45 (4.6%)	60 (5.7%)
MNA (2 groups) score, *n* (%)				
Low risk	234 (28.1%)	181 (15.2%)	415 (42.6%)	0 (0.0%)
High risk	600 (71.9%)	1013 (84.8%)	559 (57.4%)	1054 (100.0%)
Adapted MNA, *n* (%)				
Low risk	513 (61.5%)	461 (38.6%)	974 (100.0%)	0 (0.0%)
High risk	321 (38.5%)	733 (61.4%)	0 (0.0%)	1054 (100.0%)
Intervention group, *n* (%)	416 (49.9%)	599 (50.2%)	482 (49.5%)	533 (50.6%)
Admission main diagnosis, *n* (%)				
Infection	270 (32.4%)	343 (28.7%)	364 (37.4%)	249 (23.6%)
Cancer	147 (17.6%)	227 (19.0%)	152 (15.6%)	222 (21.1%)
Cardiovascular disease	84 (10.1%)	121 (10.1%)	112 (11.5%)	93 (8.8%)
Frailty	77 (9.2%)	117 (9.8%)	71 (7.3%)	123 (11.7%)
Lung disease	52 (6.2%)	73 (6.1%)	58 (6.0%)	67 (6.4%)
Gastrointestinal disease	64 (7.7%)	100 (8.4%)	63 (6.5%)	101 (9.6%)
Neurological disease	51 (6.1%)	44 (3.7%)	47 (4.8%)	48 (4.6%)
Renal disease	15 (1.8%)	53 (4.4%)	23 (2.4%)	45 (4.3%)
Metabolic disease	20 (2.4%)	42 (3.5%)	25 (2.6%)	37 (3.5%)
Other	28 (3.4%)	27 (2.3%)	32 (3.3%)	23 (2.2%)
Comorbidities, *n* (%)				
Hypertension	403 (48.3%)	706 (59.1%)	564 (57.9%)	545 (51.7%)
Malignant disease	264 (31.7%)	403 (33.8%)	296 (30.4%)	371 (35.2%)
Chronic kidney disease	238 (28.5%)	403 (33.8%)	346 (35.5%)	295 (28.0%)
Coronary artery disease	220 (26.4%)	346 (29.0%)	291 (29.9%)	275 (26.1%)
Diabetes mellitus	169 (20.3%)	259 (21.7%)	216 (22.2%)	212 (20.1%)
Congestive heart failure	145 (17.4%)	208 (17.4%)	198 (20.3%)	155 (14.7%)
Chronic obstructive pulmonary disease	115 (13.8%)	188 (15.7%)	132 (13.6%)	171 (16.2%)
Peripheral arterial disease	77 (9.2%)	109 (9.1%)	97 (10.0%)	89 (8.4%)
Cerebrovascular disease	63 (7.6%)	99 (8.3%)	84 (8.6%)	78 (7.4%)
Dementia	29 (3.5%)	46 (3.9%)	35 (3.6%)	40 (3.8%)

Abbreviations: MNA, Mini Nutritional Assessment; NRS-2002, Nutritional Risk Screening 2002.
[1] A 2-sample *t*-test was used for continuous variables and Pearson's chi-squared test for categorical and binary variables to identify differences in the distribution.

with the control group) on 30-d mortality in subgroups of patients stratified according to the original and adapted scores (Figure 2). Although patients with a high adapted NRS showed a significant benefit from nutritional support [adjusted HR of nutritional support compared with usual care 0.55 (95% CI: 0.37, 0.80), $P = 0.002$], patients with low adapted NRS score had no apparent benefit from the nutritional intervention [HR: 1.17 (95% CI: 0.70, 1.93), $P = 0.544$], a finding that showed significance in an interaction analysis ($P = 0.031$). The same analysis for the original NRS did not show that stratification by the NRS score resulted in differences in treatment response. Kaplan–Meier estimates for 30-d mortality stratified by adapted or original scores and randomization group can be found in Supplemental Figures 3 and 4. The graphs visualize that stratification according to the adapted scores leads to a significantly better separation of "responders" and "nonresponders" to nutritional intervention.

The same result was true for MNA with a much stronger and significant beneficial effect of the nutritional intervention in patients with high adapted MNA scores [adjusted HR of nutritional support compared with usual care 0.55 (95% CI: 0.36, 0.84); $P = 0.005$] compared with no effect in patients with low-risk adapted MNA [HR: 0.98 (95% CI: 0.63, 1.53); $P = 0.929$, interaction analysis $P = 0.048$]. Again, stratification by the original MNA did not result in differences in treatment response (Figure 2).

Therapeutic response according to screening tools: subgroup analysis

Considering the unbalanced baseline characteristics between the high and low adapted score groups, we compared the therapeutic response to nutritional interventions in additional subgroups with higher age (≥65 y), sex, major main diagnoses, and BMI (Figure 3). Consistent with the results of the overall cohort, patients with a high adapted NRS score had a substantial survival benefit from nutritional support in all subgroups, except for patients admitted with an infection. Patients with a low adapted NRS score again showed no benefit from

TABLE 2
Association of (adapted) risk total scores with primary and secondary outcomes[1]

	Low risk (adapted) total score	High risk (adapted) total score	HR, OR	Regression analysis (adjusted[2]) (95% CI)	PPV (%)	NPV (%)
Primary outcome						
All-cause 30-d mortality						
Adapted NRS	61/834 (7.31%)	112/1194 (9.38%)	HR	1.32 (0.97, 1.80)	9.4	92.7
NRS	103/1399 (7.4%)	70/629 (11.1%)	HR	1.56 (1.15, 2.11)	11.1	92.6
Adapted MNA	79/974 (8.1%)	94/1054 (8.9%)	HR	1.10 (0.81, 1.48)	8.9	91.9
MNA	38/415 (9.2%)	135/1613 (8.4%)	HR	0.89 (0.62, 1.28)	8.4	90.8
Secondary outcome						
All-cause 180-d mortality						
Adapted NRS	150/834 (18.0%)	327/1194 (27.4%)	HR	1.64 (1.35, 1.99)	27.4	82.0
NRS	270/1399 (19.3%)	207/629 (32.9%)	HR	1.87 (1.56, 2.24)	32.9	80.7
Adapted MNA	188/974 (19.3%)	289/1054 (27.4%)	HR	1.49 (1.24, 1.79)	27.4	80.7
MNA	71/415 (17.1%)	406/1613 (25.2%)	HR	1.50 (1.17, 1.94)	25.2	82.9
All-cause 3-y mortality						
Adapted NRS	349/834 (41.9%)	586/1194 (49.1%)	HR	1.29 (1.13, 1.48)	49.1	58.2
NRS	596/1399 (42.6%)	339/629 (53.9%)	HR	1.48 (1.30, 1.70)	53.9	57.4
Adapted MNA	412/974 (42.3%)	523/1054 (49.6%)	HR	1.31 (1.15, 1.49)	49.6	57.7
MNA	155/415 (37.4%)	780/1613 (48.4%)	HR	1.45 (1.22, 1.72)	48.4	62.7
Adverse events 30 d						
Adapted NRS	198/834 (23.7%)	306/1194 (25.6%)	OR	1.12 (0.91, 1.37)	25.6	76.3
NRS	226/974 (23.2%)	278/1054 (26.4%)	OR	1.29 (1.04, 1.60)	28.1	76.6
Adapted MNA	327/1399 (23.4%)	177/629 (18.6%)	OR	1.20 (0.98, 1.48)	26.4	76.8
MNA	96/415 (23.1%)	408/1613 (25.3%)	OR	1.14 (0.88, 1.47)	25.3	76.9
Admission to intensive care unit						
Adapted NRS	22/834 (2.6%)	27/1194 (2.3%)	OR	0.86 (0.49, 1.53)	2.3	97.4
NRS	37/1399 (2.6%)	12/629 (1.9%)	OR	0.72 (0.37, 1.40)	1.9	97.4
Adapted MNA	27/974 (2.8%)	22/1054 (2.1%)	OR	0.77 (0.44, 1.37)	2.1	97.2
MNA	16/415 (3.9%)	33/1613 (2.1%)	OR	0.53 (0.29, 0.98)	2.0	96.1
Nonelective hospital readmission						
Adapted NRS	75/834 (9.0%)	105/1194 (8.8%)	OR	0.98 (0.72, 1.33)	8.8	91.0
NRS	119/1399 (8.5%)	61/629 (9.7%)	OR	1.16 (0.84, 1.60)	9.7	91.5
Adapted MNA	73/974 (7.5%)	107/1054 (10.0%)	OR	1.44 (1.05, 1.97)	10.2	92.5
MNA	24/415 (5.8%)	156/1613 (9.7%)	OR	1.79 (1.15, 2.79)	9.7	94.2
Major complications						
Adapted NRS	66/834 (7.9%)	84/1194 (7.0%)	OR	0.89 (0.63, 1.24)	7.0	92.1
NRS	107/1399 (7.7%)	43/629 (6.8%)	OR	0.89 (0.62, 1.29)	6.8	92.4
Adapted MNA	71/974 (7.3%)	79/1054 (7.5%)	OR	1.05 (0.75, 1.47)	7.5	92.7
MNA	30/415 (7.2%)	120/1613 (7.4%)	OR	1.04 (0.69, 1.58)	7.4	92.8
Decline in functional status of >10%						
Adapted NRS	90/834 (10.8%)	156/1194 (13.1%)	OR	1.27 (0.96, 1.67)	13.1	89.2
NRS	154/1399 (11.0%)	92/629 (14.6%)	OR	1.40 (1.06, 1.86)	14.6	89.0
Adapted MNA	97/974 (10.0%)	149/1054 (14.1%)	OR	1.49 (1.13, 1.96)	14.1	90.0
MNA	36/415 (8.7%)	210/1613 (13.0%)	OR	1.57 (1.08, 2.28)	13.0	91.3
Falls						
Adapted NRS	108/834 (13.0%)	148/1194 (12.4%)	OR	0.95 (0.73, 1.24)	12.4	87.1
NRS	192/1399 (13.7%)	64/629 (10.2%)	OR	0.71 (0.53, 0.96)	10.2	86.3
Adapted MNA	132/974 (13.6%)	124/1054 (11.8%)	OR	0.84 (0.64, 1.09)	11.8	86.4
MNA	48/415 (11.6%)	208/1613 (12.9%)	OR	1.12 (0.80, 1.57)	12.9	88.4
Reaching caloric target						
Adapted NRS	512/789 (64.9%)	751/1139 (65.9%)	OR	1.04 (0.86, 1.27)	65.9	35.1
NRS	875/1330 (65.8%)	388/598 (64.9%)	OR	0.95 (0.77, 1.18)	64.9	34.2
Adapted MNA	589/916 (64.3%)	674/1012 (66.6%)	OR	1.10 (0.90, 1.34)	66.6	35.7
MNA	219/385 (56.9%)	1044/1543 (67.7%)	OR	1.63 (1.29, 2.07)	67.7	43.1
Reaching protein target						
Adapted NRS	496/789 (62.9%)	740/1134 (65.3%)	OR	1.11 (0.92, 1.35)	65.3	37.1
NRS	844/1328 (63.6%)	392/595 (65.9%)	OR	1.11 (0.91, 1.37)	65.9	36.4
Adapted MNA	565/915 (61.8%)	671/1008 (66.6%)	OR	1.25 (1.03, 1.51)	66.6	38.3
MNA	227/384 (59.1%)	1009/1539 (65.6%)	OR	1.33 (1.05, 1.69)	65.6	40.9

Abbreviations: CI, confidence interval; HR, hazard ratio; MNA, Mini Nutritional Assessment; NPV, negative predictive value; NRS, Nutritional Risk Screening 2002; OR, odds ratio; PPV, positive predictive value.

[1] Logistic regressions were used to evaluate the association between low or high scores and binary outcomes. Cox regression was used for mortality, and the results are expressed as hazard ratios.

[2] Adjusted for age, sex, randomization group, and centrum.

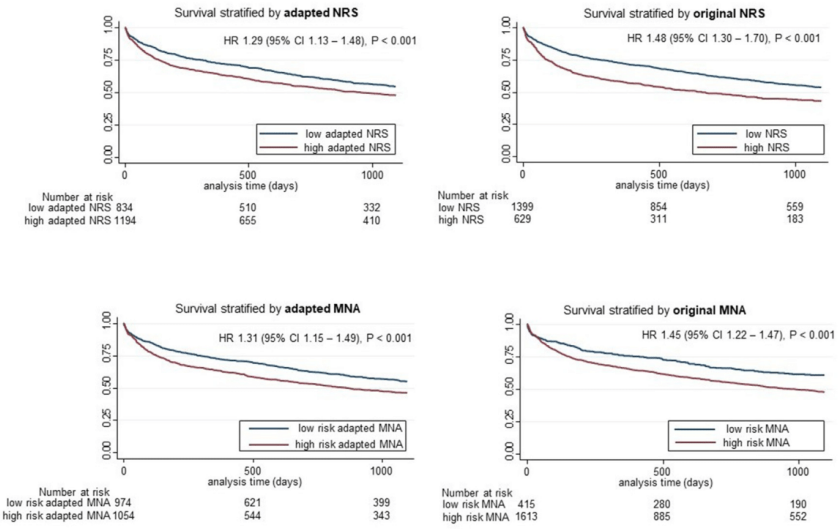

FIGURE 1. Kaplan–Meier estimate of adapted NRS and MNA and in 2 groups for time to death within 3 y. Cox regression was used to evaluate the association of low or high adapted scores with mortality. The results are expressed as hazard ratios and Kaplan–Meier curves were plotted. MNA, Mini Nutritional Assessment; NRS, Nutritional Risk Screening.

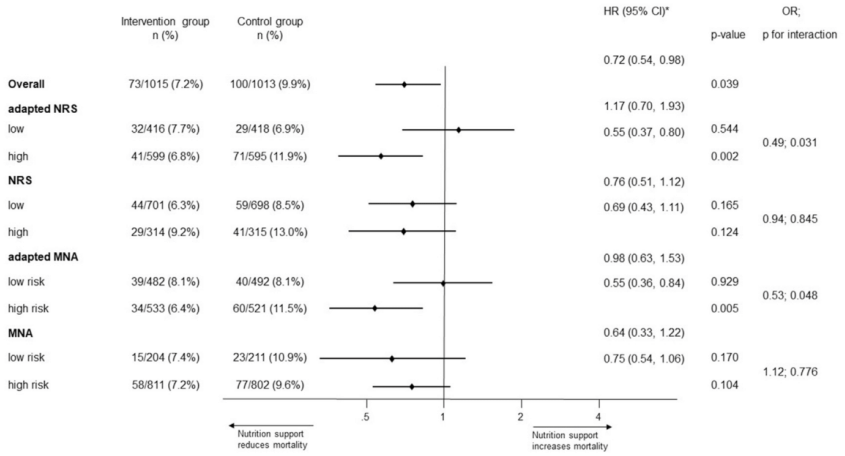

FIGURE 2. Forest plot for the response to nutritional therapy according to the screening tool. Cox regression was used to evaluate the association of low or high adapted scores with mortality. The results are expressed as hazard ratios that are plotted in a forest plot. *Adjusted for age, sex, and center. CI, confidence interval; HR, hazard ratio; MNA, Mini Nutritional Assessment; NRS, Nutritional Risk Screening.

nutritional support, regardless of subgroups. Thus, this suggests that the adapted scores are independent of age, major main diagnoses, sex, and BMI.

Discussion

This study compared the validity of 2 well-established malnutrition screening tools (NRS and MNA) with and without the inclusion of parameters reflecting disease severity in predicting clinical outcomes and response to treatment in a large cohort of patients from a randomized controlled trial. Our results indicate that the original scores with parameters reflecting disease severity were slightly superior in predicting clinical outcomes, particularly regarding short-term mortality, functional decline, and admission to the ICU, but had a limited value regarding treatment response. Importantly, removing parameters reflecting disease severity significantly improved the prediction of

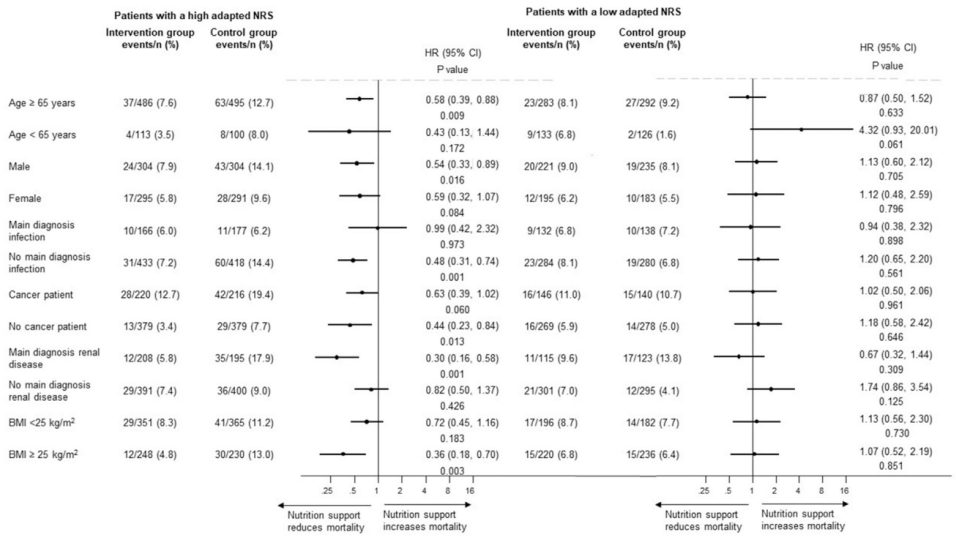

FIGURE 3. Forest plot for major subgroups for the response to nutritional therapy according to high compared with low adapted NRS score. Cox regression was used to evaluate the association of low or high adapted scores with mortality. The results are expressed as hazard ratios that are plotted in a forest plot. CI, confidence interval; HR, hazard ratio; NRS, Nutritional Risk Screening.

treatment response opening the door for more individualized approaches to the use of clinical nutrition.

It is well documented that higher risk of malnutrition assessed by the NRS or MNA is associated with higher mortality and other adverse clinical outcomes [31,32]. Specifically, within our cohort of polymorbid and elderly medical patients, high NRS and high-risk MNA scores were associated with higher risk of long-term mortality and adverse outcomes, among others [33]. These results are to be expected because most scores were developed on the basis of prognostic studies with a selection of variables that would reflect high overall clinical risk of patients. Risk screening tools are important as they also help to identify risks before malnutrition manifests itself and they are currently being re-evaluated [34]. However, it is crucial to understand that patients at high risk of adverse outcomes may not show the strongest response to a nutritional intervention. In fact, it has been long known that prevention is more effective than treatment in nutritional medicine ("praeventioni melius quam remedium") and that patients with severe cachexia may not respond to nutritional interventions [2,35]. Interestingly, the exclusion of parameters reflecting disease severity in some cases reduces the power of predicting clinical outcomes, likely because of the strong pathophysiological rationale for the impact of underlying disease and disease severity. Nevertheless, we found that the adapted scores had prognostic abilities for several other outcomes. This could be because of our group of polymorbid hospitalized patient, who already had $\geq$1 point for their disease severity. Within this comparable group, the severity of malnutrition in particular may have had a crucial influence on the time to death. This hypothesis was partially confirmed by a retrospective investigation, in which the nutritional points of the NRS had independent prognostic implications [36].

Thus, it is important to estimate the expected therapeutic benefit in patients presenting with high risk of malnutrition. Although the overall effect of nutritional support seems to be beneficial in medical inpatients, evidence now suggests that there are several subgroups of patients with different phenotypes regarding malnutrition that show variable benefits to nourishment. Several such effect-modifying conditions and parameters have been proposed. Currently, inflammation—as a key driver of disease-related anorexia, reduced food intake, and muscle catabolism—seems to be 1 of the main predictors for a lack of response to nutritional treatment [13,37,38]. In a secondary analysis of EFFORT, patients with high inflammation (defined as a concentration of CRP $>$ 100 mg/L) did not respond to nutritional support, whereas patients with lower CRP concentrations ($\leq$100 mg/L) did [13]. This may also explain differences in results depending on the clinical setting, namely studies carried out in patients with critical illness or advanced cancer. The impact of inflammation on nutritional status is also shown in the European Society for Clinical Nutrition and Metabolism (ESPEN) classification of malnutrition, which distinguishes between malnutrition with and without inflammation [39]. In addition, the Global Leadership Initiative on Malnutrition advises that inflammation should be an etiologic criterion for the diagnosis of malnutrition even without laboratory evidence [6,40]. However, both approaches relate to a different clinical question than this work, as we do not want to create new classifications or diagnoses. Our approach emphasizes the response to nutritional interventions, something that should be questioned after risk of malnutrition has been identified and before starting nutritional support.

Other modifying conditions include chronic kidney dysfunction, as patients with reduced kidney function showed a stronger response to nutritional treatment [1,21]. The heterogeneity in responses is also reflected in the recent ESPEN guidelines for polymorbid medical inpatients calling for more individualized approaches through phenotyping of patients [41]. The guideline explicitly states that patient

heterogeneity must be addressed, and that the patient's acute phase response (assessed by clinical presentation and CRP) and the underlying disease should be taken into account when initiating nutritional support. In addition, it is recommended that specific nutritional biomarkers can be used to predict response to treatment and the expected outcome of nutritional interventions [41]. Herein, our analysis confirms these concepts. Specifically, we found that removing parameters that reflect disease severity resulted in much better abilities of the scores to predict treatment response that was independent of age, major main diagnoses, sex, and BMI: patients with high adapted scores showed much more benefit from nutritional support than patients with a low adapted score. The same, however, was not true for the original scores. Excluding factors reflecting disease severity thus helps stratify patients into 2 phenotypes of malnutrition: *1*) 1 that is mainly nutrition-driven (being malnourished) and *2*) 1 that is mainly disease-driven (having malnutrition). Although the treatment of disease-driven malnutrition seems to require other therapeutic strategies than simply meeting protein and caloric needs, we can adequately treat the nutrition-driven phenotype via nutritional interventions. This is an observation and hypothesis that is also supported by other researchers such as Cardenas, who calls for a paradigm shift in clinical nutrition [18], as well as by findings from critical care or advanced cancer cachexia, where malnutrition is mainly disease-driven and refractory to therapy. They distinguish between malnutrition and being malnourished. Although being malnourished means that a person has not eaten enough to meet their needs, malnutrition describes a more complex syndrome with a multifactorial etiology [42]. It should also be noted that it is not known whether withholding nourishment to those severely inflamed or severely ill patients for an extended period of time is neutral, harmful, or beneficial because most studies in hospitalized patients are relatively shorter term (days to weeks).

This analysis suggests that a simplified tool such as the adapted NRS or MNA may help to further personalize nutritional support, which could make nutrition therapy more precise and efficient. In particular, the adapted NRS is very easy to calculate or even assess at the bedside. Using these might also help in managing the expectations of the nutrition support team and the patient. Dependence on manifestations of inflammation or disease severity to diagnose malnutrition may confuse malnourishment with disease severity. This is of concern if ongoing catabolism is attributed to inadequate nourishment, and the underlying illness is inadequately treated as a result (for example, giving more protein to raise albumin concentrations instead of treating an infection or malignancy).

Strengths and limitations

This is the first study, to our knowledge, to examine the response to nutrition therapy using adapted nutritional screening and assessment tools that exclude factors reflecting disease severity in a cohort of a large randomized controlled trial. In fact, we were able to include all patients from the original trial ($n = 2028$) and thus did not lose statistical power. Still, as this study is a secondary analysis, the results should be viewed as exploratory and hypothesis-generating rather than definite. Results clearly need to be confirmed and validated in an independent cohort in the future, as we could not stratify patients into a derivation and a validation cohort because of the limited sample size. We are aware of additional limitations because our classification into high or low (risk) groups was based on previous investigations [19], for which, however, there is no strong evidence. Furthermore, EFFORT only included patients having ≥ 1 point for disease severity, which limits the study's power for less disease-driven malnutrition.

Conclusion

Our analysis suggests that adapting the NRS and the MNA by including nutritional parameters only, but not parameters reflecting disease severity, improves their ability to predict treatment response to a nutrition intervention, but slightly reduces their overall prognostic performance for clinical outcomes. Scores dependent on disease severity may best be considered prognostic scores, rather than nutritional risk scores. Score adaptation may improve a more personalized treatment approach for nourishment interventions. The clinical implementation of these instruments and further research efforts will contribute to optimizing the effectiveness of personalized nutrition therapy and improving outcomes for patients suffering from malnutrition.

Acknowledgments

We thank all the contributors to the EFFORT for their valuable support.

Author contributions

The authors' responsibilities were as follows – CW, JS, DS, PS: designed the research; CW, JS: conducted the research and analyzed data/performed statistical analysis; CW, JS, DS, MO-M, PS: wrote the paper; PS, DS, CW, BM, ZS, PT: had primary responsibility for final content; all authors: read and approved the final version of the manuscript; all authors: confirm that they had full access to all data in this secondary analysis; and all authors: accept responsibility for the decision to submit for publication.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: PS reports a relationship with Roche, Thermo Fisher, bioMérieux, Nestlé Health Science, and Abbott Nutrition that includes: funding grants. ZS reports a relationship with Nestlé Health Science, Abbott Nutrition, and Fresenius Kabi, and B. Braun that includes: funding grants. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The funding for the EFFORT was provided by the Swiss National Science Foundation (SNSF) (PP00P3_150531) and the Research Council of the Kantonsspital Aarau (1410.000.058 and 1410.000.044).

Data availability

Data described in the manuscript, code book, and analytic code will be made available to others with the publication of this manuscript, as already outlined in the primary EFFORT publication, on receipt of a letter of intention detailing the study hypothesis and statistical analysis plan. A signed data access agreement is required from all applicants. Please send requests to the principal investigator of this trial.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.01.013.

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3.3.1 Association of glutamine and glutamate metabolism with mortality among patients at nutritional risk - a secondary analysis of the randomized clinical trial EFFORT [96]

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Conceptualization, PS and CW; formal analysis, CW, DVA, SCM; investigation, P., BM, ZS, CW, PT, PN and LB; writing—original draft preparation, CW, DVA, SCM; writing—review and editing, CW, DVA, SCM and PS; visualization, CW, DVA, SCM; project administration, PS; funding acquisition, PS, BM and ZS. All authors have read and agreed to the published version of the manuscript.

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Article

Association of Glutamine and Glutamate Metabolism with Mortality among Patients at Nutritional Risk—A Secondary Analysis of the Randomized Clinical Trial EFFORT

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Abstract: Glutamine and its metabolite glutamate serve as the main energy substrates for immune cells, and their plasma levels drop during severe illness. Therefore, glutamine supplementation in the critical care setting has been advocated. However, little is known about glutamine metabolism in severely but not critically ill medical patients. We investigated the prognostic impact of glutamine metabolism in a secondary analysis of the *Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial* (EFFORT), a randomized controlled trial comparing individualized nutritional support to usual care in patients at nutritional risk. Among 234 patients with available measurements, low plasma levels of glutamate were independently associated with 30-day mortality (adjusted HR 2.35 [95% CI 1.18–4.67, $p = 0.015$]). The impact on mortality remained consistent long-term for up to 5 years. No significant association was found for circulating glutamine levels and short- or long-term mortality. There was no association of glutamate nor glutamine with malnutrition parameters or with the effectiveness of nutritional support. This secondary analysis found glutamate to be independently prognostic among medical inpatients at nutritional risk but poorly associated with the effectiveness of nutritional support. In contrast to ICU studies, we found no association between glutamine and clinical outcome.

Keywords: malnutrition; polymorbid patient; individualized nutrition support; glutamine; glutamate; biomarker

Citation: Wunderle, C.; von Arx, D.; Mueller, S.C.; Bernasconi, L.; Neyer, P.; Tribolet, P.; Stanga, Z.; Mueller, B.; Schuetz, P. Association of Glutamine and Glutamate Metabolism with Mortality among Patients at Nutritional Risk—A Secondary Analysis of the Randomized Clinical Trial EFFORT. *Nutrients* **2024**, *16*, 222. https://doi.org/10.3390/nu16020222

Academic Editor: Enbo Ma

Received: 7 December 2023
Revised: 2 January 2024
Accepted: 9 January 2024
Published: 10 January 2024

1. Introduction

Glutamine is a non-essential amino acid, which is vital for several key stress response pathways in critical illness [1,2]. Under certain conditions, glutamine becomes essential for the maintenance of metabolic functions in the context of glutathione synthesis, nitrogen exchange, and purine and pyrimidine productions and is therefore considered a conditionally essential amino acid. Additionally, glutamine serves as a main energy substrate for immune cells and cells of the gut-associated lymphatic tissue. Converted to glutamate and α-ketoglutarate, glutamine can boost energy production across diverse cell types via the Krebs cycle [3]. During a catabolic state or acute disease, some immune cells, such

as lymphocytes and macrophages, consume even more glutamine than glucose [4,5]. In contrast, muscle cells, which are the main sites of glutamine synthesis, show reduced synthesis activity of the latter due to proteolysis, atrophy, and hypermetabolism. As a result, blood plasma glutamine levels are found to be depleted, which exacerbates the catabolic state [3].

Low plasma glutamine concentration is associated with increased mortality and morbidity [2,6–8]. Therefore, glutamine administration has been studied in various clinical settings, such as cancer and critical illness [9–11], or in patients suffering from burn injuries [12]. Glutamine supplementation was thereafter recommended for critically ill patients in the 2019 nutritional guidelines from the European Society for Clinical Nutrition and Metabolism [13]. However, a recent large, double-blind, randomized, placebo-controlled trial of 1209 burned patients showed no effect of glutamine supplementation on the time to discharge alive from the hospital [12]. Thus, there is still an ongoing controversy about the effectiveness of glutamine supplementation in the setting of critical illness.

Disease-related malnutrition (DRM) is a growing health concern among elderly and polymorbid medical inpatients, a condition that is strongly associated with increased mortality, complications, and reduced quality of life [14–16]. However, recent large trials [17,18] and a meta-analysis [19] have shown that nutritional support is an effective and cost-efficient [20] intervention to lower the risk of worse clinical outcomes [17–19,21,22]. Despite the overall beneficial effect of nutritional support, there are subgroups with certain clinical conditions, such as high inflammation [23], or severely ill patient populations [24] that show less benefit from nutritional treatment [23–25]. In fact, several studies have demonstrated that the acute-phase response and individual stress metabolism influence the way nutritional support affects the body [26,27]. In contrast to these findings, patients with impaired muscle strength [28] or advanced kidney failure [29] showed a more favorable response to nutritional support in medical inpatients [29]. A better understanding of the pathophysiology and DRM phenotype is key to improving nutritional strategies and will enable a more individualized approach. In addition to the current approach of selection for nutritional intervention using the nutritional history of patients, including changes in appetite and weight loss [19], other factors, such as severity of inflammation [23], specific comorbidities, and specific blood markers [30], might be helpful.

Despite thorough research on glutamine supplementation in the intensive care setting, little is known about glutamine metabolism in patients with severe but not critical illnesses, such as medical inpatients with acute disease. Herein, our aim was to investigate the roles of glutamine and its metabolite glutamate in predicting clinical outcomes regarding the response to nutritional support in a previous randomized controlled trial.

2. Materials and Methods

2.1. Study Design and Participants

This was a secondary analysis of the EFFORT trial, which is a pragmatic, investigator-initiated, open-label, non-commercial, multicenter, randomized controlled trial that was undertaken in eight Swiss hospitals. The participating centers were either secondary or tertiary care hospitals, such as the University Clinic in Aarau, the University Hospital in Bern, the Cantonal hospitals in Lucerne, Solothurn, St. Gallen, Muensterlingen, and Baselland, and the regional hospital in Lachen. Hospitalized patients were screened using the Nutritional Risk Screening 2002 (NRS), which is a validated risk screening tool for malnutrition. This assesses the patient's nutritional status (based on body mass index (BMI) and weight loss, as well as food intake) and disease severity. Patients received points from 0 to 3, depending on each risk predictor, and received an additional point if they were aged over 70 years. The inclusion criteria were defined as a minimum age of 18 years, an NRS total score of 3 points or greater, and an expected length of stay in the hospital for at least 5 days. Patients who were willing to give informed consent within 48 h of hospital admission were included. Patients were enrolled between 1 April 2014 and 28 February 2018. Exclusion criteria were an initial hospitalization in intensive care units

or surgical wards; inability to ingest oral nutrition; already receiving nutritional support at admission; having a terminal condition; being admitted to hospital because of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, or stem cell transplantation; received gastric bypass surgery; received contraindications for nutritional support; and being previously included in the trial. The study protocol was approved by the Ethics Committee of Northwest and Central Switzerland (EKNZ) in January 2014 (registration ID 2014_001).

2.2. Randomization and Procedures

Patients were randomly assigned (1:1) to a control or intervention group. Nutritional support was initiated in the intervention group based on an individual nutritional treatment algorithm within 48 h after hospital admission. Control group patients received usual hospital food without further nutritional support or dietary counseling. They were allowed to eat according to their appetite. Participants and investigators were aware of group assignments at any time. However, structured telephone interviews to assess clinical outcomes were conducted by trained and blinded study nurses after discharge. Patients in the intervention group received individual nutrition therapy from trained, registered dietitians to reach protein and caloric targets. The daily protein target was set at 1.2–1.5 g/kg of bodyweight. A lower protein intake goal was defined for patients with acute renal failure (0.8 g/kg of bodyweight). The weight-adjusted Harris–Benedict equation was used to predict caloric requirements [31]. Trained, registered dietitians defined individualized goals for each patient. This plan was initially based on oral nutrition provided by the hospital kitchen (including food adjustment according to patient preferences, food fortification, such as enrichment of hospital food by adding protein powder, and snacks between meals) and oral nutritional supplements. A further increase in nutritional support to enteral or parenteral feeding was recommended if at least 75% of the daily caloric and protein targets could not be reached through oral feeding within 5 days. The nutritional algorithm used during the trial can be found in the original publication [17]. Nutritional intake was reassessed every 24–48 h throughout the hospital stay. Upon hospital discharge, the intervention was discontinued.

2.3. Analysis of Blood Biomarkers

Upon study inclusion, blood samples were collected, immediately processed, frozen in aliquots, and stored under a temperature controlled at −80 °C until further analysis. Admission plasma metabolites were analyzed from February to April 2019 by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). An Ultimate 3000 UHPLC (Thermos Fisher, San Jose, CA, USA) system coupled to a Sciex QTRAP 5500 linear ion-trap quadrupole mass spectrometer (Sciex, Darmstadt, Germany) and the AbsoluteIDQ® p180 kit (BIOCRATES Life Sciences AG, Innsbruck, Austria) were used [32–34]. An inter-laboratory assessment of this commercially available kit for targeted metabolomics showed the reliability of the metabolomics assay [35–37]. Measurements without a detectable signal for glutamine or glutamate were considered incorrect and were excluded in our analysis. Finally, we analyzed a total number of 234 glutamine and glutamate measurements. The glutamate to glutamine ratio was calculated as a surrogate to estimate the consumption of glutamine.

2.4. Outcomes

Our primary endpoint was defined as all-cause, short-term mortality measured at 30 days. The secondary endpoints were chosen as mid- and long-term mortality (at 180 days, 1 year, 2 years, 3 years, and 5 years); adverse events within 30 days; admission to the intensive care unit from the medical ward; non-elective hospital readmission after discharge; major complications, such as respiratory failure, a major cardiovascular event (i.e., stroke, intracranial bleeding, cardiac arrest, myocardial infarction, or pulmonary embolism), acute renal failure, and gastro-intestinal failure (i.e., hemorrhage, intestinal

perforation, acute pancreatitis); decline in the functional status of more than 10% (measured by Barthel index); and total length of hospital stay and incidence of falls during the 180-day follow-up period. Additionally, nutritional outcomes were set as secondary endpoints, i.e., mean caloric and protein intakes per kg of bodyweight and achieving caloric and protein targets. Follow-up interviews for outcome assessment were performed at days 30 and 180 via phone calls. If necessary, family members or family physicians were contacted to verify the survival.

2.5. Statistical Analysis

STATA 17.0 was used for statistical analysis. Statistical significance was tested at 95% confidence intervals (CI), corresponding to a p-value of 0.05. Continuous variables were expressed as mean ± standard deviation (SD), and binary and categorical variables were expressed as the number or count and percentages. The Liu method was used to calculate the empirical optimal cut-off values for the primary endpoint (30-day mortality) [38]. Patients in this secondary analysis were stratified into groups based on low or high glutamine or glutamate levels [39]. The cut-off concentration for glutamine was calculated to be 595.5 µmol/L, for glutamate, it was 167.5 µmol/L, and for their ratio, it was 0.28, which we then used to stratify them into high or low groups. A two-samples t-test was used to compare continuous variables, and Pearson's chi-squared test was used for categorical and binary variables. Adjustment for potential confounding and random imbalances in regression analyses were made, including sex, baseline nutritional status (NRS total score), C-reactive protein (CRP), randomization group, and Carlson comorbidity index (CCI).

Associations between the metabolite levels and malnutrition parameters as well as secondary clinical outcomes were assessed using logistic regression models for the binary outcome, and for continuous outcomes, we used linear regression models, reported as the odds ratio (OR) and coefficient, respectively. Cox regression models were calculated for time-to-event analysis, with recorded hazard ratios (HR). The HR was calculated for all mortality endpoints (30 and 180 days and 1, 2, 3, and 5 years). Kaplan–Meier curves were used for the graphical display of the probability of all-cause mortality within 30 and 180 days.

Additionally, we investigated the response to nutritional therapy by comparing the hazards of mortality in the intervention vs. control groups, stratified by high versus low glutamine or glutamate plasma levels at admission. In all our analyses, the intention-to-treat principle was used. Limits to detect outliers were calculated by mean ±3 standard deviations of the sample (z-score method), and sensitivity analysis was performed for metabolites by comparing statistical results for data with and without outliers.

3. Results

3.1. Patient Population

We had full clinical and metabolomic data on 234 of 2028 patients (11.5%) that were included in our analyses (Figure 1). Of these, 159 patients had low plasma glutamine levels, and 160 patients had low plasma glutamate levels. Overall, the mean age of our cohort was 73.6 years (+/− 13.3 years), and 57.7% of patients were male. Overall, patients had a high burden of comorbidities, indicated by a CCI of 6.4. Most baseline characteristics, such as risk of malnutrition indicated by the NRS total score, were equally distributed. However, in the low-glutamine group, cancer as a main diagnosis was more prominent (58 [36.5%] vs. 16 [21.3%], p = 0.020), whereas diabetes as a comorbidity was less often observed (Table 1). On the other hand, stratified by high versus low glutamate, all baseline characteristics were equally distributed without any imbalances (Supplemental Table S1).

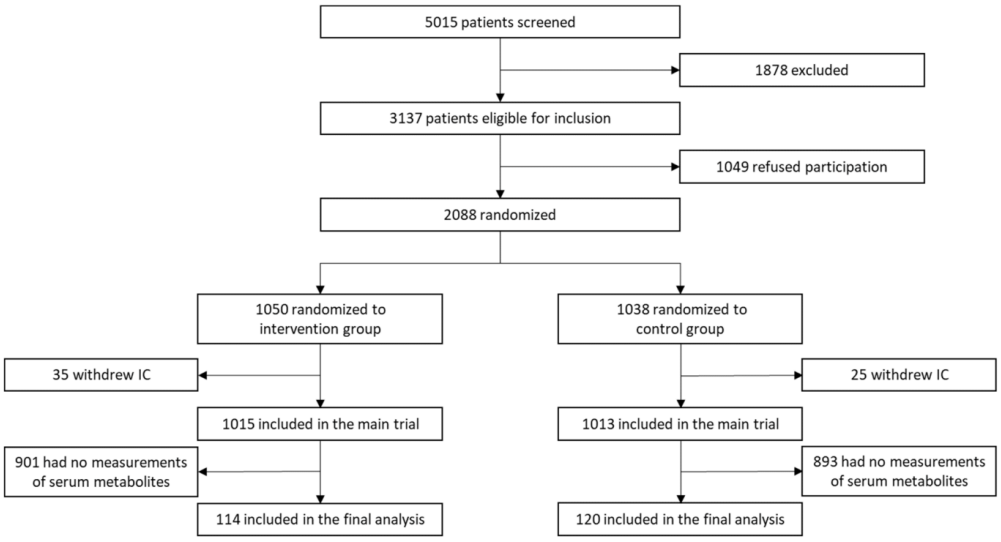

Figure 1. Study flow chart of the secondary analysis based on Schuetz et al., 2019 [17]; IC, informed consent.

3.2. Association of Glutamine and Glutamate with Nutritional Parameters and Inflammation

In the next step, we investigated the association of glutamine and glutamate levels and their ratio with different nutritional parameters, particularly the NRS total score, its components, the BMI, or CRP. Data for glutamine are presented below in Table 2. We did not find any significant results within the subgroups. Neither glutamine nor glutamate or their ratio showed any significant association with the NRS total score, its components, or baseline inflammation. The results remained consistent even in sensitivity analyses without outliners (Supplementary Tables S3 and S4). Data for glutamate can be found in the Supplementary Materials (Supplementary Table S2).

3.3. Prognostic Value of Low Glutamine or Low Glutamate to Predict Clinical Outcomes

Next, the associations of glutamine and glutamate with mortality and other predefined clinical outcomes were assessed (Table 3). We found no significant differences in short- or long-term mortality in patients with low versus high glutamine plasma concentrations. However, patients with low glutamate plasma concentrations had more than a doubling in 30-day mortality, resulting in an unadjusted HR of 2.40 (95% CI = 1.21–4.75, $p = 0.012$). These results remained robust in an adjusted model for CCI, CRP, the NRS total score, sex, and the randomization group, with an HR of 2.35 (95% CI = 1.18–4.67, $p = 0.015$). Additionally, the results stayed consistent for long-term mortality at 180 days up to 5 years (adjusted HR: 1.67, 95% CI: 1.06–2.63, and $p = 0.028$, respectively). Figure 2 visualizes the survival probability in Kaplan–Meier curves for 30- and 180-day all-cause mortality among the population with high and low glutamine or glutamate.

For secondary clinical outcomes, we observed similar trends to mortality. While there was only a little difference between high- and low-glutamine groups, we found an association between low glutamate levels and the composite endpoint of adverse clinical outcomes within 30 days (adjusted HR: 2.65, 95% CI: 1.39–5.05, $p = 0.003$), as well as major complications (adjusted HR: 5.35, 95% CI: 1.21–23.67, $p = 0.027$). Full results can be found in Supplemental Tables S5–S9.

Table 1. Baseline characteristics overall and stratified by high versus low glutamine.

	Overall (n = 234)	**Low Glutamine (n = 159)**	**High Glutamine (n = 75)**	***p*-Value**
Sociodemographic				
Male sex	135 (57.7%)	87 (54.7%)	48 (64.0%)	0.18
Mean age in years (SD)	73.6 (13.3)	73.5 (13.6)	73.9 (13)	0.81
Nutritional assessment				
Mean body mass index in kg/m^2 (SD)	24 (5)	24 (5)	25 (5)	0.32
Mean bodyweight in kg (SD)	69 (15)	68 (15)	71 (14)	0.11
Mean height in cm (SD)	168.1 (8.6)	167.5 (8.6)	169.3 (8.4)	0.15
NRS total score				0.75
3 points	60 (25.6%)	39 (24.5%)	21 (28.0%)	
4 points	79 (33.8%)	56 (35.2%)	23 (30.7%)	
≥5 points	95 (40.6%)	64 (40.3%)	31 (41.3%)	
CRP, day 1, mg/L	84.1 (79.8)	85.1 (78.2)	82.0 (83.4)	0.78
Admission diagnosis				
Infection	63 (26.9%)	40 (25.2%)	23 (30.7%)	0.38
Cancer	74 (31.6%)	58 (36.5%)	16 (21.3%)	**0.020**
Cardiovascular disease	24 (10.3%)	15 (9.4%)	9 (12.0%)	0.55
Frailty	13 (5.6%)	11 (6.9%)	2 (2.7%)	0.19
Lung disease	10 (4.3%)	6 (3.8%)	4 (5.3%)	0.58
Gastrointestinal disease	13 (5.6%)	9 (5.7%)	4 (5.3%)	0.92
Renal disease	15 (6.4%)	9 (5.7%)	6 (8.0%)	0.50
Comorbidity				
Charlson Comorbidity Index	6.4 (2.8%)	6.4 (2.9%)	6.3 (2.7%)	0.76
Hypertension	137 (58.5%)	92 (57.9%)	45 (60.0%)	0.76
Malignant disease	110 (47.0%)	77 (48.4%)	33 (44.0%)	0.53
Chronic kidney disease	81 (34.6%)	51 (32.1%)	30 (40.0%)	0.23
Coronary heart disease	54 (23.1%)	36 (22.6%)	18 (24.0%)	0.82
Diabetes mellitus	43 (18.4%)	23 (14.5%)	20 (26.7%)	**0.025**
Congestive heart failure	45 (19.2%)	33 (20.8%)	12 (16.0%)	0.39
Chronic obstructive pulmonary disease	26 (11.1%)	20 (12.6%)	6 (8.0%)	0.30
Peripheral arterial disease	26 (11.1%)	16 (10.1%)	10 (13.3%)	0.46
Cerebrovascular disease	27 (11.5%)	17 (10.7%)	10 (13.3%)	0.56
Dementia	11 (4.7%)	8 (5.0%)	3 (4.0%)	0.73
Metabolites				
Mean plasma glutamine concentration (µmol/L)	522.5 (196.2)	423.4 (130.2)	732.7 (138.3)	<0.001
Mean plasma glutamate concentration (µmol/L)	152.10 (110.35)	166.34 (124.38)	121.91 (62.87)	0.004

SD, standard derivation; NRS, nutritional risk screening 2002; CRP, C-reactive protein.

3.4. Association of Glutamine and Glutamate Levels or the Ratio with the Effectiveness of Nutritional Support

To assess whether the response to nutritional support would differ according to baseline glutamine or glutamate levels or their ratio, we compared the effects of nutritional support on 30-day all-cause mortality among patients randomized to intervention versus the control

group with high and low glutamine and glutamate or their ratio, respectively (Figure 3). The 30-day mortality did not differ in subgroups of patients according to their plasma glutamine and glutamate levels, resulting in a non-significant interaction analysis ($p = 0.771$ for high versus low glutamine, $p = 0.897$ for high versus low glutamate, and $p = 0.321$ for glutamate/glutamine ratio).

Table 2. Association of nutritional parameters with a decrease in plasma glutamine levels.

	Unadjusted	**Adjusted ***
Glutamine (decrease of 10 µmol/L)	Coef (95% CI) *p*-value	Coef (95% CI) *p*-value
Nutritional assessment		
Bodyweight (kg)	0.06 (−0.11 to 0.23) $p = 0.459$	0.06 (−0.11 to 0.24) $p = 0.474$
Body mass index (kg/m^2)	0.13 (−0.38 to 0.64) $p = 0.620$	0.12 (−0.39 to 0.63) $p = 0.640$
NRS total score		
3 points	reference	reference
4 points	−4.56 (−11.15 to 2.04) $p = 0.175$	−4.80 (−11.51 to 1.91) $p = 0.160$
≥5 points	−1.45 (−7.77 to 4.87) $p = 0.651$	−2.47 (−8.96 to 4.01) $p = 0.453$
CRP, day 1, mg/L	0.00 (−0.03 to 0.03) $p = 0.948$	−0.01 (−0.08 to 0.05) $p = 0.659$
NRS score components		
Loss of appetite **	−3,99 (−11.66 to 3.67) $p = 0.306$	−5.82 (−13.80 to 2.15) $p = 0.152$
Bodyweight loss (kg)		
<5% in 3 months	reference	reference
>5% in 3 months	6.00 (−1.03 to 13.03) $p = 0.094$	6.07 (−0.99 to 13.14) $p = 0.092$
>5% in 2 months	−3.83 (0.293 to −11.00) $p = 0.293$	−4.25 (−11.44 to 2.93) $p = 0.245$
>5% in 1 month	−3.94 (−10.52 to 2.64) $p = 0.239$	−3.55 (−10.18 to 3.07) $p = 0.292$
Reduced dietary intake **		
>75%	reference	reference
50–75%	−5.54 (−14.72 to 3.65) $p = 0.236$	−5.57 (−14.83 to 3.69) $p = 0.237$
25–50%	−7.27 (−16.00 to 1.47) $p = 0.102$	−6.95 (−15.83 to 1.92) $p = 0.124$
<25%	−0.14 (−9.77 to 9.49) $p = 0.977$	−0.26 (−9.98 to 9.47) $p = 0.958$
Severity of disease		
1	reference	reference
2	−2.89 (−8.16 to 2.38) $p = 0.281$	−3.29 (−8.82 to 2.25) $p = 0.243$
3	−7.04 (−45.16 to 31.09) $p = 0.716$	−7.69 (−46.53 to 31.14) $p = 0.697$

Unadjusted and adjusted regression analyses were performed to identify associations of glutamine concentrations at admission with nutritional parameters. The regression coefficients (95% CI) indicate the change in glutamine concentration by ten units (10 µmol/L). For binary parameters, patients with the characteristics are compared to patients without the characteristic. BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002; CRP, C-reactive protein; CI, confidence interval; Coef, coefficient. * Adjusted for CCI, CRP, sex, and intervention. ** In the week preceding hospitalization compared to usual appetite and intake.

Table 3. Prognostic values of high vs. low levels of glutamine or glutamate on mortality.

			Unadjusted	**Adjusted ***
Short- and Long-Term Mortality	**n. of Event (%)**	**n. of Event (%)**	**HR (95% CI) *p*-Value**	**HR (95% CI) *p*-Value**
30-day all-cause mortality	high	low		
Glutamine	14/75 (19%)	43/159 (27%)	1.50 (0.82 to 2.74) $p = 0.189$	1.46 (0.79 to 2.69) $p = 0.223$
Glutamate	10/74 (14%)	47/160 (29%)	2.40 (1.21 to 4.75) $p = 0.012$	2.35 (1.18 to 4.67) $p = 0.015$

Table 3. *Cont.*

			Unadjusted	Adjusted *
Short- and Long-Term Mortality	**n. of Event (%)**	**n. of Event (%)**	**HR (95% CI) *p*-Value**	**HR (95% CI) *p*-Value**
180-day all-cause mortality				
Glutamine	25/75 (36%)	73/159 (46%)	1.37 (0.88 to 2.13) $p = 0.163$	1.27 (0.81 to 1.99) $p = 0.289$
Glutamate	25/74 (34%)	75/160 (47%)	1.64 (1.05 to 2.59) $p = 0.031$	1.67 (1.06 to 2.63) $p = 0.028$
1-year all-cause mortality				
Glutamine	31/75 (41%)	83/159 (52%)	1.39 (0.92 to 2.10) $p = 0.119$	1.31 (0.86 to 1.99) $p = 0.203$
Glutamate	28/74(38%)	86/160 (54%)	1.68 (1.10 to 2.58) $p = 0.017$	1.69 (1.10 to 2.59) $p = 0.017$
2-year all-cause mortality				
Glutamine	41/75 (55%)	95/159 (60%)	1.23 (0.85 to 1.77) $p = 0.269$	1.20 (0.83 to 1.74) $p = 0.331$
Glutamate	33/74 (45%)	103/160 (64%)	1.76 (1.19 to 2.60) $p = 0.005$	1.78 (1.20 to 2.64) $p = 0.004$
3-year all-cause mortality				
Glutamine	41/75 (55%)	99/159 (62%)	1.28 (0.89 to 1.84) $p = 0.191$	1.25 (0.86 to 1.80) $p = 0.238$
Glutamate	38/74 (51%)	102/160 (64%)	1.53 (1.05 to 2.22) $p = 0.025$	1.57 (1.08 to 2.28) $p = 0.019$
5-year all-cause mortality				
Glutamine	45/75 (60%)	108/159 (68%)	1.28 (0.90 to 1.81) $p = 0.167$	1.24 (0.87 to 1.77) $p = 0.224$
Glutamate	46/74 (62%)	107/160 (67%)	1.38 (0.98 to 1.96) $p = 0.067$	1.42 (1.00 to 2.01) $p = 0.050$

Cox regression models reporting adjusted hazard ratios according to levels stratified by cut-off values of glutamine (595.5 µmol/L) and glutamate (167.5 µmol/L). Low levels are defined as less than or equal to the cut-off value, and high levels are defined as greater than the cut-off value. Abbreviations: HR, hazard ratio; CI, confidence interval. * Adjusted for CCI, CRP, NRS total score, sex, and intervention.

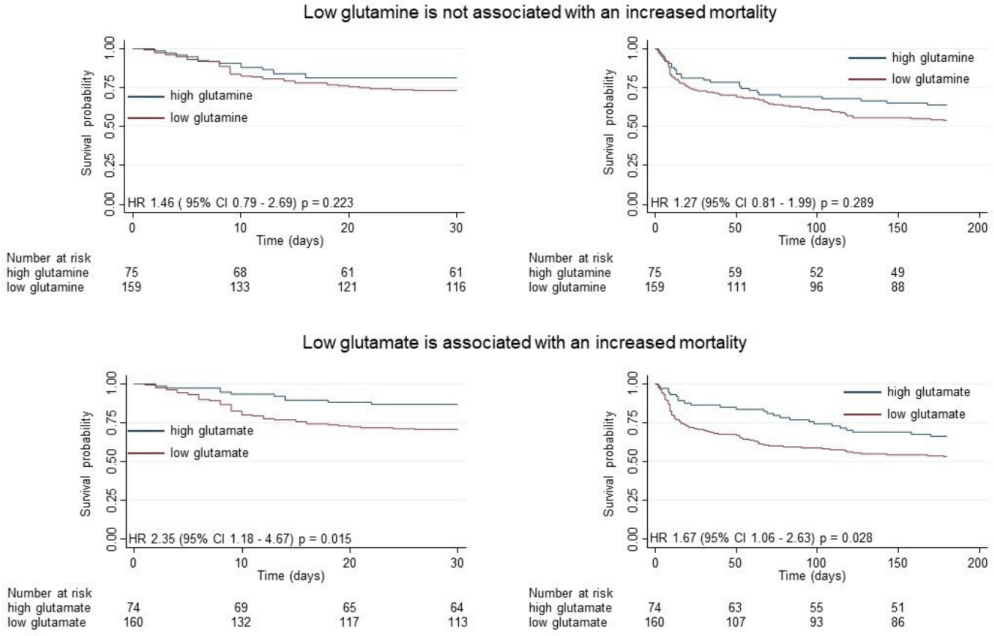

Figure 2. Kaplan–Meier estimate for 30-day and 180-day mortality according to high versus low glutamine (Gln) or glutamate (Glu) levels. Glutamine and glutamate levels at admission were stratified by the cut-off value (Gln 595.5 µmol/L; Glu 167.5 µmol/L). Low levels are defined as less than or equal to the cut-off value, and high levels are defined as greater than the cut-off value. All HR shown are adjusted for CCI, CRP, NRS total score, sex, and intervention.

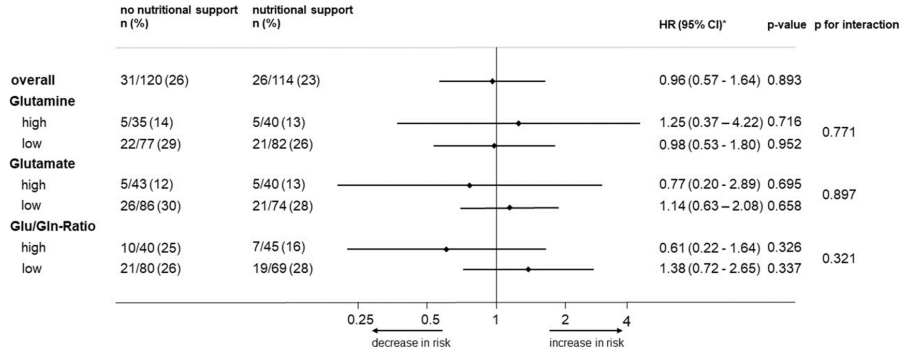

Figure 3. Forest plot for 30-day mortality and subgroup analysis for response to nutritional support. HR, hazard ratio. * Adjusted for CCI, CRP, NRS total score, sex, and intervention.

4. Discussion

This secondary analysis of a randomized trial investigating possible implications of glutamine, glutamate, and their ratio, respectively, regarding outcome and treatment response has several key findings. First, among medical inpatients at nutritional risk, neither glutamine nor glutamate are well correlated with established nutritional markers and thus may not be viewed as markers for malnutrition. Second, patients with low glutamine levels did not show an increased mortality, whereas patients with low glutamate levels had a significantly higher risk of dying within 30 days. Glutamate was also a strong prognostic marker for other adverse outcomes. Our findings remained robust in different statistical models adjusted for possible confounders. Third, low glutamine levels, low glutamate levels, or a low ratio of glutamate to glutamine were not associated with a more pronounced response to individualized nutritional therapy in terms of 30-day mortality. Therefore, these metabolites may not be considered predictive markers of response to nutritional treatment. Several of these findings need further comment.

We found no association between low plasma levels of glutamine or glutamate and several malnutrition parameters. Nevertheless, glutamine was low in our cohort, compared to a healthy French cohort [35] that was using the same analysis kit (mean glutamine plasma level 522.5 µmol/L versus 627.9 µmol/L) and to a cancer patient cohort (522.5 µmol/L versus 574.0 µmol/L) [9]. This finding is in line with previous trials that showed glutamine depletion during severe illness and under catabolic conditions [2,6,7,40]. However, low glutamine levels were not associated with a worse clinical outcome, which differs from previous data from the ICU or after major surgery [7]. This may be explained by the less severely ill patient cohort, in which glutamine depletion may also have been less severe and, thus, had no negative implications for the clinical outcome. While most studies in the ICU show that low glutamine levels are associated with poorer clinical outcomes, there is also evidence that high glutamine levels are associated with increased mortality, mainly due to impaired hepatic glucose metabolism [41]. We could not find this U shape in our data, and we assumed that most patients had a functioning glucose metabolism because we did not include critically ill patients and had liver failure as an exclusion criterion. Regarding glutamate levels, we observed increased concentrations in our patient population: the average glutamate level was 152.1 µmol/L. This is about three times higher, as compared to 46.2 µmol/L in healthy French subjects and 63.2 µmol/L in cancer patients, respectively. Since our population was polymorbid and at nutritional risk, we assumed that high plasma glutamate levels could result from high degradation and consumption rates of glutamine, a phenomenon that was observed in secondary analyses investigating cardiometabolic risk and diabetes [42] but not in malnourished patients from the large NOURISH trial [43], where glutamate was also low. However, we found that patients with high glutamate levels had a survival benefit, a finding contrary to findings from ICU trials [44] but in line with a secondary analysis of medical inpatients [43]. Metabolic pathways are complex and can be influenced by several clinical conditions. Since we found high glutamate levels, we assumed that the deamination of glutamate to α-ketoglutarate by the glutamate dehydrogenase and feeding into the Krebs cycle was the limiting step in energy production by glutamine, which is the upstream metabolite.

We found substantially more patients with low glutamine levels (159 low glutamine vs. 75 high glutamine) in our patient population. This is consistent with evidence that glutamine is depleted in conditions of high inflammation, cancer [9], and infection [4], as well as in patients with burn injuries, which is associated with weaker immune system performance [45]. Therefore, several trials have investigated whether glutamine supplementation, as recommended in various guidelines [13,46], has a benefit on clinical outcomes, such as mortality and rehospitalization, due to its immune-enhancing effects [45]. However, the most recent multicenter, double-blind, randomized control trial by Heyland et al. in 2022 failed to show the benefit of enteral guideline-compliant glutamine supplementation in severe burn patients when accounting for time to discharge alive from the hospital, 6-month mortality, or the occurrence of bacteremia [12]. Besides this study, there were some

smaller trials [11] demonstrating the beneficial effect of glutamine supplementation. Nevertheless, a systematic review and meta-analysis confirmed that supplementation has no effect on the reduction in hospital mortality, infectious complications, or the intensive care unit stay in patients with critical illness [10]. Whether glutamine supplementation in less severely ill and malnourished medical inpatients would be beneficial remains unclear and needs further investigations. Although we found elevated glutamate levels in our patient population, high glutamate levels were also associated with better survival. Therefore, the role of glutamate supplementation remains unclear.

We also investigated the response to nutritional interventions as a function of glutamine or glutamate levels, yet no difference in the efficacy of nutritional support was found between patients with high and low glutamine or glutamate concentrations. Our findings, thus, do not support the measurement of these metabolites to explain variability in response to treatment and to further personalize nutritional support.

Strengths and Limitations

The greatest strengths of this study include the well-characterized patient cohort, the randomized design, and the prospectively collected short- and long-term outcomes. This allowed us to adjust our analysis for potential confounders, such as comorbidities and nutritional parameters, and we obtained consistent results. Still, as this study is a secondary analysis, the results should be viewed as exploratory and hypothesis-generating, rather than definite, requiring confirmation in larger prospective samples. We are aware of additional limitations, including the design of our subgroup analysis at a single center, which results in lower statistical power and lower external validity. Additionally, we measured glutamine and glutamate plasma levels at admission only, so the dynamics over time and the effect of nutritional support on metabolite remains unclear. There are also restraints regarding the metabolomic kit used. So far, it has mainly been used for research purposes, and there is a lack of well-validated reference values.

5. Conclusions

This secondary analysis of a prospective randomized trial found glutamate to be an independent prognostic parameter among medical inpatients at nutritional risk, but it was poorly associated with the effectiveness of nutritional support. In contrast to findings from intensive care, low glutamine levels in medical inpatients were not associated with worse clinical outcomes. A better understanding of glutamine metabolism may help to further improve risk assessment for unfavorable outcomes in medical patients at nutritional risk. In addition, the effect of glutamine or glutamate supplementation in this less severely ill patient population remains an open question for further research.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu16020222/s1, Table S1: Baseline characteristics overall and stratified by high and low glutamate. Table S2: Association of nutritional parameters with a decrease in plasma glutamate levels. Table S3: Association of nutritional parameters with a decrease in plasma glutamate levels (without outliers). Table S4: Association of nutritional parameters with a decrease in plasma glutamate levels (logarithmic calculation). Table S5: Prognostic value of high vs. low levels of glutamine or glutamate on secondary clinical outcomes. Table S6: Prognostic value of high vs. low levels of glutamine or glutamate on secondary clinical outcomes. Table S7: Prognostic value of high vs. low glutamate-to-glutamine-ratio on mortality. Table S8: Prognostic value of high vs. low glutamate-to-glutamine-ratio on secondary clinical outcomes. Table S9: Prognostic value of high vs. low glutamate-to-glutamine-ratio on secondary clinical outcomes.

Author Contributions: Conceptualization, P.S. and C.W.; formal analysis, D.v.A., S.C.M. and C.W.; investigation, P.S., B.M., Z.S., C.W., P.T., P.N. and L.B.; writing—original draft preparation, D.v.A., S.C.M. and C.W.; writing—review and editing, D.v.A., S.C.M., C.W. and P.S.; visualization, D.v.A., S.C.M. and C.W.; project administration, P.S.; funding acquisition, P.S., B.M. and Z.S. All authors have read and agreed to the published version of the manuscript.

Funding: The original EFFORT trial was funded by the Research Council of the Kantonsspital Aarau (1410.000.058 and 1410.000.044) and the Swiss National Science Foundation (SNSF) (PP00P3_150531 and PP00P3_176972).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki. And the Ethics Committee of Northwest and Central Switzerland (EKNZ) approved the protocol of the EFFORT trial in January 2014 (registration ID 2014_001).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ongoing investigations.

Acknowledgments: We thank all participating patients and hospital staff for their support of the EFFORT trial.

Conflicts of Interest: The institution of P.S. has previously received unrestricted grant money unrelated to this project from Roche, Thermo Fisher, bioMérieux, Nestlé Health Science, and Abbott Nutrition. The institution of Z.S. received research support from Nestlé Health Science, Abbott Nutrition, Fresenius Kabi, and B. Braun. All other authors declare no conflicts of interest.

Abbreviations

ATP	adenosine triphosphate
BMI	body mass index
CCI	Charlson comorbidity index
CI	confidence interval
CRP	C-reactive protein
DRM	disease-related malnutrition
EFFORT	Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial
EKNZ	Ethics Committee of Northwest and Central Switzerland
GA	glutaminase
HR	hazard ratio
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
NH3	ammonia
NRS	nutritional risk screening 2002
OR	odds ratio
SD	standard deviation
UHPLC	ultra-high-pressure liquid chromatography

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3.3.2 Association of Tryptophan Pathway Metabolites with Mortality and Effectiveness of Nutritional Support among Patients at Nutritional Risk. Secondary Analysis of a Randomized Clinical Trial [97]

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frontiers | Frontiers in Nutrition

TYPE Original Research
PUBLISHED 15 February 2024
DOI 10.3389/fnut.2024.1335242

OPEN ACCESS

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RECEIVED 08 November 2023
ACCEPTED 31 January 2024
PUBLISHED 15 February 2024

CITATION
Ritz J, Wunderle C, Stumpf F, Laager R, Tribolet P, Neyer P, Bernasconi L, Stanga Z, Mueller B and Schuetz P (2024) Association of tryptophan pathway metabolites with mortality and effectiveness of nutritional support among patients at nutritional risk: secondary analysis of a randomized clinical trial.
Front. Nutr. 11:1335242.
doi: 10.3389/fnut.2024.1335242

Association of tryptophan pathway metabolites with mortality and effectiveness of nutritional support among patients at nutritional risk: secondary analysis of a randomized clinical trial

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Tryptophan is an essential amino acid and is the precursor of many important metabolites and neurotransmitters. In malnutrition, the availability of tryptophan is reduced, potentially putting patients at increased risks. Herein, we investigated the prognostic implications of the tryptophan metabolism in a secondary analysis of the Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial (EFFORT), a randomized, controlled trial comparing individualized nutritional support to usual care in patients at risk for malnutrition. Among 238 patients with available measurements, low plasma levels of metabolites were independently associated with 30-day mortality with adjusted hazard ratios (HR) of 1.77 [95% CI 1.05–2.99, p 0.034] for tryptophan, 3.49 [95% CI 1.81–6.74, $p < 0.001$] for kynurenine and 2.51 [95% CI 1.37–4.63, p 0.003] for serotonin. Nutritional support had more beneficial effects on mortality in patients with high tryptophan compared to patients with low tryptophan levels (adjusted HR 0.61 [95% CI 0.29–1.29] vs. HR 1.72 [95% CI 0.79–3.70], p for interaction 0.047). These results suggest that sufficient circulating levels of tryptophan might be a metabolic prerequisite for the beneficial effect of nutritional interventions in this highly vulnerable patient population.

KEYWORDS

tryptophan, kynurenine, serotonin, biomarker, metabolomics, malnutrition, nutritional support

1 Introduction

Malnutrition is frequent in medical inpatients with a prevalence of more than 30% and is strongly associated with an increased risk for mortality, morbidity, functional decline, and impairments in quality of life (1–3). The Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial (EFFORT) and other trials demonstrated that early individualized nutritional support improves clinical outcomes in patients at risk for malnutrition (4–6). Still, recent data suggest that individual response to nutrition treatment may vary and that not all patients show clinical benefit when nutritional support is initiated. In fact, several novel analyses have found disease-related conditions and blood biomarkers that identified patients with a strong benefit from nutritional support (7–9). For example, patients with high levels of inflammation have shown to benefit less from nutritional support compared to patients with moderate or low inflammation levels (8). These findings are consistent with previous trials conducted in critically ill patients (10, 11). To further personalize and improve the efficiency of nutritional support, metabolites from different metabolic pathways, including amino acids, may also serve as biomarkers to predict treatment response.

Herein, tryptophan, an essential amino acid whose dietary intake is necessary for protein synthesis, and its metabolites are potential nutritional biomarkers. Tryptophan is the precursor of neurotransmitters, such as serotonin and melatonin, and other physiologically important metabolites involved in redox reactions or the citrate cycle (12). Deficient protein intake results in low tryptophan plasma levels and thus low tryptophan availability (13, 14). Furthermore, tryptophan level is known to decrease with age (15). About 95% of tryptophan is metabolized to kynurenine by the rate-limiting enzymes tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) (16, 17). IDO is localized in extrahepatic tissue and is induced, e.g., by interferon-gamma. Initially, this was thought to be a defense mechanism for reducing the availability of tryptophan to intracellular parasites, cancer cells, or pathogens (18, 19). However, recent studies have demonstrated that IDO activity inhibits T cell proliferation and like this modulates inflammatory response (20). Tumor cells take advantage of this mechanism by expressing IDO and thus suppress antitumor immunity (21). Activation of the tryptophan/kynurenine pathway with high IDO activity has been observed in several clinical conditions, such as infection, inflammation, and malignant disease and may contribute to disease severity and adverse clinical outcomes (22–24). Less than 5% of tryptophan is metabolized to serotonin and other neurotransmitters. Tryptophan hydroxylase (TPH) catalyzes the oxygenation of tryptophan to 5-hydroxytryptophan (5-HTP) which, in a second step, is decarboxylated to serotonin. In addition to central effects as a neurotransmitter, serotonin leads to vasoconstriction and endothelial hyperpermeability in the periphery (25). Accordingly, activation of the serotonin pathway was found in several diseases including chronic obstructive pulmonary disease (COPD), coronary artery disease and sepsis and each time associated with severity and outcomes (22, 26, 27). Yet, today, little is known about the role of tryptophan and its metabolites in malnutrition. Herein, we investigated the association of tryptophan metabolites with clinical outcomes and the response to nutritional therapy among patients at risk for malnutrition.

2 Methods

2.1 Study design

This is a secondary analysis of EFFORT, a multicenter, pragmatic, randomized, controlled clinical trial comparing individualized nutritional support to usual care in patients at risk for malnutrition (6). The study was conducted in eight Swiss hospitals between April 2014 and February 2018. The Ethics Committee of Northwest and Central Switzerland (EKNZ) approved the study protocol in January 2014 (registration ID 2014_001). The trial was registered at ClinicalTrial.gov (NCT02517476) in August 2015.

2.2 Patient population

The EFFORT trial enrolled 2,088 patients. Inclusion criteria were: age ≥ 18 years, Nutritional Risk Screening [NRS 2002; (28)] total score of ≥3 points and an expected hospital stay of more than 4 days. The NRS 2002 includes assessment of the patient's nutritional status (based on weight loss, body mass index, and food intake), disease severity, and age. All patients or their authorized representatives provided written informed consent. Patients initially admitted to intensive care or surgical units were excluded. Other exclusion criteria were inability of oral food intake, nutritional support on admission, anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, terminal condition, stem-cell transplantation, and after gastric bypass surgery.

In this secondary analysis, we included patients from the Medical University Clinic at the Cantonal Hospital Aarau with available measurements of tryptophan, serotonin, and kynurenine.

2.3 Study intervention

Patients were randomly assigned (1:1) to receive either individualized nutritional support (intervention group) or usual hospital food (control group). In the intervention group, nutritional support was initiated as soon as possible after randomization but within 48 h after hospital admission. Individualized nutritional goals were defined for each patient upon hospital admission by a trained registered dietitian based on a previous consensus protocol following international guidelines, detailed elsewhere (29, 30). The intervention started with oral nutritional support. However, if less than 75% of caloric and protein targets were reached within 5 days; nutritional support was escalated to enteral or parenteral feeding. Every 24–48 h, the nutritional intake was re-assessed. Patients in the control group received standard hospital food without nutritional consultation or recommendation for additional nutritional support.

2.4 Analysis of blood biomarkers

Blood samples were systematically collected upon study inclusion for later measurement of biomarkers by drawing a venous blood sample into BD Vacutainer Serum Separator Tubes. Samples were immediately processed, i.e., sent to the laboratory and centrifugated, frozen in aliquots, and stored under temperature control at −80°C

until further analysis. Admission plasma metabolites were analyzed from February to April 2019 by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). An Ultimate 3000 HPLC (Thermo Fisher, San Jose, United States) system coupled to a Sciex 5500 quadrupole linear ion trap mass spectrometer (Sciex, Darmstadt, Germany) and the AbsoluteIDQ® p180 kit (BIOCRATES Life Sciences AG, Innsbruck, Austria) were used (31–33). An inter-laboratory assessment of the commercially available kit for targeted metabolomics showed reliability of the metabolomics assay (34). Measurement variation was monitored via three different quality control levels as provided by the kit manufacturer (Biocrates, Innsbruck, Austria) which were analyzed in the same way as the samples. Variation was within of the manufacturer's specifications and no relevant batch effects were observed with the final measurements. One questionable plate was rerun after a technical issue with the chromatographic instrument had been identified.

The ratio of kynurenine to tryptophan was used as a sensitive indicator of IDO activity (22, 35). The same principle was applied to calculate activity of TPH (ratio of serotonin to tryptophan).

2.5 Endpoints

The primary outcome was 30-day all-cause mortality. Secondary endpoints were all-cause mortality within 180 days and adverse clinical outcomes within 30 days including all-cause mortality, admission to the intensive care unit, hospital readmission after discharge, major complications (including nosocomial infection, respiratory failure, major cardiovascular event, acute renal failure, or gastro-intestinal failure), and a decline in functional status of ≥10% measured by the Barthel index. The scores of Barthel index range from 0 to 100 points. Higher scores indicate better performance of daily activities. Follow-up interviews at day 30 and 180 were conducted with blinding to group assignment. Mortality during follow-up was verified by relatives or the patient's family doctor.

2.6 Statistical analysis

All statistical analyses were performed using Stata 17. A p value of <0.05 was considered to indicate statistical significance. Due to the limited sample size, we did not adjust for multiple testing. Optimal cut off values for each metabolite were calculated using ROC analysis according to the Liu method (36) for 30-day mortality because no reference values in this patient population was available.

Continuous variables were expressed as mean values with the corresponding standard deviation (SD) and categorical variables as percentages or numbers. We compared frequencies using Pearson's chi-squared test and continuous variables using a two-sample t-test. We used logistic regression models for binary outcomes reporting odds ratios (OR) and linear regression models for continuous outcomes reporting coefficients (Coef) with the corresponding 95% confidence interval (CI). For time-to-event data we used cox regression models reporting hazard ratios (HR). We adjusted for comorbidities, age, sex, randomization group, and NRS 2002 total score. Age adjusted Charlson Comorbidity Index (CCI) (37) was used to quantify comorbidities and age for each patient. Kaplan Meier curves were used to graphically represent the survival rate.

3 Results

3.1 Patient characteristics

From the initial cohort including 2,088 patients, metabolite measurements were performed in samples of 238 patients from one study center participating in this sub-study. Of these 238 patients, 116 were assigned to the intervention group and 122 to the control group (Figure 1).

In total, we had 238 tryptophan, 236 kynurenine, and 213 serotonin measurements in our cohort. Calculated cut off values based on the ROC curve analysis were 36.2 µmol/L for tryptophan, 3.4 µmol/L for kynurenine, 0.25 µmol/L for serotonin, 66.6 for IDO, and 4.3 for TPH. The mean value of tryptophan was 41.1 µmol/L (SD 16.5) and 93 patients (39.1%) had tryptophan levels below the calculated cut off value (36.2 µmol/L). The mean patient age was 73 years and 57.6% of patients were male. Per inclusion criteria, all patients were at risk for malnutrition with NRS 2002 total scores of 3 (N = 62, 26.1%), 4 (N = 80, 33.6%), or above 5 (N = 96, 40.3%). Most patients were polymorbid and the most common diagnoses at admission were cancer (N = 75, 31.5%), infection (N = 65, 27.3%), and cardiovascular disease (N = 24, 10.1%). The 30-day all-cause mortality was 24.4% (N = 58). Additional baseline characteristics of the overall population and stratified according to tryptophan levels are shown in Table 1.

3.2 Association of nutritional parameters and inflammation with tryptophan metabolites

In a first step, we investigated the association of nutritional parameters and inflammation with tryptophan metabolites (Supplementary Table 1). Higher body mass index was positively associated with tryptophan levels in a linear regression model (Coef 3.52 [95% CI 1.16–5.88, p 0.004]). Furthermore, disease severity was associated with low tryptophan plasma levels (<36.2 µmol/L) in a logistic regression model (OR 2.12 [95% CI 1.26–3.56, p 0.005]). No correlation was found with inflammation (assessed by CRP) or nutritional risk based on the NRS 2002 total score.

3.3 Association of tryptophan metabolites with mortality and clinical outcomes

Next, to understand prognostic implications, we investigated the association of tryptophan and its metabolites with clinical outcomes (Table 2). Low plasma levels of all metabolites were associated with an increased risk of 30-day mortality in a multivariate cox regression model with adjusted HRs of 1.77 [95% CI 1.05–2.99, p 0.034] for tryptophan, 3.49 [95% CI 1.81–6.74, p < 0.001] for kynurenine, and 2.51 [95% CI 1.37–4.63, p 0.003] for serotonin (Figure 2). Likewise, low values of the calculated enzymes TPH and IDO were associated with 30-day mortality in a univariate model with HRs of 2.41 [95% CI 1.39–4.17, p 0.002] for TPH and 1.73 [95% CI 1.03–2.90, p 0.038] for IDO. These results remained consistent in an adjusted model for TPH, but not for IDO.

Regarding the long-term outcome, low plasma levels of tryptophan, kynurenine, and serotonin were associated with increased mortality after 180 days with adjusted HRs of 1.74 [95% CI 1.16–2.61,

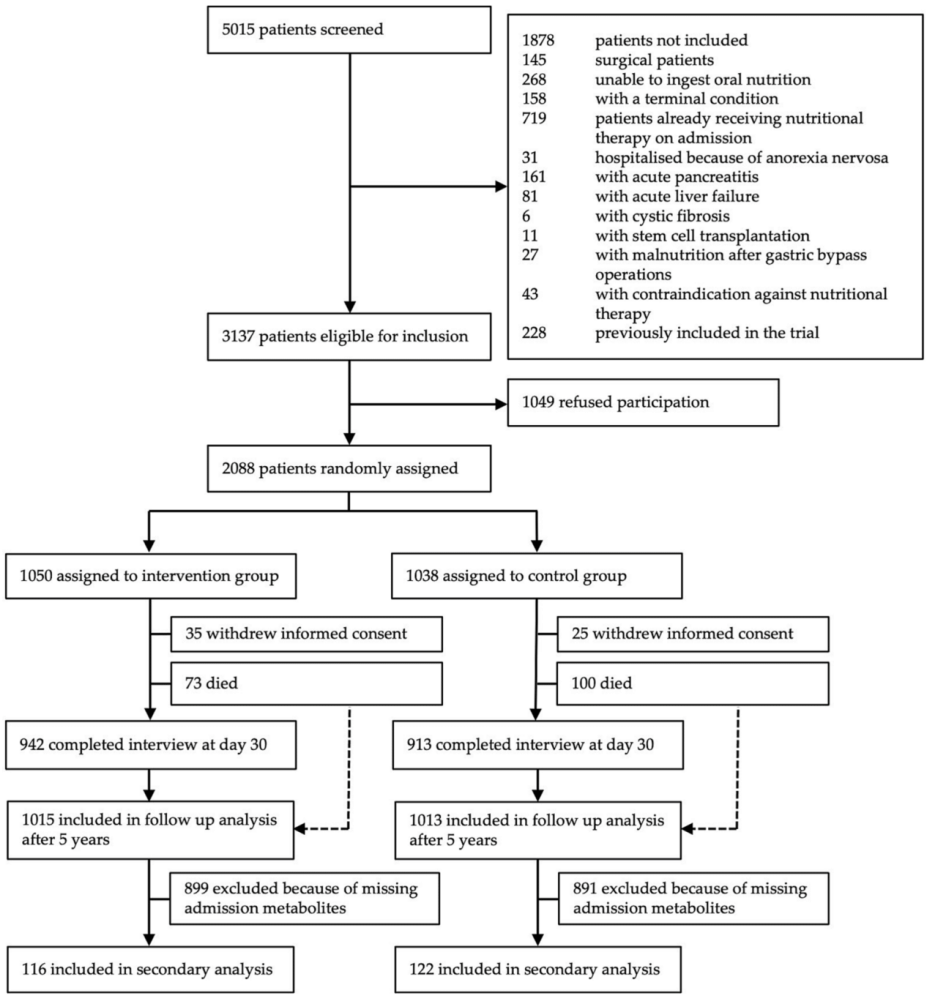

FIGURE 1
Study flow chart.

p 0.007] for tryptophan, 1.77 [95% CI 1.17–2.69, *p* 0.007] for kynurenine, and 1.63 [95% CI 1.06–2.51, *p* 0.026] for serotonin.

Regarding the combined endpoint of adverse events, we found significant association with low values of kynurenine (adjusted OR 3.15 [95% CI 1.72–5.77, $p < 0.001$]) but not with other metabolites.

3.4 Association of tryptophan metabolites with response to nutritional support

To understand whether the treatment response to nutritional support would differ according to admission tryptophan levels, we compared clinical outcomes based on the initial randomization (intervention vs. control) in patients stratified by high or low levels of tryptophan and its metabolites. The nutritional support intervention showed a trend toward a beneficial effect and lower risk of 30-day mortality in patients with high tryptophan levels (adjusted HR 0.61 [95% CI 0.29–1.29, *p* 0.195]), but not in patients with low tryptophan levels (adjusted HR 1.72 [95% CI 0.79–3.70, *p* 0.169]) (Figure 3). This difference in effect was significant in interaction analysis (*p* for interaction 0.047). Similar analyses with the other metabolites and enzymes under investigation (kynurenine, serotonin, IDO, and TPH) did not show similar results regarding the effectiveness of the response to nutritional therapy (Figure 4).

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TABLE 1 Baseline characteristics.

	Overall	High tryptophan levels (≥36.2 μmol/L)	Low tryptophan levels (<36.2 μmol/L)	*p* value
Sociodemographic				
Patient number, *n* (%)	238	145 (60.9%)	93 (39.1%)	
Male sex, *n* (%)	137 (57.6%)	87 (60.0%)	50 (53.8%)	0.34
Age, mean (SD)	73.4 (13.5)	73.8 (13.1)	72.7 (14.3)	0.57
Nutritional assessment, mean (SD)				
Body mass index (kg/m^2)	24.3 (5.0)	24.6 (5.1)	23.7 (4.7)	0.18
Mean body weight (kg)	68.7 (14.9)	70.2 (15.3)	66.3 (14.0)	**0.05**
Height (cm)	168.1 (8.6)	168.9 (8.6)	166.9 (8.5)	0.078
NRS 2002 total score, *n* (%)				0.78
3 points	62 (26.1%)	40 (27.6%)	22 (23.7%)	
4 points	80 (33.6%)	47 (32.4%)	33 (35.5%)	
≥5 points	96 (40.3%)	58 (40.0%)	38 (40.9%)	
Musclefunction, mean (SD)				
Handgrip strength (kg)	23.7 (11.6)	24.3 (11.5)	22.9 (11.6)	0.47
Admission diagnosis, *n* (%)				
Infection	65 (27.3%)	33 (22.8%)	32 (34.4%)	**0.049**
Cancer	75 (31.5%)	39 (26.9%)	36 (38.7%)	0.056
Cardiovascular disease	24 (10.1%)	18 (12.4%)	6 (6.5%)	0.14
Frailty	13 (5.5%)	8 (5.5%)	5 (5.4%)	0.96
Lung disease	11 (4.6%)	11 (7.6%)	0 (0.0%)	**0.007**
Gastrointestinal disease	13 (5.5%)	10 (6.9%)	3 (3.2%)	0.22
Neurological disease	4 (1.7%)	3 (2.1%)	1 (1.1%)	0.56
Renal disease	15 (6.3%)	11 (7.6%)	4 (4.3%)	0.31
Metabolic disease	6 (2.5%)	4 (2.8%)	2 (2.2%)	0.77
Other	3 (1.3%)	2 (1.4%)	1 (1.1%)	0.84
Comorbidity, *n* (%)				
Hypertension	139 (58.4%)	92 (63.4%)	47 (50.5%)	**0.049**
Malignant disease	113 (47.5%)	65 (44.8%)	48 (51.6%)	0.31
Chronic kidney disease	81 (34.0%)	49 (33.8%)	32 (34.4%)	0.92
Coronary heart disease	54 (22.7%)	35 (24.1%)	19 (20.4%)	0.51
Diabetes	43 (18.1%)	28 (19.3%)	15 (16.1%)	0.53
Congestive heart failure	45 (18.9%)	31 (21.4%)	14 (15.1%)	0.22
COPD	28 (11.8%)	19 (13.1%)	9 (9.7%)	0.42
Peripheral arterial disease	26 (10.9%)	16 (11.0%)	10 (10.8%)	0.95
Stroke	27 (11.3%)	16 (11.0%)	11 (11.8%)	0.85
Dementia	11 (4.6%)	8 (5.5%)	3 (3.2%)	0.41

Groups based on high or low tryptophan plasma levels. We compared frequencies using Person's chi-squared test and continuous variables using a two-sample t-test.
COPD, Chronic obstructive pulmonary disease; NRS 2002, Nutritional Risk Screening 2002. The values in bold indicate that they are statistically significant (*p* value of <0.05).

4 Discussion

In this secondary analysis of a one-center subset from a large, multicenter, randomized, controlled clinical trial, we investigated the prognostic implications of tryptophan pathway metabolites regarding clinical outcomes and response to nutritional support among patients at nutritional risk. This study has several key findings. First, the availability of tryptophan was in general reduced in our malnourished patient cohort. Second, low levels of tryptophan were associated with disease severity, but not with nutritional intake or nutritional risk based on the NRS 2002 total score. Third, low levels of tryptophan, kynurenine, and serotonin were also associated with an increased risk in 30-day and 180-day mortality, respectively. This suggest that these metabolites provide prognostic information in patients at nutritional

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TABLE 2 Prognostic value of tryptophan metabolites to predict clinical outcomes.

All-cause mortality	Low plasma levels	High plasma levels	HR* (95% CI)	*p* value
30-day all-cause mortality				
Tryptophan	28/93 (30.1%)	30/145 (20.7%)	1.77 (1.05–2.99)	**0.034**
Kynurenine	47/139 (33.8%)	11/97 (11.3%)	3.49 (1.81–6.74)	**<0.001**
Serotonin	41/119 (34.5%)	14/94 (14.9%)	2.51 (1.37–4.63)	**0.003**
IDO	32/101 (31.7%)	26/135 (19.3%)	1.59 (0.94–2.69)	0.084
TPH	35/96 (36.5%)	20/117 (17.1%)	2.52 (1.45–4.38)	**0.001**
180-day all-cause mortality				
Tryptophan	48/93 (51.6%)	54/145 (37.2%)	1.74 (1.16–2.61)	**0.007**
Kynurenine	67/139 (48.2%)	34/97 (35.1%)	1.77 (1.17–2.69)	**0.007**
Serotonin	59/119 (49.6%)	33/94 (35.1%)	1.63 (1.06–2.51)	**0.026**
IDO	45/101 (44.6%)	56/135 (41.5%)	1.15 (0.77–1.71)	0.499
TPH	46/96 (47.9%)	46/117 (39.3%)	1.46 (0.97–2.20)	0.073
3-year all-cause mortality				
Tryptophan	60/93 (64.5%)	83/145 (57.2%)	1.41 (1.00–1.98)	**0.049**
Kynurenine	87/139 (62.6%)	55/97 (56.7%)	1.50 (1.06–2.12)	**0.021**
Serotonin	77/119 (64.7%)	52/94 (55.3%)	1.35 (0.95–1.93)	0.093
IDO	61/101 (60.4%)	81/135 (60.0%)	1.09 (0.77–1.53)	0.634
TPH	62/96 (64.6%)	67/117 (57.3%)	1.31 (0.93–1.86)	0.127
Other clinical outcomes	**Low plasma levels**	**High plasma levels**	**OR* (95% CI)**	***p* value**
Adverse events within 30-day				
Tryptophan	40/93 (43.0%)	53/145 (36.6%)	1.39 (0.97–1.00)	0.247
Kynurenine	68/139 (48.9%)	24/97 (24.7%)	3.15 (1.72–5.77)	**<0.001**
Serotonin	53/119 (44.5%)	32/94 (34.0%)	1.47 (0.82–2.65)	0.200
IDO	45/101 (44.6%)	47/135 (34.8%)	1.44 (0.82–2.53)	0.200
TPH	44/96 (45.8%)	41/117 (35.0%)	1.56 (0.87–2.79)	0.140
Major complications within 30-day				
Tryptophan	9/93 (9.7%)	13/145 (9.0%)	1.11 (0.45–2.72)	0.826
Kynurenine	16/139 (11.5%)	6/97 (6.2%)	1.99 (0.75–5.33)	0.169
Serotonin	12/119 (10.1%)	7/94 (7.5%)	1.32 (0.49–3.52)	0.585
IDO	10/101 (9.9%)	12/135 (8.9%)	1.12 (0.46–2.74)	0.805
TPH	11/96 (11.5%)	8/117 (6.8%)	1.66 (0.64–4.34)	0.300
Barthel decline >10%				
Tryptophan	29/93 (31.2%)	36/145 (24.8%)	1.58 (0.84–2.97)	0.157
Kynurenine	48/139 (34.5%)	17/97 (17.5%)	2.78 (1.40–5.53)	**0.003**
Serotonin	40/119 (33.6%)	20/94 (21.3%)	1.73 (0.88–3.39)	0.109
IDO	35/101 (34.7%)	30/135 (22.2%)	1.82 (0.97–3.43)	0.062
TPH	33/96 (34.4%)	27/117 (23.1%)	1.73 (0.90–3.33)	0.101

Groups based on high or low metabolite plasma levels. Data are number of events (%).
*HR and *OR were adjusted for comorbidity, age, sex, randomization group and nutritional risk Screening 2002 total score.
CI, Confidence interval; HR, Hazard ratio; IDO, Indoleamine 2,3-dioxygenase; OR, Odds ratio; and TPH, Tryptophan hydroxylase. The values in bold indicate that they are statistically significant (p value of <0.05).

risk that is independent from their nutritional status. Finally, although patients with low tryptophan levels had higher risk for mortality, nutritional support appeared to have the smallest effects in these patients as compared to patients with higher tryptophan levels.

Our data differ from previously conducted studies in pneumonia, COPD, and sepsis, where an activation of the kynurenine and serotonin pathways was associated with adverse outcomes (22, 24, 38). Metabolic pathways are complex and can be influenced by several clinical conditions. The selection of our rather heterogenous medical patient cohort at risk for malnutrition with various underlying diseases might explain these differences. Deficient protein intake leads to low tryptophan plasma levels and hence its availability. Although

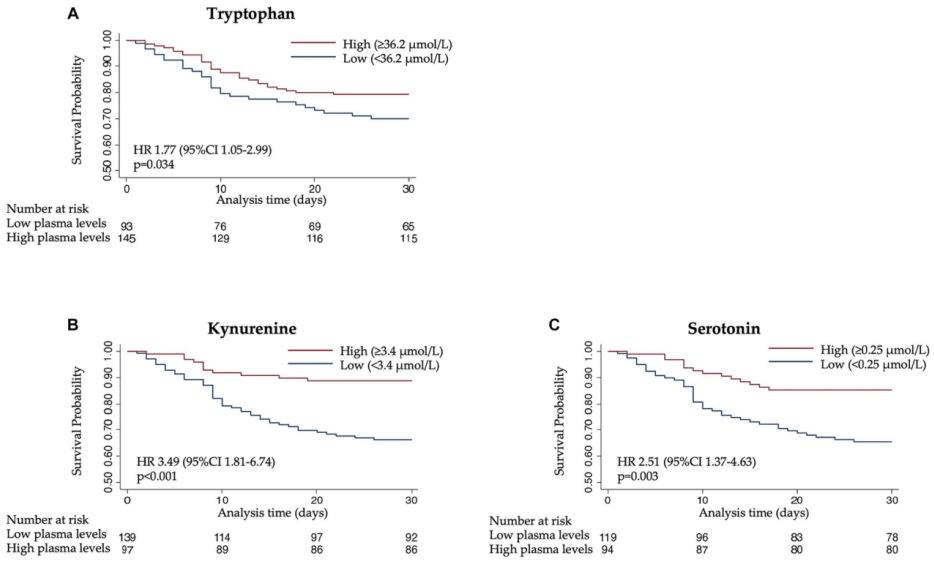

FIGURE 2
Kaplan–Meier estimate for time to death within 30 days according to **(A)** tryptophan, **(B)** kynurenine, and **(C)** serotonin levels.

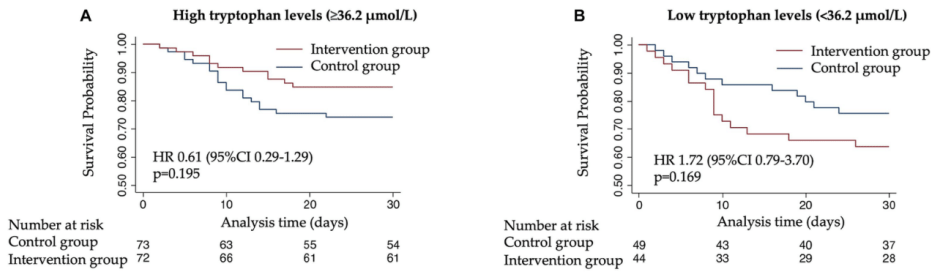

FIGURE 3
Kaplan–Meier estimate for time to death within 30 days according to randomization group. **(A)** 30-day mortality among patients with high tryptophan plasma levels (≥36.2 µmol/L). **(B)** 30-day mortality among patients with low tryptophan plasma levels (<36.2 µmol/L).

we could not demonstrate an association of tryptophan with the NRS 2002 total score, tryptophan levels were low in our patient cohort compared to healthy volunteers in France (median tryptophan levels 40.1 vs. 62.7 µmol/L) (15). Also, in comparison to a study with a COPD patient cohort with similar age distribution and comorbidities, tryptophan levels were lower in our malnourished patient cohort (40.1 vs. 50.3 µmol/L) (24). This supports the hypothesis of low tryptophan levels due to malnutrition, and thus its decreased availability for the subsequent metabolic pathways, likely leading to a general downregulation of the involved enzymes. Furthermore, tryptophan levels depend on age and decrease over time (15). This may have an influence on tryptophan levels in our rather older patient population. Several underlying conditions can also influence tryptophan levels and the activity of the enzymes. High IDO activity and thus activation of the kynurenine pathway was associated with inflammation and malignant disease in previous studies (21, 22). In our study, we found an association between infectious diseases and low tryptophan levels, probably due to an activation of the kynurenine pathway and IDO activity. However, no association was found with levels of inflammation (CRP). Due to the sample size, we did not further explore effects in subgroup analyses regarding the underlying diseases and outcomes.

An important and new finding of this study was that, although low tryptophan levels were associated with higher mortality,

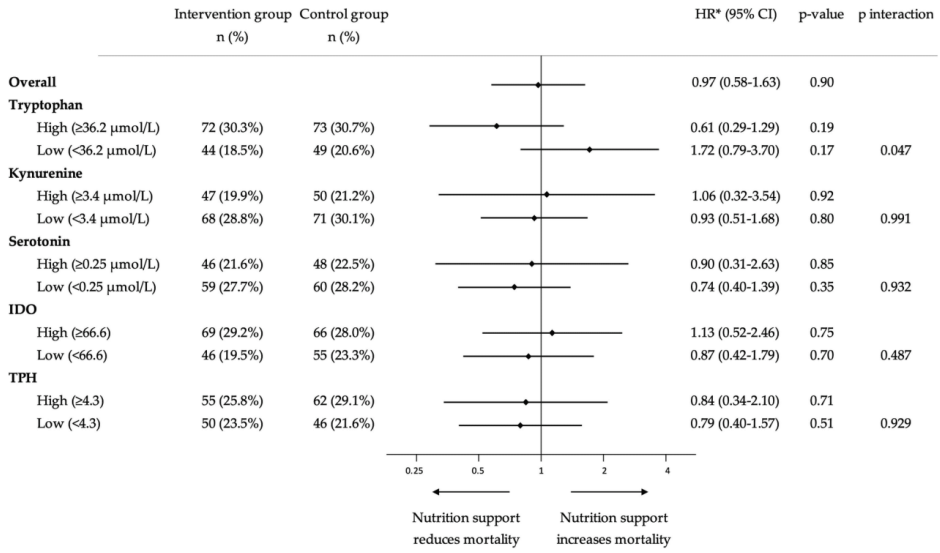

FIGURE 4
Hazard ratio plot for 30-day all-cause mortality, subgroup analysis for response to nutritional support. Data are presented in a logarithmic scale. *HR were adjusted for comorbidity, age, sex, randomization group, and Nutritional Risk Screening 2002 total score. HR, Hazard ratio; IDO, Indoleamine 2,3-dioxygenase; and TPH, Tryptophan hydroxylase.

nutritional support in those patients with low tryptophan levels was less effective in improving outcomes compared to patients with higher levels. This finding is comparable with data observed in critically ill patients, where only little benefit from full-replacement feeding could be shown in several clinical trials (10, 11). In fact, high nutritional intake during severe illness has been suggested to reduce autophagy, a mechanism important for cell detoxication during illness, which may explain lack of effect in these patients (39). Similarly, in our patient cohort, low tryptophan levels may identify patients with severe disease and high metabolic stress in whom reaching protein and caloric goals may not translate to clinical benefit. Whether low tryptophan levels are a consequence or cause of the observed poor outcomes and thus specific nutritional intervention including tryptophan could have beneficial effects in this highly vulnerable patient population, needs to be further investigated. To the best of our knowledge, there are no treatment studies answering the question of whether tryptophan supplementation or modification of the tryptophan/kynurenine pathway have an impact on survival.

This secondary analysis has several strengths and limitations. The main strength of this study includes the well characterized patient cohort, the randomized design, and the prospectively collected short- and long-term outcomes. Thus, we were able to adjust our analysis for potential confounders including comorbidities and nutritional parameters. We had consistent results also after adjusting for those confounders. To our knowledge, this is the first analysis based on a randomized, controlled clinical trial to examine the prognostic value of tryptophan metabolites and their role as predictors for the effectiveness of nutritional support. However, we are aware of the limitations in our analysis. Metabolite measurements were only available in a small subset of the original patient cohort, and blood samples were collected from one study center only. This limits the power and external validity of the analysis. In light of the limited sample size and the exploratory nature of this study, we also did not adjust for multiple testing. Given the exploratory nature of this secondary analysis, this study should be considered hypothesis generating rather than definitive. There are also limitations regarding the used metabolomic kit. So far, it has been mainly used for research purposes and lacks well validated reference values. Due to internal validation, results can differ between laboratories and comparison of the measured values are only possible to a limited extend. Furthermore, the enzymes IDO and TPH could not be measured and were therefore estimated through the ratio of kynurenine/ serotonin to tryptophan, making them vulnerable to errors. Since plasma levels of tryptophan metabolites were only measured upon study inclusion, no statement could be made regarding the influence of nutritional therapy on the metabolites.

In conclusion, our data suggest that levels of tryptophan, kynurenine, and serotonin are low in patients at nutritional risk, and strongly associated with mortality and adverse outcomes. However, nutritional support for patients with tryptophan levels below a calculated cut point was less effective in improving these outcomes. This may be due to an association of disease severity in patients with low tryptophan levels. Whether specific nutritional interventions including tryptophan may have beneficial effects in this highly vulnerable patient population needs to be analyzed. Further prospective studies are required to validate our results, evaluate the impact of nutritional support on levels of tryptophan metabolites, and whether therapeutic modulations of these pathways have positive effects on outcomes.

Data availability statement

The data analyzed in this study are subject to the following licenses/restrictions: Data described in the manuscript, codebook, and analytic code are available upon request after other secondary projects related to the study are completed. Requests to access these datasets should be directed to schuetzph@gmail.com.

Ethics statement

The studies involving humans were approved by 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

JR: Formal analysis, Visualization, Writing – original draft, Writing – review & editing. CW: Conceptualization, Formal analysis, Investigation, Writing – review & editing. FS: Formal analysis, Writing – review & editing. RL: Formal analysis, Writing – review & editing. PT: Investigation, Writing – review & editing. PN: Investigation, Writing – review & editing. LB: Investigation, Writing – review & editing. ZS: Funding acquisition, Investigation, Writing – review & editing. BM: Funding acquisition, Investigation, Writing – review & editing. PS: Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The original EFFORT trial was funded by the Research Council of the Kantonsspital Aarau (1410.000.058 and 1410.000.044) and the Swiss National Science Foundation (SNSF) (PP00P3_150531 and PP00P3_176972).

Acknowledgments

We thank all participating patients and hospital staff for their support of the EFFORT trial.

Conflict of interest

The institution of PS has previously received unrestricted grant money unrelated to this project from Roche, Thermo Fisher, bioMérieux, Nestlé Health Science and Abbott Nutrition. The institution of ZS received research support from Roche, Nestlé Health Science, Abbott Nutrition, Fresenius Kabi and B. Braun.

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.2024.1335242/full#supplementary-material

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3.3.3 Prognostic implications of the arginine metabolism in patients at nutritional risk: A secondary analysis of the randomized EFFORT trial [98]

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FS, CW, and PS: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing - original draft, writing - review & editing. BM, ZS, PT: conceptualization. PS and the EFFORT Team: investigation. SCB: supervision. PS, ZS, BM: resources, supervision, project administration, funding acquisition. All authors read and approved the final version of the manuscript. All authors confirm, they had full access to all data in this secondary analysis. All authors accept responsibility for the decision to submit for publication.

Clinical Nutrition 43 (2024) 660–673

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Prognostic implications of the arginine metabolism in patients at nutritional risk: A secondary analysis of the randomized EFFORT trial

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ARTICLE INFO

Article history:
Received 16 October 2023
Accepted 14 January 2024

Keywords:
Arginine
Immune response
Mortality
Nutritional risk
Nutritional support

SUMMARY

Background: Arginine, a conditionally essential amino acid, is key component in metabolic pathways including immune regulation and protein synthesis. Depletion of arginine contributes to worse outcomes in severely ill and surgical patient populations. We assessed prognostic implications of arginine levels and its metabolites and ratios in polymorbid medical inpatients at nutritional risk regarding clinical outcomes and treatment response.

Methods: Within this secondary analysis of the randomized controlled *Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial* (EFFORT), we investigated the association of arginine, its metabolites and ratios (i.e., ADMA and SDMA, ratios of arginine/ADMA, arginine/ornithine, and global arginine bioavailability ratio) measured on hospital admission with short-term and long-term mortality by means of regression analysis.

Results: Among the 231 patients with available measurements, low arginine levels ≤90.05 μmol/l (n = 86; 37 %) were associated with higher all-cause mortality at 30 days (primary endpoint, adjusted HR 3.27, 95 % CI 1.86 to 5.75, p < 0.001) and at 5 years (adjusted HR 1.50, 95 % CI 1.07 to 2.12, p = 0.020). Arginine metabolites and ratios were also associated with adverse outcome, but had lower prognostic value. There was, however, no evidence that treatment response was influenced by admission arginine levels.

Conclusion: This secondary analysis focusing on medical inpatients at nutritional risk confirms a strong association of low plasma arginine levels and worse clinical courses. The potential effects of arginine-enriched nutritional supplements should be investigated in this population of patients.

Clinical trial registration: clinicaltrials.gov as NCT02517476 (registered 7 August 2015).

1. Introduction

Not only due to its immunomodulatory effects, arginine metabolism had become of great interest in a variety of clinical conditions, especially in critical illness [1–4]. The conditionally essential amino acid exerts immune regulatory functions by regulating T cell proliferation and function, and through its catabolite nitric oxide (NO) [1,5]. Besides, it is as a substrate for protein synthesis and exerts extra anabolic effects on the muscle tissue [6]. Moreover, arginine is involved in other metabolic pathways such as the urea cycle, regulation of hormone secretion, cell growth, vasodilation, bronchodilation, and wound healing [1,2,7,8]. Low arginine levels are associated with higher disease severity and worse outcomes in different clinical conditions

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https://doi.org/10.1016/j.clnu.2024.01.012

including cancer, cardiac and pulmonary diseases, and in patients with trauma, sepsis, or critical illness [9–13]. Besides arginine, other components of its pathway, namely asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), also have prognostic implications in different diseases [13–15]. They limit arginine transport and synthesis of NO, of which arginine is the sole precursor. The ratio of arginine to ADMA (Arg/ADMA) may thus serve as an indicator for availability of arginine and NO. Similarly, the ratio of arginine to ornithine (Arg/Orn) and the ratio of arginine to (ornithine plus citrulline), the so-called global arginine bioavailability ratio (GABR), are suggested arginine bioavailability ratios [16].

Several mechanisms including decreased synthesis and intake of amino acids such as arginine and increased protein catabolism contribute to the pathophysiology of disease-related malnutrition (DRM) [17,18]. DRM is a complex syndrome associated with poor prognosis affecting approximately one third of hospitalized patients [17–20]. In fact, imbalanced arginine metabolism have been found to be related with inflammation and impaired renal, intestinal, or metabolic functions, which also occur in DRM [17,18,21]. Subsequently, arginine is recommended as component of immune-modulating formulae in specific patient populations due to its immune-regulating and wound-healing properties and regulatory function in protein synthesis [1,22–24]. Arginine and its metabolites are thus interesting parameters in the evaluation of DRM patients and may help to further advance the pathophysiological understanding of this condition and open the door for personalized nutritional approaches [17].

Herein, we investigated the prognostic implications of arginine metabolism by measuring levels of arginine, ADMA and SDMA, and the bioavailability ratios Arg/ADMA, Arg/Orn, and GABR in medical inpatients at nutritional risk included in the previous *Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial* (EFFORT).

2. Material and methods

2.1. Study design and setting

This is a secondary analysis of EFFORT, an open-label, pragmatic, investigator-initiated randomized controlled trial (RCT), conducted in 8 Swiss medical centers [25,26]. EFFORT investigated the effect of individualized nutritional support compared to standard of care in medical inpatients at nutritional risk on clinical outcomes. Further details on the study design and setting are described elsewhere [25,26]. The main results and long-term follow-up as well as several secondary analyses have been published previously [27–40]. The Ethics Committee of Northwest/Central Switzerland approved the study protocol in January 2014 (EKNZ; 2014_001).

2.2. Patient population

For this secondary analysis, we focused on patients from one center participating in the original trial (Cantonal Hospital Aarau) with available samples for measurement of admission arginine levels and its metabolites. Overall, patients at nutritional risk defined by a total score of 3 or more in the Nutritional Risk Screening 2002 (NRS 2002) met the inclusion criteria if they had an expected length of hospital stay (LOS) of more than 4 days and provided informed consent. Besides admission to intensive care unit (ICU) or surgical unit, exclusion criteria were: inability to tolerate oral nutrition intake, nutritional support at admission, presence of certain diseases (anorexia nervosa, acute pancreatitis, acute liver failure, or cystic fibrosis), terminal condition, stem cell transplantation, gastric bypass surgery, contraindications for nutritional support, and previous inclusion in the trial.

2.3. Nutritional intervention

Nutritional support in the intervention group was initiated within 48 h of hospital admission. Trained dietitians developed an individual plan for each patient guided by a preset nutritional algorithm that was based on international guidelines. If oral supply route was insufficient to achieve daily energy and protein targets at least by 75 % within 5 days, therapy was escalated to enteral nutrition and to parenteral nutrition if nutritional targets were still not met. More details of the nutritional algorithms have been published previously [25,26,41]. Patients in the control group received a standard hospital food and no nutritional counselling.

2.4. Patient management throughout the trial

Adult patients were consecutive screened for nutritional risk by the NRS 2002 [42]. Additionally, malnutrition diagnosis according to modified Global Leadership Initiative on Malnutrition (GLIM) criteria were assessed retrospectively as described [32]. Further data were systematically collected after enrollment by a trained study dietitian as described [25,26]. The *secuTrial*© software was used for data collection and management. In addition to clinical data, blood samples were systematically collected upon study inclusion, immediately processed, frozen in aliquots, and stored under temperature control at −80 °C until further analysis. Admission plasma metabolites were analyzed from February to April 2019 by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). An *Ultimate 3000 UHPLC* (*Thermo Fisher*, San Jose, USA) system coupled to a *Sciex 5500* quadrupole mass spectrometer (*Sciex*, Darmstadt, Germany) and the *AbsoluteIDQ® p180* kit (*BIOCRATES Life Sciences AG*, Innsbruck, Austria) were used [43–45]. An inter-laboratory assessment of this commercially available kit for targeted metabolomics showed reliability of the metabolomics assay [46–48]. Levels of arginine, ADMA, SDMA, ornithine, and citrulline were measured and bioavailability ratios Arg/ADMA, Arg/Orn, and GABR were calculated (hereafter compiled as “metabolites”).

2.5. Endpoints

The primary endpoint was all-cause mortality within 30 days. Secondary endpoints were mid- and long-term all-cause mortality (within 2 years and 5 years, respectively), adverse events within 30 days, major complications, decline in functional status of more than 10 % (measured by Barthel index [49]), incidence of falls during the 180-day follow-up period, and nutritional outcomes, i.e., mean caloric and protein intake, and reaching caloric and protein targets (at least 75 % of calculated targets). Endpoints were obtained by blinded study nurses in telephone interviews at 30 days, and 2 and 5 years after trial inclusion.

2.6. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), binary and categorical variables as number or count

and percentage. Statistical significance was tested at 95 % confidence intervals (CI), corresponding to a p-value of 0.05. Patients were stratified by metabolite concentration into groups with low or high levels on the basis of empirical optimal cutoff values calculated by the Liu method via Receiver Operating Characteristics (ROC) for the primary endpoint (30-day mortality) [50]. Baseline characteristics of included patients were compared to those of the original EFFFORT trial, and additionally between patients with low or high arginine levels using the calculated cutoff value; 2-sample t-test was used for continuous and Pearson's chi-squared test for categorical and binary variables. To adjust for potential confounding and random imbalances in regression analyses, 11 covariates were pre-specified [51], including sex, age, BMI, baseline nutritional status (NRS 2002 score), three admission main diagnoses (infectious, cancer, and cardiovascular disease), and four comorbidities (chronic kidney disease, diabetes mellitus, chronic heart failure, and chronic obstructive pulmonary disease). Linear regression analyses were calculated, first, to evaluate baseline characteristics for their prognostic value for metabolite levels and, second, to investigate associations of the metabolites with malnutrition parameters; results are reported as coefficient (95 % CI). To investigate a possible prognostic value of the metabolites, their association with clinical outcomes was assessed using Cox regression analysis. Hazard ratios (HR) are calculated, and Kaplan-Meier curves were plotted. Likewise, logistic, and linear regression models were performed for binary and continuous endpoints, respectively, to investigate the associations of metabolites with other secondary endpoints; odds ratio (OR) and coefficient are reported. To study whether response to nutritional support is related to arginine concentration at admission, we compared the hazards of mortality in intervention vs. control group patients stratified for individuals with low and high arginine levels. HR and Kaplan-Meier curves are presented. We used the intention-to-treat principle in all our analyses. Observations without a detectable signal for arginine were dropped from statistical analysis (complete-case analysis) [52]. Limits to detect outliers were calculated by mean ± 3 standard deviations of the sample (z-score method) [53] and sensitivity analysis was performed for metabolites by comparing statistical results for data with and without outliers [54]. *Stata* version 15 (*StataCorp*) was used for the statistical analysis.

3. Results

3.1. Patient population

From 2088 patients included in the original trial, we had complete data in 231 (11 %) patients from one center including levels of admission arginine used for this analysis. Figure 1 shows the patient flow including exclusion criteria of patients. A total of 37 % patients had low arginine levels on admission, defined by levels ≤90.05 μmol/l. Table 1 shows patients baseline characteristics according to low and high arginine levels. Overall, patients had similar baseline parameters compared to the overall trial with, however, notable differences regarding NRS scores (Supplemental Table 1).

3.2. Association of Patient Characteristics and nutritional parameters with arginine metabolism

We assessed the association of different baseline characteristics with arginine metabolite levels to identify potential influencing factors for levels of arginine, ADMA, SDMA and

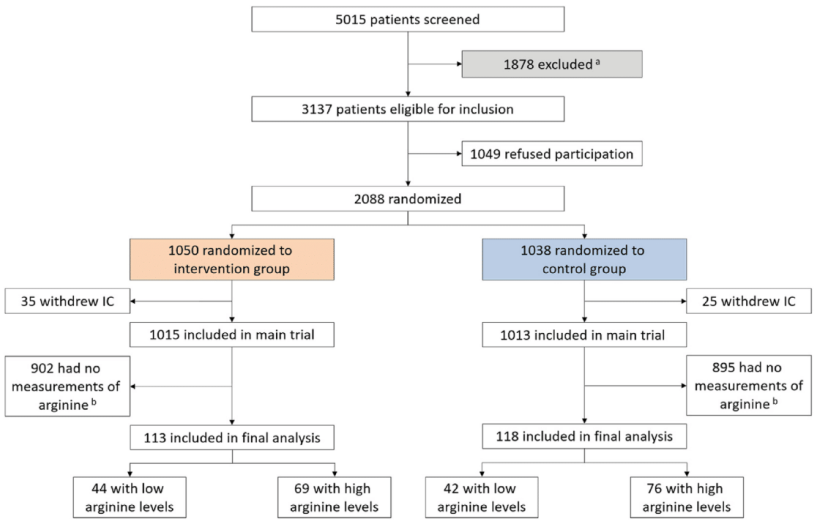


Fig. 1. Study Flow Chart.
Abbreviation: IC, informed consent
[a] Reasons for exclusion: 145 surgical patients, 268 unable to ingest oral nutrition, 158 terminal condition, 719 already receiving nutritional therapy, 31 anorexia nervosa, 161 acute pancreatitis, 81 acute liver failure, 6 cystic fibrosis, 11 stem-cell transplantation, 27 after gastric bypass operation, 43 contraindication against nutritional support, 228 earlier inclusion.
[b] Including 3 patients in intervention group, and 5 patients in control group without detectable signal for arginine level.

Table 1
Baseline Characteristics stratified by Arginine Concentration.

	Overall	High arginine >90.05 μmol/l	Low arginine ≤90.05 μmol/l	p-value
n (%)	231 (11.4 %)	145 (62.8 %)	86 (37.2 %)	
Demographic factors				
Male sex	134 (58.0 %)	80 (55.2 %)	54 (62.8 %)	0.26
Age, mean (SD), years	73.5 (13.2)	73.8 (13.2)	73.2 (13.3)	0.74
Nutritional assessment				
BMI, mean (SD), kg/m^2	24.3 (5.0)	24.2 (5.2)	24.4 (4.5)	0.73
Weight, mean (SD), kg	68.6 (15.0)	68.1 (15.5)	69.4 (14.2)	0.51
Height, mean (SD), cm	168.1 (8.6)	167.8 (8.8)	168.5 (8.3)	0.54
NRS 2002 score				0.64
3	59 (25.5 %)	36 (24.8 %)	23 (26.7 %)	
4	77 (33.3 %)	46 (31.7 %)	31 (36.0 %)	
≥5	95 (41.1 %)	63 (43.4 %)	32 (37.2 %)	
mGLIM-positive	153 (74.6 %)	103 (80.5 %)	50 (64.9 %)	**0.013**
CRP day 1, mg/l	71.8 (85.6)	72.8 (68.26)	113.0 (97.25)	**<0.001**
Admission main diagnosis				
Infectious disease	63 (27.3 %)	32 (22.1 %)	31 (36.0 %)	**0.021**
Cancer disease	74 (32.0 %)	46 (31.7 %)	28 (32.6 %)	0.90
CV disease	22 (9.5 %)	17 (11.7 %)	5 (5.8 %)	0.14
Frailty	12 (5.2 %)	5 (3.4 %)	7 (8.1 %)	0.12
Lung disease	11 (4.8 %)	8 (5.5 %)	3 (3.5 %)	0.48
Gastrointestinal disease	12 (5.2 %)	10 (6.9 %)	2 (2.3 %)	0.13
Renal disease	15 (6.5 %)	9 (6.2 %)	6 (7.0 %)	0.82
Other disease[a]	13 (5.6 %)	12 (8.3 %)	1 (1.2 %)	**0.023**
Comorbidities				
Charlson Comorbidity Index	6.4 (2.8)	6.4 (2.8)	6.4 (2.8)	0.93
Hypertension	133 (57.6 %)	85 (58.6 %)	48 (55.8 %)	0.68
Malignant disease	112 (48.5 %)	69 (47.6 %)	43 (50.0 %)	0.72
Chronic kidney disease	80 (34.6 %)	47 (32.4 %)	33 (38.4 %)	0.36
Coronary heart disease	53 (22.9 %)	32 (22.1 %)	21 (24.4 %)	0.68
Diabetes mellitus[b]	41 (17.7 %)	28 (19.3 %)	13 (15.1 %)	0.42
Congestive heart failure	44 (19.0 %)	29 (20.0 %)	15 (17.4 %)	0.63
COPD	27 (11.7 %)	19 (13.1 %)	8 (9.3 %)	0.38
Peripheral arterial disease	26 (11.3 %)	21 (14.5 %)	5 (5.8 %)	**0.044**
Stroke	25 (10.8 %)	17 (11.7 %)	8 (9.3 %)	0.57
Dementia	11 (4.8 %)	7 (4.8 %)	4 (4.7 %)	0.95
Laboratory parameter				
Arginine, mean (SD), μmol/l	102.8 (52.9)	137.4 (29.9)	44.3 (23.8)	**<0.001**
ADMA, mean (SD), μmol/l	0.59 (0.34)	0.64 (0.40)	0.49 (0.15)	**0.001**
SDMA, mean (SD), μmol/l	1.06 (1.27)	1.26 (1.53)	0.71 (0.47)	**0.002**
Arg/ADMA, mean (SD)	187.8 (102.7)	240.6 (84.3)	97.8 (59.8)	**<0.001**
Arg/Orn, mean (SD)	1.46 (0.82)	1.84 (0.67)	0.83 (0.62)	**<0.001**
GABR, mean (SD)	1.09 (0.62)	1.38 (0.53)	0.60 (0.44)	**<0.001**

Analysis to compare baseline characteristics between patients with high (>90.05 μmol/l) and low (≤90.05 μmol/l) arginine levels at admission. Pearson's chi-squared test was used to compare binary and categorical variables, and n (%) is reported if not indicated otherwise. The 2-sample t-test was used to compare continuous variables and mean (SD) is reported as indicated.
Abbreviations: BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002; mGLIM, modified Global Leadership Initiative on Malnutrition (positive meaning fulfilling the criteria); CRP, C-reactive protein; CV, cardiovascular; COPD, chronic obstructive pulmonary disease; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio.
[a] Other disease included, but was not limited to, metabolic/endocrinological and neurological/psychological diseases.
[b] Type 1 or type 2.

arginine ratios. Several factors were identified to be associated with the metabolite levels: In multivariable models, SDMA was positively associated with age and negatively associated with chronic kidney disease and COPD, and Arg/ADMA was positively associated with cardiovascular main diagnoses (Supplemental Table 2). Additionally, we investigated the association of nutritional parameters with metabolite levels, few significant associations were observed between ADMA, SDMA, and Arg/ADMA with NRS 2002 parameters (Supplemental Table 3). Moreover, a significant inverse association was observed between arginine levels and bioavailability ratios with concentration of C-reactive protein (CRP), which however was only robust in fully adjusted models for Arg/Orn and GABR. Moreover, arginine, Arg/Orn, and GABR were positively associated with the fulfilment of modified GLIM criteria; Arg/ADMA demonstrated a similar trend.

3.3. Prognostic value of arginine metabolism on outcomes

In a further step, the prognostic value to predict clinical outcome of arginine metabolites was investigated. Low arginine (≤90.05 μmol/l), SDMA (≤0.709 μmol/l), Arg/ADMA (≤178.41), and GABR (≤0.828) were significantly associated with increased 30-day mortality (adjusted OR 3.27, 2.64, 1.87, and 2.26, respectively) (Table 2, Fig. 2). The prognostic value of low arginine levels remained robust for short- and long-term mortality in fully adjusted model. This was also true when adding CRP to the model (Supplemental Table 4). Low Arg/ADMA was also associated with increased mortality at 2 years and 5 years, whereas SDMA was not; GABR was associated with short- and mid-term but not with long-term mortality (Table 2). Besides, low arginine, SDMA, and GABR were significantly related with an increased risks for adverse events (adjusted OR 2.35, 2.55, and 2.04, respectively) (Supplemental

Table 2
Prognostic Value of high vs. low Levels of Arginine, Dimethylarginines, and Arginine Bioavailability Ratios on Mortality.

	30-day mortality			5-year mortality		
	n/total (%)	HR (95 % CI)	p-value	n/total (%)	HR (95 % CI)	p-value
Arginine						
high arginine	23/145 (15.9)	reference		94/145 (64.8)	reference	
low arginine	33/86 (38.4)	3.27 (1.86–5.75)	**<0.001**	58/86 (67.4)	1.50 (1.07–2.12)	**0.020**
ADMA						
high ADMA	20/104 (19.2)	reference		70/104 (67.3)	reference	
low ADMA	36/126 (28.6)	1.50 (0.84–2.68)	0.174	82/126 (65.1)	1.00 (0.71–1.43)	0.986
SDMA						
high SDMA	16/112 (14.3)	reference		79/112 (70.5)	reference	
low SDMA	37/115 (32.2)	2.64 (1.44–4.83)	**0.002**	70/115 (60.9)	1.05 (0.75–1.47)	0.767
Arg/ADMA						
high Arg/ADMA	22/120 (18.3)	reference		75/120 (62.5)	reference	
low Arg/ADMA	34/110 (30.9)	1.87 (1.08–3.24)	**0.026**	77/110 (70.0)	1.55 (1.12–2.16)	**0.009**
Arg/Orn						
high Arg/Orn	20/109 (18.4)	reference		74/106 (69.8)	reference	
low Arg/Orn	36/121 (29.8)	1.68 (0.94–3.00)	0.079	77/117 (65.8)	1.08 (0.76–1.51)	0.679
GABR						
high GABR	28/147 (19.1)	reference		98/141 (69.5)	reference	
low GABR	28/81 (34.6)	2.26 (1.30–3.91)	**0.004**	52/80 (65.0)	1.23 (0.87–1.75)	0.237

Cox regression models reporting adjusted hazard ratios according to levels stratified by cutoff values of arginine (90.05 µmol/l), ADMA (0.556 µmol/l), SDMA (0.709 µmol/l), Arg/ADMA (178.41), Arg/Orn (1.44), and GABR (0.828). Low levels are defined as less or equal the cutoff value, high levels as greater the cutoff value.
Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio; HR, hazard ratio; CI, confidence interval.
Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease), and randomization group.

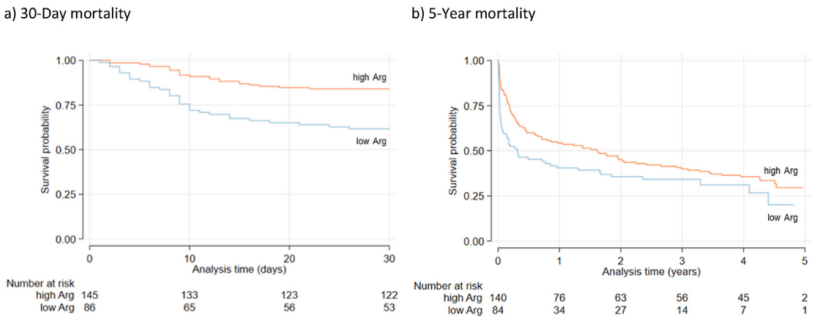


Fig. 2. Kaplan-Meier Estimate for Time to Death comparing high vs. low Arginine Concentration.
Arginine levels at admission are stratified by the cutoff value (90.05 µmol/l). Low levels are defined as less or equal the cutoff value, high levels as greater the cutoff value.
Abbreviations: Arg, arginine.

Table 5). Low levels of arginine and bioavailability ratios were also related with a higher rate of functional decline of >10 %. Moreover, low Arg/Orn was associated with higher rates of major complications (Supplemental Table 5). Considering nutritional outcomes, we found some association between low levels of arginine, ADMA, and Arg/Orn and higher mean intake, or higher rates of achieving intake targets (Supplemental Table 6). ROC curves for the calculation of the cutoff values are presented in Supplemental Fig. 1. Results from regression analyses on continuous levels of arginine, dimethylarginines (ADMA and SDMA), and arginine bioavailability ratios are presented in Supplemental Table 7 and Supplemental Table 8.

3.4. Predictive value of arginine metabolism on response to nutritional support

Finally, we compared the effect of nutritional support on mortality among patients with low and high arginine levels. However, interaction analyses and graphical display in Kaplan-Meier estimates did not indicate that the response to nutritional support was different in patients with low vs. high plasma arginine (adjusted HR for 30-day mortality: high arginine: 0.77, p = 0.551; low arginine: 0.85, p = 0.699; p for interaction = 0.974) (Table 3, Supplemental Fig. 2).

3.5. sensitivity analysis

In a sensitivity analysis, we repeated the above analyses in the population after excluding any observations classified as outlying values of the metabolites. A small number of outliers were detected for dimethylarginines and arginine ratios, while no outliers were evident for arginine. Exclusion of outliers did not result in changed cutoff values. Thus, most results were robust, including all analyses on arginine levels and the prognostic value of the arginine metabolites (Supplemental Table 9).

Table 3
Predictive value of arginine concentration on response to nutritional support.

	No nutritional support	Nutritional support			
	n/total (%)	n/total (%)	HR (95 % CI)	p-value	p for interaction
30-day mortality					
High Arginine	14/76 (18.4)	9/69 (13.0)	0.77 (0.32–1.83)	0.551	
Low Arginine	16/42 (38.1)	17/44 (38.6)	0.85 (0.38–1.90)	0.699	0.974
5-year mortality					
High Arginine	53/74 (71.6)	41/66 (62.1)	0.96 (0.62–1.48)	0.838	
Low Arginine	24/41 (58.5)	34/43 (79.1)	1.09 (0.59–2.02)	0.786	0.639

Cox regression models reporting adjusted hazard ratios according to arginine level stratified by the cutoff value (90.05 μmol/l). Arginine levels stratified by the cutoff value (90.05 μmol/l). Low levels are defined as less or equal the cutoff value, high levels as greater the cutoff value.
Abbreviations: HR, hazard ratio; CI, confidence intervals.
Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease).

4. Discussion

This secondary analysis of the randomized controlled EFFORT trial examining the value of arginine and its metabolites as prognostic nutritional biomarkers among medical inpatients at nutritional risk has several novel findings. First, our data show that only few patient characteristics and nutritional parameters were associated with arginine metabolites suggesting that levels may depend more on severity of illness and inflammation than nutrition. Second, low levels of arginine, SDMA, Arg/ADMA, and GABR were associated with lower survival rates at short- and long-term, and higher risk for adverse outcomes and functional decline. This finding is in line with the critical care literature, but novel for non-critically ill medical inpatients at nutritional risk. Finally our data did not suggest that patients with low arginine levels show a more prono9uned response to nutritional support and arginine and its metabiolites thus may not help in selecting patients regarding nutritional support interventions. The following points are worth to be discussed in more detail.

Low supply of arginine or its precursors and compromised endogenous arginine metabolism due to inflammation or dysfunctional metabolic, intestinal, and renal function [18,21,55] may contribute to low plasma concentration and bioavailability in DRM. However, in our analyses only few nutritional parameters were related to levels of arginine metabolism including an association of high inflammatory levels with low levels of arginine, its metabolites and arginine ratios. Other studies have already pointed out the importance of the endogenous pathways, disease severity and inflammatory mechanisms for arginine metabolism [1,9,56,57]. Comparing measurements in patients at nutritional risk to suggested reference ranges, we found similar arginine levels, while mean ADMA levels were lower in healthy volunteers [46]. Besides, 40 %–80 % of all measurements of arginine and its metabolites were within suggested reference ranges and up to one third of the levels below the calculated cutoff values would be considered normal [46,58,59] (Supplemental Table 10). The broad and divergent nature of reference ranges nevertheless may restrict their practical application [60]. Arginine homeostasis in disease and malnutrition might be more tightly regulated than previously assumed and DRM-specific clinical decision limits would facilitate risk determination and interpretation of arginine measurements. These findings indicate a greater impact of disease-related factors on arginine metabolism in DRM compared to nutritional factors. Due to the design of the present study, we could not conclusively clarify the relationship between arginine metabolism and DRM. Nevertheless, pathophysiological mechanisms mentioned above suggest an interaction of both.

Similar to studies in other clinical conditions including critical illness and sepsis, cardiovascular, pulmonary, and renal conditions, and various cancer entities [11,13,16,61–66], we found low plasma arginine, Arg/ADMA, and GABR to predict worse clinical outcomes. Arginine showed the strongest prognostic value, most notably a 3.3-fold increase in the risk of dying within 30 days in patients with low compared to high arginine levels. Several mechanisms may explain these associations with worse outcomes including compromised immune response via regulation of T cell development and function as well as cytokine production due to arginine- and NO-depleted states [1,59,67] [68]. Moreover, arginine depletion may enhance oxidative stress [18,69], and subsequent acceleration of apoptosis may contribute to pathophysiology of DRM [70,71]. Besides, amino acid deficiency per se contributes to decreased protein synthesis and increased muscle catabolism in DRM [6,17] but arginine is an amino acid especially relevant in protein synthesis [18]. If depleted, arginine might not sufficiently activate mTOR signaling pathways in muscle tissue, thereby contributing to a negative muscle protein balance [21,72–74]. In fact, we found functional decline to be strongly associated with low arginine levels. Besides, low arginine availability may lead to various other pathophysiological pathways potentially contributing to worse clinical outcomes, which concern exceeding ornithine and polyamines, as well as hormone regulation and the urea cycle [1,7,75,76].

Meanwhile, the higher protein and energy intake in patients with low arginine levels, who were likely to be sicker, did not improve clinical outcome – an observation we know from critical care medicine and other highly inflamed patients [17,77,78].

Both, citrulline and ornithine, are synthesized from arginine by arginase and NOS [1]. Upregulated arginase in pathophysiological conditions resulting in may explain the prognostic value of GABR since subsequently increased ornithine competes with arginine for transport with CAT-1, thereby further limiting arginine availability [16,21,59,65]. We found GABR to be superior to Arg/Orn in predicting clinical outcome, which might be due to the additional incorporation of citrulline to account for its synthesis from arginine [16]. Citrulline however can be synthesized from ornithine as well as and moreover is an endogenous precursor of arginine. The interpretation of Arg/Orn and GABR thus appears to be similarly complex to that of Arg/ADMA, since the ratios may be altered by a variety of pathophysiological pathways.

Moreover, and in contrast to other trials, we found low rather than high SDMA levels to predict adverse clinical outcomes [11,56]. Similarly contradicting findings in other patient populations [15], SDMA was not increased in patients with impaired renal function

(i.e., CKD) and ADMA was not related to clinical outcome in DRM. We found levels of ADMA and SDMA to be lower if arginine levels were low. Mechanisms considered to increase their synthesis in various diseases [79,80] might not apply in DRM, and dimethylarginine synthesis might be compromised in arginine depletion due to shortage of their precursor [81]. Thus, our findings implicate that worse clinical outcomes in low SDMA levels is attributed to low arginine, which is accompanied by low dimethylarginine levels.

This is the first study to look at response to nutritional support in relation to arginine levels. Yet, no significant difference was found in efficacy of nutritional support comparing patients with low vs. high arginine concentration. Our findings, thus, do not support the measurement of arginine levels to explain variability in treatment response and to further personalize nutritional support. Interestingly, high protein intake supports muscle maintenance and functional status [82–84], but higher intake in low arginine patients did not lower mortality or maintain function. Concurrently, supplementation of arginine or citrulline has been suggested to compensate for arginine depletion [18,24,85], and thus positively influence survival and functional status by limiting protein breakdown, exerting anabolic effects [6,72–74], and improving T cell function and immune status [86,87]. However, the effectiveness of arginine supplementation and remains controversial with some studies showing negative effects on outcome [24,88] [22,82,89-94]. In a lower-risk medical population with DRM, arginine supplementation nevertheless might be beneficial, but clearly, further research is needed to assess its overall efficacy and evaluate potential side effects.

4.1. Strengths and limitations

The strengths of this study are the prospective measurement of arginine and its metabolites within a well characterized interventional trial with a follow-up of over 5 years. Nevertheless, we are aware of several limitations including the single center design of the analysis resulting in a smaller patient population, reduced power, and limited external validity; the limited measurement of admission levels for which reason the effect of nutritional support on the metabolite levels remains unsolved; and the variation in timing of sample collection although strict adherence to pre-analytical instructions was followed to minimize measurement bias, and a recent evaluation demonstrated reliability and reproducibility of the *AbsoluteIDQ® p180* kit [46–48]. In addition, patients with low levels of arginine were sicker and had higher levels of inflammation, compared to patients with higher arginine levels, which could explain some of the associations with outcome. Although we did adjust the analysis for some confounders, residual confounding is possible and larger data sets would be needed. Thus, this secondary analysis should be viewed as exploratory and hypothesis-generating rather than definite, requiring confirmation in larger samples.

5. Conclusion

In conclusion, this secondary analysis focusing on medical inpatients at nutritional risk confirms findings from other patient populations showing a strong association of low plasma arginine levels and worse clinical courses. The potential effects of arginine-enriched nutritional supplements must be further investigated in this population of patients in a prospective controlled intervention trial before conclusive therapeutic recommendations can be made.

Funding statement

This trial was supported by grants from the Swiss National Science Foundation (PP00P3_150531), and from the Research Council of the Kantonsspital Aarau (1410.000.058 and 1410.000.044). The funders had no influence over the design and conduct of this study, the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Ethics approval and consent to participate

The Ethics Committee of Northwestern Switzerland (EKNZ; 2014_001) approved the study protocol. All participants or their authorized representatives provided written informed consent. The trial was registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02517476).

Availability of data and materials

Our data will be made available to others with the publication of this manuscript, as already outlined in the primary EFFORT publication, on receipt of a letter of intention detailing the study hypothesis and statistical analysis plan. A signed data access agreement is required from all applicants. Please send requests to the principal investigator of this trial.

Conflict of interest

Philipp Schuetz and Beat Mueller reports grants from Nestlé Health Science, Thermo Fisher, bioMérieux, Abbott Nutrition and Roche Diagnostics, not related to this project. *Zeno Stanga* reports consulting fees from Nestlé Health Science, Abbott Nutrition, Fresenius Kabi and B.Braun, not related to this project. *Stephan C. Bischoff* reports grants from Nestlé and Symbiopharm, and honoraria from Nestlé, Falk, Memomed and Nutrimmun, not related to this project. No other disclosures are reported.

Author contributions

Franziska Stumpf, Carla Wunderle, and Philipp Schuetz: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing - original draft, writing - review & editing. *Beat Mueller, Zeno Stanga, and Pascal Tribolet*: conceptualization. *Philipp Schuetz and the EFFORT Team*: investigation. *Stephan C. Bischoff*: supervision. *Philipp Schuetz, Zeno Stanga, and Beat Mueller*: resources, supervision, project administration, funding acquisition. *All authors* read and approved the final version of the manuscript. All authors confirm, they had full access to all data in this secondary analysis. All authors accept responsibility for the decision to submit for publication.

Acknowledgements

We thank all the contributors to the EFFORT trial for their valuable support.

Appendix

Supplemental Table 1
Baseline Characteristics Subgroup vs. Overall EFFORT Cohort

	Subgroup	EFFORT cohort	p-value
n (%)	231 (11.4 %)	2028 (100 %)	
Demographic factors			
Male sex	134 (58.0 %)	1064 (52.5 %)	0.11
Age, mean (SD), years	73.5 (13.2)	72.6 (14.1)	0.33
Nutritional assessment			
BMI, mean (SD), kg/m^2	24.3 (5.0)	24.8 (5.3)	0.14
Weight, mean (SD), kg	68.6 (15.0)	70.0 (16.8)	0.24
Height, mean (SD), cm	168.1 (8.6)	167.7 (9.3)	0.55
NRS 2002 score			**0.01**
3	59 (25.5 %)	624 (30.8 %)	
4	77 (33.3 %)	775 (38.2 %)	
≥5	95 (41.1 %)	629 (31.0 %)	
mGLIM-positive	153 (74.6 %)	1181 (61.6 %)	**<0.001**
CRP day 1, mg/l	71.8 (85.6)	87.7 (82.3)	**0.01**
Admission main diagnosis			
Infectious disease	63 (27.3 %)	613 (30.2 %)	0.35
Cancer disease	74 (32.0 %)	374 (18.4 %)	**<0.001**
CV disease	22 (9.5 %)	205 (10.1 %)	0.78
Frailty	12 (5.2 %)	194 (9.6 %)	**0.03**
Lung disease	11 (4.8 %)	125 (6.2 %)	0.40
Gastrointestinal disease	12 (5.2 %)	164 (8.1 %)	0.12
Renal disease	15 (6.5 %)	68 (3.4 %)	**0.02**
Other disease [a]	13 (5.6 %)	212 (10.5 %)	**0.02**
Comorbidities			
Charlson Comorbidity Index	6.4 (2.8)	n. a.	n. a.
Hypertension	133 (57.6 %)	1109 (54.7 %)	0.40
Malignant disease	112 (48.5 %)	667 (32.9 %)	**<0.001**
Chronic kidney disease	80 (34.6 %)	641 (31.6 %)	0.35
Coronary heart disease	53 (22.9 %)	566 (27.9 %)	0.11
Diabetes mellitus [b]	41 (17.7 %)	428 (21.1 %)	0.23
Congestive heart failure	44 (19.0 %)	353 (17.4 %)	0.53
COPD	27 (11.7 %)	303 (14.9 %)	0.18
Peripheral arterial disease	26 (11.3 %)	186 (9.2 %)	0.30
Stroke	25 (10.8 %)	162 (8.0 %)	0.14
Dementia	11 (4.8 %)	75 (3.7 %)	0.42
Laboratory parameter			
Arginine, mean (SD), µmol/l	102.8 (52.9)	n. a.	n. a.
ADMA, mean (SD), µmol/l	0.59 (0.34)	n. a.	n. a.
SDMA, mean (SD), µmol/l	1.06 (1.27)	n. a.	n. a.
Arg/ADMA, mean (SD)	187.8 (102.7)	n. a.	n. a.
Arg/Orn, mean (SD)	1.46 (0.82)	n. a.	n. a.
GABR, mean (SD)	1.09 (0.62)	n. a.	n. a.

Analysis to compare baseline characteristics between patients with high (>90.05 µmol/l) and low (≤90.05 µmol/l) arginine levels at admission. Pearson's chi-squared test was used to compare binary and categorical variables, and n (%) is reported if not indicated otherwise. The 2-sample t-test was used to compare continuous variables and mean (SD) is reported as indicated.
Abbreviations: BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002; mGLIM, modified Global Leadership Initiative on Malnutrition (mGLIM-positive meaning fulfilling the criteria); CRP, C-reactive protein; CV, cardiovascular; COPD, chronic obstructive pulmonary disease; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio.
[a] Other disease included, but was not limited to, metabolic/endocrinological and neurological/psychological diseases.
[b] Type 1 or type 2.

Supplemental Table 2
Association of Patient Characteristics with Arginine Concentration

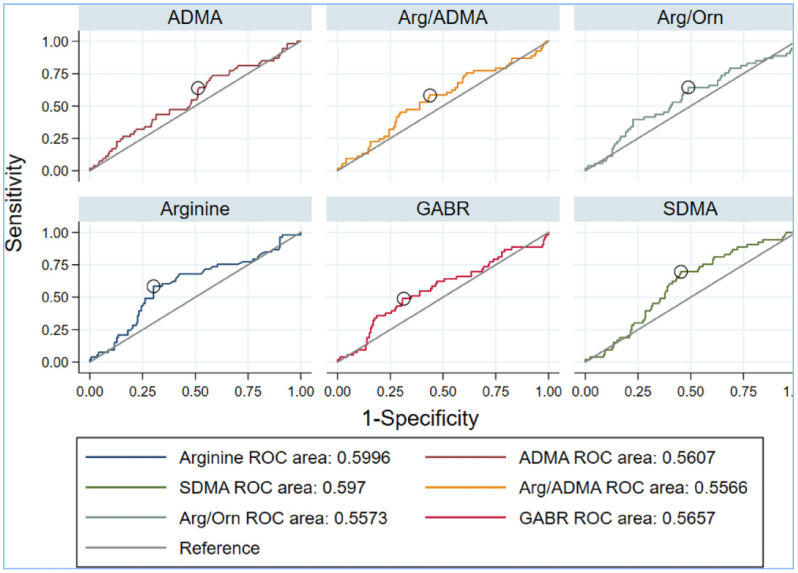
	Arginine		ADMA		SDMA		Arginine/ADMA Ratio	
	Coefficient (95 % CI) [a]	p-value	Coefficient (95 % CI)	p-value	Coefficient (95 % CI) [a]	p-value	Coefficient (95 % CI) [a]	p-value
Demographic factors								
Male sex	−0.70 (−2.16 to 0.77)	0.350	0.06 (−0.04 to 0.15)	0.235	−20.2 (−48.23 to 7.83)	0.815	−20.2 (−48.23 to 7.83)	0.157
Age, years	−0.01 (−0.07 to 0.05)*	0.659	0.002 (−0.002 to 0.006)*	0.295	−1.02 (−2.16 to 0.12)*	**0.002**	−1.02 (−2.16 to 0.12)*	0.078
Admission main diagnosis								
Infectious disease	−1.24 (−3.07 to 0.59)	0.184	−0.07 (−0.19 to 0.05)	0.238	−9.07 (−44.16 to 26.03)	0.869	−9.07 (−44.16 to 26.03)	0.611
Cancer disease	−0.62 (−2.49 to 1.26)	0.516	−0.07 (−0.19 to 0.04)	0.220	−5.00 (−40.81 to 30.81)	0.933	−5.00 (−40.81 to 30.81)	0.783
CV disease	2.17 (−0.66 to 5.01)	0.132	−0.11 (−0.29 to 0.07)	0.220	57.98 (3.92–112.05)	0.116	57.98 (3.92–112.05)	**0.036**
Comorbidities								
Chronic kidney disease	0.24 (−1.37 to 1.85)	0.769	−0.01 (−0.11 to 0.09)	0.806	5.79 (−24.97 to 36.55)	**0.014**	5.79 (−24.97 to 36.55)	0.711
Diabetes mellitus [b]	1.44 (−0.47 to 3.35)	0.139	0.12 (0.00–0.24)	0.057	5.7 (−30.77 to 42.18)	0.140	5.7 (−30.77 to 42.18)	0.758
Congestive heart failure	−0.90 (−2.95 to 1.16)	0.391	0.12 (−0.01 to 0.25)	0.076	24.74 (−63.96 to 14.48)	0.131	24.74 (−63.96 to 14.48)	0.215
COPD	1.54 (−0.72 to 3.80)	0.180	−0.09 (−0.23 to 0.05)	0.217	43 (−0.15 to 86.15)	**0.036**	43 (−0.15 to 86.15)	0.051

Multivariate linear regression analysis to identify predictors for levels of arginine, ADMA, SDMA and arginine/ADMA ratio at admission. The regression coefficients (95 % CI) indicate the change in level by one unit (1 μmol/l for arginine, ADMA and SDMA). For binary parameters, patients with the characteristics are compared to patients without. Coefficients for continuous parameters are marked with *.
Abbreviations: CV, cardiovascular; COPD, chronic obstructive pulmonary disease; CI, confidence interval.
[a] Other disease included, but was not limited to, metabolic/endocrinological and neurological/psychological diseases.
[b] Type 1 or type 2.

Supplemental Table 3
Association of Nutritional Parameters with Arginine Concentration

	unadjusted		adjusted [a]	
	Coefficient (95 % CI)	p-value	Coefficient (95 % CI)	p-value
Weight, kg	−0.01 (−0.05 to 0.04)*	0.708	−0.001 (−0.05 to 0.05)*	0.963
BMI, kg/m^2	−0.02 (−0.16 to 0.12)*	0.768	−0.01 (−0.15 to 0.14)*	0.933
NRS 2002 score				
3	reference		reference	
4	0.83 (−0.98 to 2.63)	0.368	0.97 (−0.90 to 2.83)	0.309
≥5	1.07 (−0.66 to 2.80)	0.224	1.22 (−0.69 to 3.12)	0.209
mGLIM-positive	2.54 (0.87–4.22)	**0.003**	2.46 (0.65–4.27)	**0.008**
CRP day 1, mg/l	−0.01 (−0.02 to 0.00)*	**0.014**	−0.01 (−0.02 to 0.00)*	0.076
HGS, kg	−0.04 (−0.12 to 0.03)*	0.268	−0.04 (−0.14 to 0.07)*	0.521
NRS 2002 components				
Weight loss	reference		reference	
≤5 % in 3 months	0.82 (−1.11 to 2.74)	0.403	0.83 (−1.18 to 2.84)	0.418
>5 % in 3 months	1.13 (−0.85 to 3.10)	0.263	1.26 (−0.86 to 3.39)	0.242
>5 % in 2 months	0.21 (−1.65 to 2.07)	0.823	0.48 (−1.58 to 2.54)	0.647
>5 % in 1 month	−0.09 (−2.17 to 1.99)	0.931	−0.14 (−2.27 to 1.99)	0.897
Loss of appetite [b]				
Reduced dietary intake [b]	reference		reference	
>75 %	−0.04 (−2.54 to 2.47)	0.976	−0.05 (−2.59 to 2.49)	0.967
>50 to ≤75 %	−0.13 (−2.51 to 2.26)	0.917	−0.16 (−2.56 to 2.24)	0.896
>25 to ≤50 %	1.12 (−1.53 to 3.76)	0.406	1.22 (−1.46 to 3.90)	0.372
≤25 %				
Disease severity score	reference		reference	
1	−0.57 (−2.00 to 0.86)	0.432	−0.40 (−2.04 to 1.24)	0.631
2	−9.28 (−19.71 to 1.15)	0.081	−8.06 (−18.75 to 2.64)	0.139
3	−0.01 (−0.05 to 0.04)	0.708	−0.001 (−0.05 to 0.05)	0.963

Unadjusted and adjusted linear regression analysis to identify associations of arginine concentration at admission with nutritional parameters. The regression coefficients (95 % CI) indicate the change in arginine concentration by ten units (10 μmol/l). For binary parameters, patients with the characteristics are compared to patients without. Coefficients for continuous parameters are marked with *.
Abbreviations: BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002; mGLIM, modified Global Leadership Initiative on Malnutrition (mGLIM-positive meaning fulfilling the criteria); CRP, C-reactive protein; HGS, handgrip strength; CI, confidence interval.
[a] Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease).
[b] In the week preceding hospitalization compared to usual appetite and intake.

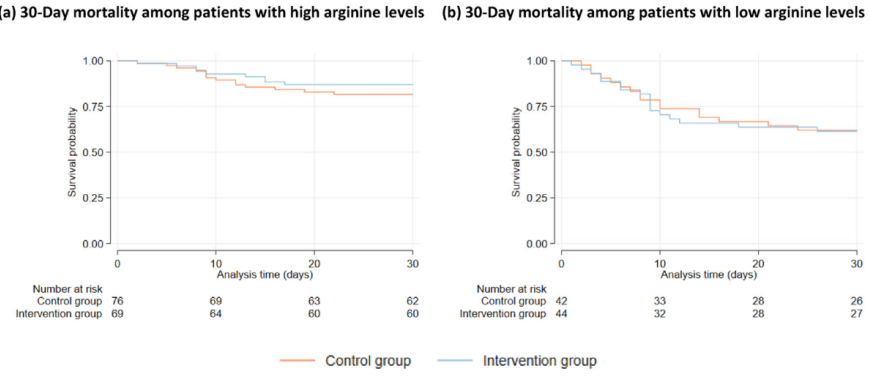


Supplemental Fig. 1. ROC Curves and Cutoff Values for Arginine, Dimethylarginines, and Arginine Bioavailability Ratios.
The Area under the Curve ("ROC area") and the cutoff values (marked with a circle on the ROC curve) are presented.
Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio; ROC, Receiver Operating Characteristics.

Supplemental Table 4
Prognostic Value of high vs. low Arginine Levels on Mortality (adjusted for inflammation)

	30-day mortality		2-year mortality		5-year mortality	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Low arginine	2.72 (1.52–4.87)	**<0.001**	1.57 (1.08–2.28)	**0.017**	1.39 (0.98–1.99)	0.067

Cox regression model reporting adjusted hazard ratios of low value (≤90.05 μmol/l) vs. high arginine levels (>90 μmol/l).
Abbreviations: HR, hazard ratio; CI, confidence interval.
Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease), randomization group, and C-reactive Protein.



Supplemental Fig. 2. Kaplan-Meier Estimate for 30-Day Mortality in Intervention and Control Group According to Arginine Concentration.
Arginine levels at admission are stratified by the cutoff value (90.05 μmol/l). Low levels are defined as less or equal the cutoff value, high levels as greater the cutoff value.

Supplemental Table 5
Prognostic Value of high vs. low Arginine Concentration on Clinical Outcomes (Without Mortality)

	events	unadjusted		adjusted [a]	
	n/total (%)	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Adverse events, 30 days [b]					
High Arginine	47/145 (32.4)	reference		reference	
Low Arginine	43/86 (50.0)	2.09 (1.21–3.60)	**0.009**	2.35 (1.26–4.36)	**0.007**
Major complications [c]					
High Arginine	12/145 (8.3)	reference		reference	
Low Arginine	7/86 (8.1)	0.98 (0.37–2.60)	0.971	0.92 (0.33 to 2.56)	0.872
Decline in functional status [d]					
High Arginine	29/145 (20)	reference		reference	
Low Arginine	33/86 (38.4)	2.49 (1.37–4.52)	**0.003**	3.09 (1.54–6.19)	**0.002**
Falls, 180 days					
High Arginine	14/144 (9.7)	reference		reference	
Low Arginine	9/86 (10.5)	1.09 (0.45–2.63)	0.856	1.28 (0.40–4.05)	0.674
	mean (SD)	**Coefficient (95 % CI)**	**p-value**	**Coefficient (95 % CI)**	**p-value**
QoL index, 180 days					
High Arginine	0.85 (0.18)	reference		reference	
Low Arginine	0.87 (0.13)	0.02 (−0.03 to 0.06)	0.429	0.005 (−0.04 to 0.05)	0.836

Regression models reporting odds ratios and coefficients according to arginine levels stratified by the cutoff value (90.05 μmol/l). Binary variables were assessed through logistic regression models, continuous variables through linear regression models. Low levels are defined as less or equal the cutoff value, high levels as greater the cutoff value.
Abbreviations: QoL, Quality of Life; SD, standard deviation; OR, odds ratio; CI, confidence intervals.
[a] Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease), and randomization group.
[b] Include all-cause mortality, admission to intensive care unit, non-elective hospital readmission, major complications, and decline in functional status of ≥10 %.
[c] Include nosocomial infection, respiratory failure, major cardiovascular events, acute renal failure, or gastrointestinal failure.
[d] Decline in functional status of ≥10 % from admission to day 30 as measured by the Barthel index.

Supplemental Table 6
Prognostic Value of Admission Arginine Level on Nutritional Outcomes

	Achieving caloric-intake targets [a]		Achieving protein-intake targets [a]		Mean caloric intake, kcal/kg/day [b]		Mean protein intake, g/kg/day [b]	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value	Coefficient (95 % CI)	p-value	Coefficient (95 % CI)	p-value
Low Arginine	0.71 (0.39–1.31)	0.278	2.13 (1.14–3.99)	**0.017**	4.30 (1.10–7.50)	**0.008**	0.10 (0.00–0.20)	**0.047**
Low ADMA	1.30 (0.72–2.38)	0.386	2.63 (1.41–4.92)	**0.002**	3.57 (0.47–6.67)	**0.024**	0.11 (−0.01 to 0.23)	0.076
Low SDMA	1.03 (0.57–1.86)	0.915	1.49 (0.83–2.70)	0.184	1.85 (−1.25 to 4.95)	0.240	0.03 (−0.09 to 0.16)	0.575
Low Arg/ADMA	0.57 (0.31–1.03)	0.061	1.05 (0.58–1.90)	0.867	1.09 (−2.00 to 4.18)	0.487	0.02 (−0.11 to 0.14)	0.799
Low Arg/Orn	0.79 (0.44–1.43)	0.441	1.58 (0.87–2.88)	0.136	2.71 (−0.39 to 5.81)	0.087	0.13 (0.01–0.25)	**0.039**
Low GABR	0.79 (0.43–1.46)	0.458	1.73 (0.93–3.23)	0.084	1.26 (−1.98 to 4.49)	0.444	0.11 (−0.02 to 0.24)	0.091

Adjusted regression models reporting odds ratios and coefficients according to arginine level stratified by the cutoff value (90.05 μmol/l). Binary variables were assessed through logistic regression models, continuous variables through linear regression models. Low levels are defined as less or equal the cutoff value and are compared to high levels.
Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio; SD, standard deviation; OR, odds ratio; CI, confidence intervals.
Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease), and randomization group.
[a] Refer to achieve 75 % of calculated targets.
[b] Per kg of bodyweight until day 10 of hospitalization.

Supplemental Table 7
Prognostic Value of Levels of Arginine, Dimethylarginines, and Arginine Bioavailability Ratios on Mortality

	30-day mortality		2-year mortality		5-year mortality	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Arginine	0.93 (0.88–0.99)	**0.012**	0.96 (0.93–1.00)	**0.036**	0.97 (0.94–1.01)	0.112
ADMA	1.19 (0.61–2.34)	0.613	1.51 (0.92–2.48)	0.100	1.47 (0.89–2.45)	0.135
SDMA	0.55 (0.35–0.87)	**0.011**	0.97 (0.84–1.12)	0.705	0.96 (0.84–1.11)	0.603
Arg/ADMA	1.00 (0.995–1.001)	0.130	1.00 (0.996–1.000)	**0.016**	1.00 (0.997–1.000)	0.065
Arg/Orn	0.82 (0.58–1.18)	0.293	0.92 (0.74–1.15)	0.476	0.97 (0.78–1.19)	0.739
GABR	0.76 (0.46–1.23)	0.264	0.86 (0.64–1.16)	0.330	0.92 (0.70–1.22)	0.579

Cox regression models reporting adjusted hazard ratios for continuous levels of arginine, ADMA, SDMA, Arg/ADMA, Arg/Orn, and GABR at admission. Data are presented for arginine in 10 μmol/l increments (10 units), for ADMA and SDMA in 1 μmol/l increments (1 unit), and for Arg/ADMA, Arg/Orn, and GABR in 1 unit increments.
Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio; HR, hazard ratio; CI, confidence interval.
Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease), and randomization group.

Supplemental Table 8
Prognostic Value of Levels of Arginine, Dimethylarginines, and Arginine Bioavailability Ratios on Clinical Outcomes (without Mortality)

	Adverse events, 30 days [a]		Major complications [b]		Decline in functional status [c]		Falls, 180 days		QoL index, 180 days	
	OR (95 % CI)	p-value	OR (95 % CI)	p-value	OR (95 % CI)	p-value	OR (95 % CI)	p-value	Coefficient (95 % CI)	p-value
Arginine	0.96 (0.91–1.01)	0.136	1.03 (0.94–1.12)	0.582	0.93 (0.87–0.99)	**0.022**	0.99 (0.89–1.11)	0.888	0.0002 (−0.004 to 0.004)	0.918
ADMA	1.00 (0.44–2.31)	0.991	1.08 (0.21–5.49)	0.930	0.19 (0.03–1.34)	0.096	0.95 (0.21–4.29)	0.942	0.01 (−0.05 to 0.08)	0.727
SDMA	0.59 (0.39–0.89)	**0.012**	0.78 (0.40–1.51)	0.456	0.67 (0.43–1.03)	0.069	1.00 (0.70–1.42)	0.988	−0.01 (−0.03 to 0.01)	0.301
Arg/ADMA	1.00 (0.997–1.003)	0.916	1.00 (0.997–1.006)	0.435	1.00 (0.995–1.001)	0.267	1.00 (0.994–1.005)	0.824	0.0001 (−0.0001 to 0.0003)	0.499
Arg/Orn	0.84 (0.59–1.21)	0.354	0.77 (0.42–1.43)	0.416	0.76 (0.50–1.14)	0.179	1.14 (0.59–2.19)	0.690	0.001 (−0.03 to 0.03)	0.915
GABR	0.83 (0.52–1.32)	0.424	0.75 (0.33–1.68)	0.478	0.65 (0.37–1.12)	0.121	1.24 (0.53–2.93)	0.621	0.01 (−0.03 to 0.04)	0.752

Adjusted regression models reporting hazard ratios for continuous levels of arginine, ADMA, SDMA, Arg/ADMA, Arg/Orn, and GABR at admission. Binary variables were assessed through logistic regression models, continuous variables through linear regression models. Data are presented for arginine in 10 μmol/l increments (10 units), for ADMA and SDMA in 1 μmol/l increments (1 unit), and for Arg/ADMA, Arg/Orn, and GABR in 1 unit increments.
Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; Arg/Orn, arginine/ornithine ratio; GABR, Global Arginine Bioavailability Ratio; HR, hazard ratio; CI, confidence interval.
[a] Include all-cause mortality, admission to intensive care unit, non-elective hospital readmission, major complications, and decline in functional status of ≥10 %.
[b] Include nosocomial infection, respiratory failure, major cardiovascular events, acute renal failure, or gastrointestinal failure.
[c] Decline in functional status of ≥10 % from admission to day 30 as measured by the Barthel index.

Supplemental Table 9
Sensitivity Analysis: Prognostic Value of Levels of Arginine/ADMA Ratio on Clinical Outcomes (without outliers)

	HR, OR or coefficient (95 % CI)	p-value
Mortality		
All-cause 30-day mortality	0.997 (0.994–1.000)	0.070
All-cause 5-year mortality	0.999 (0.997–1.000)	0.106
Secondary clinical outcomes		
Adverse events, 30 days [a]	0.999 (0.996–1.002)	0.520
Major complications [b]	0.999 (0.993–1.004)	0.644
Decline in functional status of >10 % [c]	0.997 (0.994–1.001)	0.161
Falls, 180 days	0.998 (0.993–1.003)	0.470
QoL index, 180 days	0.0001 (−0.0002 to 0.0003)	0.618

Adjusted regression models reporting hazard ratios, odds ratios and coefficients for continuous levels of Arg/ADMA at admission. Mortality was assessed through Cox regression models. For secondary outcomes, binary variables were assessed through logistic regression models, continuous variables through linear regression models. Data are presented for Arg/ADMA in 1 unit increments.
Abbreviations: ADMA, asymmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; HR, hazard ratio; OR, odds ratio; CI, confidence interval.
Adjusted for sex, age, body mass index, Nutritional Risk Screening 2002, main diagnoses (cancer, cardiovascular, and infectious disease), comorbidities (chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease), and randomization group.
[a] Include all-cause mortality, admission to intensive care unit, non-elective hospital readmission, major complications, and decline in functional status of ≥10 %.
[b] Include nosocomial infection, respiratory failure, major cardiovascular events, acute renal failure, or gastrointestinal failure.
[c] Decline in functional status of ≥10 % from admission to day 30 as measured by the Barthel index.

Supplemental Table 10
Comparison of Suggested Reference Ranges with Levels of Arginine, ADMA, SDMA, and Arginine/ADMA Ratio in DRM

	Suggested Reference Ranges	Values measured within the Reference Ranges
		n/total (%)
Arginine		
[46]	16–148 μmol/l	174/231 (75.3)
[58]	41–114 μmol/l	80/231 (34.6)
ADMA		
[46]	<0.86 μmol/l	212/238 (89.1)
[58]	0.311–0.732 μmol/l	182/230 (79.1)
[95]	0.4–0.9 μmol/l	185/230 (80.4)
SDMA		
[95]	0.3–0.7 μmol/l	91/227 (40.1)
Arg/ADMA		
[58]	74 to 225	118/230 (51.3)

Abbreviations: ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; Arg/ADMA, arginine/ADMA ratio; DRM, disease-related malnutrition.

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4. Discussion

This dissertation covers the following main findings: First, raising evidence on the impact of nutritional therapy in polymorbid patients is now incorporated in an updated and practical guideline, giving clinicians up-to-date and valid advice in their daily practice. Second, it highlights the differences in malnutrition phenotype and revealed new insights into amino acid metabolism in the acute phase of a disease. Third, a simple adaption of an existing screening or assessment tool could help to translate findings on heterogeneity of treatment response into clinical practice.

4.1 Clinical practice guideline on nutritional support in polymorbid medical inpatients – need for individualization

ESPEN is the most important society for nutritional medicine in Europe and the application of its guidelines is the first choice in clinical practice. Therefore, updating them has a direct impact on the quality of patient care. Large trials of the past decade, such as the NOURISH trial by Nicolaas Deutz [45] or the EFFORT study by Philipp Schuetz [44] and our own meta-analysis on polymorbid patients [90], have provided high-quality evidence that has now been incorporated into the updated guidelines and strengthen the proposed recommendations. To give an example, the use of oral nutritional supplements is now also recommended to reduce the risk of mortality in hospitalized patients with the highest level of evidence (grade A) and a strong consensus (100% agreement in the vote). In addition, the issue of appropriate protein targets in patients with or without impaired renal function is now better addressed in the guideline and better supported by studies. [91] We found high protein interventions to be most effective in malnourished medical patients in a systematic review and meta-analysis [57], and high protein targets or therapies were also used in the large studies mentioned above. [44, 45] Therefore, we can now support a target of 1.2 grams of protein per kilogram body weight per day in patients with an estimated glomerular filtration rate (eGFR) greater than 30 ml/min/1.73 m^2, which is 0.2 grams higher than the previously recommended target. The crucial role of protein intake in patients with malnutrition is due to the pathophysiological rationale and observations in the clinics. While our fat cells store fat and the liver stores carbohydrates, we have no protein storage organ in our body and most amino acids are found in the skeletal muscles, and the need for amino acids is accelerated during acute illness, also because of the cross-talk between muscle and immune system. [99] Malnutrition and acute and chronic diseases are accelerators for muscle loss, which is directly associated with worse clinical outcomes, making muscle the most important clinical target of nutritional therapy. [100] However, in patients with impaired kidney function, defined by an eGFR below 30 ml/min/1.73 m^2, we have found that protein targets below 0.8 grams per kilogram of body weight per day

resulted in improved clinical outcomes. [75] To date, there is a lack of studies comparing different protein targets in patients with impaired renal function no kidney replacement therapy head-to-head. Considering this gap, a recent critical review supported by the European Renal Nutrition Group of the European Renal Association (ERN-ERA) and ESPEN concluded that nutritional support should carefully be assessed to identify the most urgent clinical need and the consequent treatment priority. The presence of manifest malnutrition suggests the need to avoid or postpone protein restriction, especially when renal function is more stable and considering the patient's preferences and quality of life. Chronic kidney disease progression and an advanced stage argue for prioritizing protein restriction in patients with a good nutritional status. [101] These different interpretations of the current evidence emphasize the need for an individualized approach depending on nutritional status and kidney disease, and that renal and nutritional priority (protein restriction vs. no protein restriction) may replace each other over time.

One topic that is not yet adequately addressed in the current updated guideline is the application of micronutrients. To date, there are few studies that specifically address or investigate the use of micronutrients, although polymorbid inpatients with more than one chronic condition may be particularly at risk of deficiency. [102] A meta-analysis of mixed study populations found that micronutrient supplementation in addition to a therapeutic diet [83] already containing micronutrients did not reduce mortality or positively affect other clinical outcome such as readmissions or length of hospital stay. [103] However, other studies, e.g. in polymorbid patients with Covid-19, have shown that micronutrient supplementation can shorten the time to recovery. [104] Therefore, the recommendation on the use of micronutrients has a very low level of evidence to date, although it has reached a strong consensus of 100%. [91]

For the first time, the updated guideline addresses the heterogeneity of the patient population and the response to nutritional treatment. Is it now recommended to consider the severity of acute-phase response when providing nutritional support to a patient. [91] We know from large trials conducted in intensive care units with severely ill patients that a complete replacement feeding strategy is often not translated into improved clinical outcomes. [65] However, also in medical wards there is raising evidence that we need to assess the acute phase of the patient, which is now also being incorporated into the clinical guideline. Thereby, inflammation and the neuroendocrine response to a stressor are key factors with several important metabolic effects on a cellular level (e.g., increase in insulin resistance leading to an inhibition of nutrition entering cells) and on different organs such as the brain (e.g., causing disease-related anorexia and reduced food intake), the intestines and on muscle (e.g., causing catabolism and low muscle mass). [94] Interestingly, recent data also suggest that inflammation modulates the

response to nutritional treatment. A randomized double-blind trial of nutritional supplementation published in 2006 by Gariballa et al., including 445 polymorbid patients, concluded that the acute-phase response was strongly associated with poor nutritional status and worse clinical outcomes. [70] This is in line with the secondary analysis of EFFORT, that suggests that patients with CRP levels of ≥100 mg/l no longer showed improved survival receiving nutritional therapy, while patients with lower levels did. [68] These effects were independent of infection and disease severity and suggest that individuals affected by severe inflammation may require a different nutritional approach than patients with lower levels of inflammation. Thus, CRP as an acute phase protein cannot represent the entire systemic inflammatory response, is influenced by infectious and noninfectious factors (e.g., cardiovascular diseases, cirrhosis, cancer, or systemic lupus erythematosus), has a high interpersonal variability, and values can fluctuate from day to day. [105] Therefore, in addition to CRP, several other factors and conditions should be considered when trying to predict whether a patient benefits from nutritional therapy: these include illness-specific factors (comorbidities, inflammation, acute vs. chronic course) or patient-specific factors (age, gender and genetic vulnerability). [6] Focusing on a disease-related factor Bargetzi et al. examined the impact of nutritional support on mortality in according to their admission kidney function in the EFFORT cohort. [75] Hospitalized patients with chronic kidney disease are often at risk of malnutrition or already malnourished, and their condition may deteriorate further during hospitalization. [10] Bargetzi et al. demonstrated that within this population the more vulnerable patients with a lowered kidney function (eGFR 15 -59 ml/min/1.73 m^2) had an even more pronounced survival benefit through nutritional support compared to the overall population and patients with an eGRF above 60 ml/min/1.73 m^2. Investigating potential predictive biomarkers in critically ill patients, Van Dyck et al. aimed to find a "ready-to-feed indicator" within a secondary analysis of the EPaNIC trial. They investigated on the circulating growth differentiation factor 15 (GDF15), a cellular stress marker that abruptly increases during critical illness. Within the EPaNIC cohort GDF15 was elevated throughout ICU stay but similarly in early PN and late PN patients and remained high beyond ICU discharge. However, it was only weakly related to gastrointestinal tolerance and the potential as "ready-to-feed indicator" appears limited. [71]

There are several potential biomarkers to help phenotype malnutrition and to predict treatment response. [89] However, the results mainly come from secondary analysis should be viewed as exploratory and hypothesis-generating rather than definite, requiring confirmation in larger samples. Nevertheless, the first step towards a more personalized approach in nutritional care of polymorbid patients has been taken, and the nutritional guidelines can change clinical practice and potentially policy makers.

4.2 Understanding the metabolism of key amino acids to improve patient phenotyping and nutritional care

To understand the differences in response to treatment and improve nutritional interventions, the underlying pathophysiology needs to be investigated and understood. Our metabolism is complex, and new approaches and technologies, such as the various omic disciplines, have led to a novel understanding of individual differences. In healthcare systems and nutritional medicine, the 'one size fits all' approach is no longer appropriate and many areas are moving to a more precise approach. [106, 107] Although this might sound like the future, metabolomics already has a wide range of applications in our daily clinical practice. For example, glycated haemoglobin (HbA1c) is used to diagnose diabetes, to classify patients, to monitor the effect of a certain treatment or to determine the positive effect of therapy, the response to treatment. [108] However, for the nutritional therapy of malnutrition there is nothing comparable yet. Protein is a critical component of nutritional therapy due to its physiologic and metabolic role described earlier [99] and has been intensively studies in the ICU. [109] It is also of interest in medical wards, where interventions with high-protein strategies appear to be most effective. [57] In addition to the clinical treatment guideline on polymorbid patients, guidelines for other patient populations have also increased the recommended amount of protein within the latest updates [110], demonstrating the importance of this macronutrient. The basic nutritional rationale of protein interventions is to compensate for a deficit in order to stimulate protein synthesis, support muscle function, and promote the specific metabolic functions of each amino acid. [111] Therefore acknowledging the role of specific amino acids and their metabolites in medical inpatients is crucial to understand and improve treatment. In our secondary analyses of EFFORT, we found that most of the investigated amino acids were not correlated with established nutritional markers and thus may not be viewed as markers for malnutrition. [96-98] Surprisingly, we neither consistently observed depleted levels of the examined amino acids or further metabolites in metabolic pathway, as anticipated. Nevertheless, glutamine level was lower in our cohort compared to a healthy French cohort [112], in a comparable study using the same analysis kit (mean glutamine plasma level 522.5 µmol/L compared to 627.9 µmol/L) and to a cancer patient cohort (522.5 µmol/L compared to 574.0 µmol/L) [66]. This finding aligns with previous trials, that showed glutamine depletion during severe illness and catabolic conditions [113-116]. However, in our patient population low glutamine levels were not associated with adverse clinical outcomes, contrary to findings in intensive care units and post-major surgery settings [115]. This could be clarified by considering the less critically ill group of patients, in which glutamine depletion may also have been less severe, resulting in no adverse effects on clinical outcomes. While most studies in the ICU show that low glutamine levels are associated with poorer clinical outcome, there is also data suggesting that elevated glutamine levels can lead to higher mortality rates, primarily

due to compromised hepatic glucose metabolism [117]. However, our data did confirm a U-shaped risk pattern. It can be assumed that most EFFORT patients had a functioning glucose metabolism, as we excluded critically ill patients and specifically defined liver failure as an exclusion criterion.

When examining the role and metabolism of tryptophan, we observed that low levels of tryptophan, kynurenine, and serotonin were associated with worse clinical outcome, in particular with an increased risk in 30-day and 180-day all-cause mortality. These results differ from previously studies that were conducted in patients with pneumonia, COPD, and sepsis, where an activation of the kynurenine and serotonin pathways and high plasma concentrations were associated with adverse outcomes. [118-120] With the investigation on arginine, on the other hand, the situation is as expected from other clinical studies. Low plasma arginine, Arg/ADMA and GABR concentrations were associated with worse clinical outcomes, in line with studies including other clinical conditions like critical illness and sepsis, cardiovascular, pulmonary, and renal diseases and various cancers. [121-129] Arginine exhibited the most robust prognostic value, with a 3.3-fold increase in the risk of all-cause mortality within 30 days in patients with low arginine levels compared to those with high levels. Several mechanisms could explain these observed associations, including impaired immune response through regulation of T cell development and function, and cytokine production due to arginine- and NO-depleted states [130-133]. In addition, arginine depletion may increase oxidative stress [134, 135], and the subsequent acceleration of apoptosis may contribute to pathophysiology of DRM [136, 137]. When arginine is deficient, mammalian target of rapamycin (mTOR) signaling pathways in muscle tissue may not be sufficiently activated, contributing to a negative muscle protein balance [138-141]. Consistent with this, we have found that functional decline is strongly associated with low arginine levels. [98]

The next important step in improving nutrition therapy is to examine whether patients at high risk for adverse outcome does also show the strongest benefit of a nutritional intervention. The hypotheses regarding amino acid metabolism, particularly arginine and glutamine, has been that normalizing depleted levels would have a positive impact on clinical outcomes. [115, 142] This is based on the fact that glutamine serves as a main energy substrate for immune cells and that low plasma glutamine level is associated with increased mortality and morbidity across various clinical settings [113-115, 143]. Consequently, glutamine administration in acute conditions such as in patient with cancer or critical illness [66, 142, 144], or in patients suffering from burn injuries [145] has been intensively investigated. Notably, the 2019 nutritional guidelines on critically ill patients from ESPEN recommended glutamine supplementation. [146] However, a recent large double-blind, randomized, placebo-controlled trial of 1'209 burned patients from Heyland et al. showed no effect of glutamine supplementation on the

primary endpoint time to discharge alive from the hospital. [147] Thus, there is still an ongoing controversy about the effectiveness of normalizing depleted levels of glutamine and other amino acids. Consistent with previous thinking, our hypothesis was that nutritional support and increased intake of protein, and therefore amino acids, would best improve clinical outcomes in patients admitted to the hospital with low levels. However, we found no difference in the efficacy of nutritional support between patients with high and low glutamine concentrations. Thus, our results do not support the measurement of these metabolites to explain variability in response to treatment, nor do they support the hypothesis that increased intake of amino acids and eventual normalization of levels will improve clinical outcomes. [96] The same was true when investigating arginine metabolism: we found no differences in the response to nutritional therapy in patients with high versus low arginine admission concentrations. [98] However, also arginine or citrulline supplementation has been suggested to compensate for arginine deficiency [134, 148, 149] and thus positively influence survival and functional status by limiting protein breakdown, exerting anabolic effects [139-141, 150], and improving T cell function and immune status [151, 152]. The efficacy of arginine supplementation remains controversial with studies showing negative effects on outcome, mainly due to hemodynamic instability caused by nitric oxide (NO) production with its vasodilatory effects [60, 148, 153-160]. In a lower-risk medical population with DRM, arginine supplementation nevertheless might be beneficial, but clearly, further research is needed to assess its overall efficacy and evaluate potential side effects. In line with the findings of glutamine metabolism, the results of our secondary analysis on arginine again did not support the hypothesis that normalization of serum concentrations is a causal treatment and can improve outcomes.

In line with this finding and even showing trends towards the opposite hypothesis, reveals the analysis on tryptophan metabolism. Although low tryptophan levels were associated with higher mortality, nutritional support in those patients with low tryptophan levels was less effective in improving outcomes compared to patients with higher levels. [97] This result is comparable with data observed in critically ill patients, where only little benefit from full-replacement feeding could be shown in several clinical trials. [65, 74, 161] In fact, full feeding during severe illness has been suggested to reduce autophagy, a mechanism important for cell detoxication during illness, which might contribute to the lack of effect in these patients. [162] Additionally, metabolic changes in the acute phase of a disease, such as impaired intestinal motility, hyperglycemia with peripheral insulin resistance and further activated catabolic pathways [13] appear to mechanistically hinder the beneficial effect of nutritional therapy. The general question remains whether low amino acid levels are a consequence or cause of the poor outcomes observed. Consequently, it is questionable whether a specific nutritional intervention designed to balance serum levels could have a positive impact on this highly vulnerable patient group outside the ICU.

4.3 Transfer of findings and concepts into clinical practice and future considerations

Historically, nutritional therapy has been used in patients at risk for adverse outcomes associated with malnutrition, but which may not always be directly caused by malnutrition. A better understanding of the malnutrition phenotype, reflecting the specific pathophysiology, could allow better selection of patients who will benefit most from nutrition, contributing to a more personalized approach. The search for biomarkers or scores to predict the response to a specific nutritional therapy is therefore crucial to the concept of personalized medicine. [6] Taking together the previous findings on the amino acid metabolism with the insights from the guideline work [91, 92] and narrative reviews [93, 94], which focused on the impact of acute disease and response to nutritional treatment, we aimed to make them usable for clinical practice. By adapting the NRS and MNA-LF, we found that removing parameters that reflect disease severity led to a much better ability of the scores to predict response to treatment, independent of age, major main diagnoses, sex, and BMI. Patients with a high adapted score showed much greater benefit from nutritional support than patients with a low adapted score. This predictive power of the adapted score was not found for the original scores. [95] A possible explanation is that the exclusion of factors that reflect disease severity thus might help to better stratify patients into two different phenotypes of malnutrition. One phenotype might be mainly nutrition-driven (being malnourished) and based on a nutritional problem. A possible case would be a geriatric patient with recurrent falls, that slowly impaired his nutritional state by not meeting his nutritional needs. The other possible phenotype of malnutrition is one that is mainly disease-driven (having malnutrition). This is a complex syndrome [6] that is often observed in patients coming with multiple acute and chronic medical conditions and severe short-term problems with their nutritional intake, for example because of a pneumonia. While the treatment of disease-driven malnutrition seems to be more complex [65] and might require novel therapeutic strategies than simply meeting protein and caloric targets, we can adequately treat the nutrition-driven phenotype through classical high-energy and high-protein nutritional interventions. [37, 90] This observation and hypothesis is also supported by other researchers such as Cardenas, who calls for a paradigm shift in clinical nutrition [163], as well as by evidence from critical care or advanced cancer cachexia, where malnutrition is mainly disease driven and refractory to therapy. [65, 110] However, till now we don't have data that shows whether its beneficial, harmful, or indifferent to not nourish severely inflamed or critically ill patients for an extended period. Additionally, the observational period of most clinical studies in hospitalized patients are relatively short from days to weeks.

In addition to advances in clinical research, it is also important to translate these findings into clinical practice to improve patients care, as pointed out earlier. It is also important to find

simple and practical solutions, as even adherence to nutritional guidelines does not always take place. [7] Therefore, we believe that the adapted NRS [95] could make nutrition therapy more precise and efficient if confirmed in larger, prospective studies. In particular, the adapted NRS is very easy to calculate or even assess at the bedside. Its use could also help to manage the expectations of the nutrition support team and the patient as using inflammation signs or disease severity alone to diagnose malnutrition can lead to confusion between malnutrition and disease severity. [25] This is important because it can be misunderstood, and persistent catabolism can be interpreted as a result of inadequate nutrition. This can lead to incorrect clinical decisions, such as in some cases where more protein or even albumin is given to increase albumin levels instead of treating an infection or malignancy and the underlying inflammation.

Looking forward, measuring catabolism, or rather endogenous energy production, in acute phase of disease could be key to setting realistic nutritional targets and reducing the risk and the adverse effects of overfeeding. [164] In this way, a positive influence on mainly disease driven malnutrition, also in critical care settings, is possible. Currently, there isn't an easy method for accurately measuring catabolism in clinical practice, and there are limited studies focusing on this issue. [165] Catabolism therefore often goes unnoticed until muscle loss and weakness are observed because it isn't routinely measured. The lack of validated and routinely available biomarkers of catabolism hinders in-depth research in this field so far. [166] Potential biomarkers such as urinary urea excretion [167] or urea-creatinine ratios [162] offer avenues for exploration, yet their validation and routine use remain pending.

5. Acknowledgements

I would like to take this opportunity to thank my companions, supporters, and enablers. Research is always teamwork, and I am very grateful to be able to work in our team.

First, I would like to thank Philipp Schütz, my supervisor. Dear Philipp, you are an outstanding mentor and have the art of encouraging, motivating, and guiding your employees with a lot of freedom. Thank you for your support and for giving me every possible opportunity. I owe it to you to take over the leadership of the ESPEN working group, to supervise various doctoral students, to coordinate EFFORTII and to give numerous international lectures for you.

Dear Prof. Eckert, thank you very much for your uncomplicated and always competent support and advice. Thank you also for the freedom to set our own research priorities.

Furthermore, I would like to thank our research team, especially the inner core, for the last three years: Nina, Claudia, Pascal T., and Alex: infinite thanks for your warm welcome into the team, which went very quickly after the initial language barrier. I have learned an incredible amount from you and have made you friends. In addition to professional discussions, projects, and even minor low points together, we have experienced and achieved so many wonderful things. I wouldn't want to miss the humor and emotional support at various aperos and the numerous adventures, be it at the legendary summer dinners or congresses.

In addition to the core team, other researchers, students, doctoral students, and contributors to the EFFORT study provided support. I would especially like to thank Filomena Gomes for her mentoring during the guideline work and Jacqueline and Franziska for their excellent work on their metabolomics projects.

Work is only one part of life, and I would like to take this opportunity to thank my loved ones. Dear Pascal, your ease in going through life fascinates me every day anew and you help me to switch off my head. You are my husband, my support, and my best friend. I would also like to thank my family, who have always supported me and made it possible for me to go abroad, study and pursue various time-consuming hobbies. In addition to my mom Sabine, my dad Manfred, my sister Nora, and my brother Steffen, who have been my closest confidants for almost 33 years, this also includes my Swiss family with Chriggi, Reto, Lukas, Francesca, Florentin, Sonja, Sandro, Nadua and Balu.

I thank you all from the bottom of my heart and look forward to many more moments and memories together.

6. Curriculum Vitae

7. Publication list

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Works (20 of 20)

Adaptation of nutritional risk screening tools may better predict response to nutritional treatment: a secondary analysis of the randomized controlled trial Effect of early nutritional therapy on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT)

The American Journal of Clinical Nutrition

2024-03 | journal-article

DOI: 10.1016/j.ajcnut.2024.01.013

ESPEN practical guideline: Nutritional support for polymorbid medical inpatients

Clinical Nutrition

2024-03 | journal-article

DOI: 10.1016/j.clnu.2024.01.008

Prognostic implications of the arginine metabolism in patients at nutritional risk: A secondary analysis of the randomized EFFORT trial

Clinical Nutrition

2024-03 | journal-article

DOI: 10.1016/j.clnu.2024.01.012

Association of tryptophan pathway metabolites with mortality and effectiveness of nutritional support among patients at nutritional risk: secondary analysis of a randomized clinical trial

Frontiers in Nutrition

2024-02-15 | journal-article

DOI: 10.3389/fnut.2024.1335242

Red blood cell distribution width (RDW) – A new nutritional biomarker to assess nutritional risk and response to nutritional therapy?

Clinical Nutrition

2024-02 | journal-article

DOI: 10.1016/j.clnu.2024.01.001

Reply-letter to the editor - Red blood cell distribution width is an inflammatory but not a nutritional biomarker

Clinical Nutrition

2024-02 | journal-article

DOI: 10.1016/j.clnu.2024.02.012

Association of Glutamine and Glutamate Metabolism with Mortality among Patients at Nutritional Risk—A Secondary Analysis of the Randomized Clinical Trial EFFORT

Nutrients

2024-01-10 | journal-article

DOI: 10.3390/nu16020222

Inflammation and response to nutrition interventions

Journal of Parenteral and Enteral Nutrition

2024-01 | journal-article

DOI: 10.1002/jpen.2534

Changes in serum albumin concentrations over 7 days in medical inpatients with and without nutritional support. A secondary post-hoc analysis of a randomized clinical trial

European Journal of Clinical Nutrition

2023-10 | journal-article

DOI: 10.1038/s41430-023-01303-w

ESPEN guideline on nutritional support for polymorbid medical inpatients

Clinical Nutrition

2023-09 | journal-article

DOI: 10.1016/j.clnu.2023.06.023

Inflammation and Nutrition: Friend or Foe?

Nutrients

2023-02-25 | journal-article

DOI: 10.3390/nu15051159

Letter to the Editor: Is nutritional support effective in malnourished polymorbid medical inpatients?

Clinical Nutrition

2023-01 | journal-article

DOI: 10.1016/j.clnu.2022.11.007

The association between prealbumin, all-cause mortality and response to nutritional treatment in patients at nutritional risk. Secondary analysis of a randomized-controlled trial

Journal of Parenteral and Enteral Nutrition

2023-01 | journal-article

DOI: 10.1002/jpen.2470

Low T3 Syndrome on Admission and Response to Nutritional Support in Malnourished Medical Inpatients

The Journal of Clinical Endocrinology & Metabolism

2022-12-22 | journal-article

DOI: 10.1210/clinem/dgac743

Nutrition issues in the general medical ward patient: From general screening to specific diagnosis and individualized treatment

Journal of Parenteral and Enteral Nutrition

2022-12-05 | journal-article

DOI: 10.1002/jpen.2423

Nutritional issues concerning general medical ward patients: feeding patients recovering from critical illness

2022-11-28 | journal-article

DOI: 0.1097/MCO.0000000000000894

Nutritional support after hospital discharge improves long-term mortality in malnourished adult medical patients: Systematic review and meta-analysis

Clinical Nutrition

2022-11 | journal-article

DOI: 10.1016/j.clnu.2022.09.011

Prospective validation of five malnutrition screening and assessment instruments among medical inpatients: Secondary analysis of a randomized clinical trial

Clinical Nutrition

2022-06 | journal-article

DOI: 10.1016/j.clnu.2022.04.025

Handgrip Strength Values Depend on Tumor Entity and Predict 180-Day Mortality in Malnourished Cancer Patients

Nutrients

2022-05-23 | journal-article

DOI: 10.3390/nu14102173

Record last modified Apr 9, 2024, 2:41:15 PM

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