



Original article

Are all low-NUTRIC-score patients the same? Analysis of a multi-center observational study to determine the relationship between nutrition intake and outcome



Michael Chourdakis^{a, *}, Maria G. Grammatikopoulou^a, Andrew G. Day^b,
Emmanouil Bouras^a, Daren K. Heyland^{b, c}

^a Department of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

^b Department of Critical Care Medicine, Queen's University, Kingston, Ontario, Canada

^c Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada

ARTICLE INFO

Article history:

Received 6 July 2018

Accepted 3 December 2018

Keywords:

Critically ill

Mortality

Nutrition risk

ICU

Enteral/parenteral nutrition

Protein

SUMMARY

Background: The NUTRITION Risk in the Critically Ill (NUTRIC) scoring system is a tool useful, discriminating critically-ill patients benefiting from optimal nutrition intake (>80% of prescription). Recent recommendations advocate for withholding artificial nutrition among low-NUTRIC patients, however, we hypothesized that some low-NUTRIC patients would show an association between nutrition intake and outcome.

Methods: Patients were selected from the 2013–2014 International Nutrition Surveys when ICU length of stay (LICU) ≥ 72 h, baseline mNUTRIC score ≤ 4 and had at least three evaluable nutrition days ($N = 2781$). Proportion of prescription received during evaluable days was associated to 60-day hospital mortality by a logistic regression modelling. A priori, we expected that the association between proportion of prescription received and mortality might differ according to: LICU, BMI and prior unintentional weight loss or reduced oral intake.

Results: A total of 2781 patients fulfilled the inclusion criteria and participated in the study. Ten percent of the sample had a BMI < 20 kg/m² and 20% experienced either unintentional weight loss during the last 3 months, or reduced food intake over the last week. Sixty-day hospital mortality was 15% and median LICU reached 11.3 [6.3–21.7] days. Mean total prescription received by any means of nutritional support during the first 12 evaluable days was $57.4 \pm 28.1\%$ for energy and $53.7 \pm 29.2\%$ for protein. In the pooled, subgroup and sensitivity analyses, no significant associations were identified.

Conclusion: Low-NUTRIC (≤ 4) patients demonstrate a prolonged LICU, while experiencing significant mortality and a high prevalence of malnutrition risk factors. Although improvements in mortality were not achieved with increased nutritional intake, this should not be construed as a rationale for withholding artificial nutrition among this patient group.

© 2018 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

Abbreviations: ASPEN, American Society for Enteral and Parenteral Nutrition; APACHE-II, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index; CI, Confidence Intervals; EN, Enteral Nutrition; GEE, generalized estimating equations; ICU, Intensive Care Unit; LICU, Length of Intensive Care Unit stay; LOS, Length of hospital stay; NRS2002, Nutritional Risk Screening 2002; NUTRIC, Nutrition Risk in the Critically Ill; mNUTRIC, modified NUTRIC; OR, Odds Ratio; PN, Parenteral Nutrition; SD, Standard deviation; SOFA, Sequential Organ Failure Assessment; SPSS, Statistical Package for Social Sciences.

* Corresponding author. University Campus, Aristotle University of Thessaloniki, Entrance 4, 54124 Thessaloniki, Greece.

E-mail addresses: mhourd@auth.gr (M. Chourdakis), mariagram@auth.gr (M.G. Grammatikopoulou), daya@kgh.kari.net (A.G. Day), ebouras@auth.gr (E. Bouras), dkh2@queensu.ca (D.K. Heyland).

<https://doi.org/10.1016/j.clnu.2018.12.006>

0261-5614/© 2018 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.

1. Background

During the last decade, nutritional screening and assessment has become an integral part of in-patient care with a plethora of relevant tools and guidelines for the health professional to choose from. Due to the increased pro-inflammatory state among critical care patients, consequences of malnutrition are likely to be augmented [1,2] leading to greater infection risk, increased length of stay (LOS), increased morbidity and mortality [3–5]. However, it appears that for most critical care patients, nutritional needs (in both energy and protein) are not adequately met [6]. In 2011 an intensive care unit (ICU) specific scoring algorithm was proposed for the identification of critical care patients most likely to benefit from aggressive nutrition therapy [7], creating a paradigm shift in connecting screening and treatment, with successful quality outcome health measures [8].

The Nutrition Risk in Critically Ill (NUTRIC) score is calculated with easy-to-obtain illness severity indexes, taking into account comorbidities and additional risk factors [7]. Patients demonstrating high NUTRIC scores are benefiting from closer-to-goal energy or protein provision by exhibiting reduced mortality rates, while on the other hand, no relationship between nutrition intake and outcome has been observed among low NUTRIC patients [9,10]. The NUTRIC score has been validated [11] and used by independent investigators in different populations [12–14], whereas in the absence of interleukin-6 the modified NUTRIC score (mNUTRIC) can be used [11].

Recent guidelines from the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition (ASPEN) for the provision and assessment of nutritional therapy in the adult critically ill patients [15] advocate withholding nutritional support among patients of low nutritional risk (low NRS2002/NUTRIC). This was neither the intended use of the NUTRIC score, nor how it was validated. In the developmental and validation process for NUTRIC, the examined hypothesis was whether NUTRIC score would help define a patient group that would benefit from optimal nutrition (defined as receiving >80% of prescribed requirements) [7] compared to those who would not derive such a benefit. Undeniably, high-NUTRIC score patients endure an increased mortality risk and prolonged length of hospital stay (LOS) [14], however, low-NUTRIC patients are neither risk-free, nor do they all share the same severity. Additionally, nutrition prescription during the first week in the ICU is pivotal for increasing long-term survival and impeding physical recovery [16]. Thus, depending on pre-ICU malnutrition status [17], disease severity, body mass index (BMI) [10], or expected LOS, there may be some low-NUTRIC patients that would still benefit from optimal nutrition intake.

The present study aims to investigate associations between proportion of nutrition prescription (energy and protein) received and hospital mortality amongst low-NUTRIC score patients. A priori, we also aim in identifying sub-groups of low-NUTRIC patients that may benefit from optimal nutrition. In particular, we assessed whether among patients with a mNUTRIC score ≤ 4 , the association between % of prescription received and 60-day hospital mortality varied by: 1) length in the ICU (LICU), 2) BMI and 3) prior unintentional weight loss and/or reduced oral intake.

2. Methods

2.1. Study design and population

The sample was selected from the 2013 and 2014 Improving Nutrition Practices in the Critically Ill International Nutrition Surveys data (DKH, principal investigator). Inclusion criteria were 1) having remained in the ICU for at least 72 h, 2) having a baseline

mNUTRIC score ≤ 4 on the first day of ICU admission and 3) having at least three evaluable nutrition days. Evaluable nutrition days were considered as the days spent in the ICU with the patient being alive, prior to (not including) the date of death, ICU discharge, or progression to permanent exclusive oral feeding, up to a maximum of 12 days in ICU. Nutrition days were counted from midnight to midnight, with the date of ICU admission being the first evaluable nutrition day; thus, all patients in this analysis had over 48 h eligible for nutrition support. Evaluable days without nutrition received were counted as zero.

In the context of the survey, among the data collected were hospital and ICU characteristics (such as feeding protocol information), patient characteristics such as sex, age, admission information (medical, surgical elective or surgical emergency), different scores (APACHE II, SOFA, NUTRIC), BMI as well information on Energy and protein prescribed/received, but also information regarding co-morbidities such as (hypertension, diabetes mellitus, obesity, smoking, depression and others) as per Table 1. We also collected data regarding baseline nutrition assessment and daily nutrition that are further elaborated in the next two sections.

The study was conducted under ethics approval by Queens University, in Ontario, Canada. The need for informed consent was waived as this was an observational study, without interventions.

2.2. Nutritional risk

Data for all variables of the NUTRIC score [7], with the exception of IL-6 levels were collected. The recorded variables included age, Acute Physiology and Chronic Health Evaluation (APACHE) II [18] and Sequential Organ Failure Assessment (SOFA) scores [19], number of comorbidities, and days from hospital admission until ICU admission. We considered a mNUTRIC score ≤ 4 as indicative of lower risk. Additionally, body weight and height of participants was measured during admission, and BMI was calculated. BMI, LICU,

Table 1

Patient characteristics and nutrition summary (among those with NUTRIC score ≤ 4 and at least 3 evaluable days), expressed as *n* (%), or mean \pm standard deviation.

	<i>N</i> = 2781 ^a
Age (years)	48.6 \pm 17.1
Sex (men/women)	1748 (62.9%)/1033 (37.1%)
Admission type:	
Medical	1588 (57.1%)
Surgical elective	231 (8.3%)
Surgical emergency	962 (34.6%)
One or more comorbidities (i.e. co-morbidities such as hypertension, diabetes mellitus, obesity, smoking, depression and others)	1781 (64.0%)
APACHE II	16.2 \pm 6.1
SOFA	9.8 \pm 5.6
NUTRIC score	3.0 \pm 1.1
BMI (kg/m ²) ^a	26.8 \pm 7.2
Energy requirements (kcal/d)	1878.1 \pm 463.2
Energy intake (kcal/d)	1074.0 \pm 577.8
Energy intake (kcal/kg/d)	14.5 \pm 7.9
Proportion of energy prescription received (%)	57.4 \pm 28.1
Protein requirements (g/d)	94.8 \pm 32.2
Protein intake (g/d)	50.6 \pm 31.8
Protein intake (g/kg/d)	0.7 \pm 0.4
Proportion of protein prescription received (%)	53.7 \pm 29.2

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; NUTRIC: Nutrition Risk in Critically Ill; SOFA: Sequential Organ Failure Assessment.

^a BMI based on *n* = 2755 due to 26 missing all other variables available for all 2781 patients.

prior unintentional weight loss or reduced oral intake were recorded as additional malnutrition risk factors.

2.3. Dietary intake

Since this was an observational study, nutrition provision was recorded, without any nutritional interventions being performed. Energy and protein provision was noted during all evaluable nutrition days prior to (not including) the date of death, ICU discharge, progression to permanent exclusive oral feeding up, or for a maximum of 12 ICU days. Energy intake includes calories received from enteral nutrition (EN) including supplemental protein and non-protein modular supplements, parental nutrition (PN), and propofol, but not IV glucose which was collected only at burn sites. Protein intake includes EN (including supplemental protein) and PN sources. The proportion of nutrition prescription received was calculated as the average energy or protein received over the evaluable nutrition days divided by the baseline prescription. The modelling was repeated in sensitivity analyses, including only patients with 12 evaluable days, in order to surpass the need for adjustment of the evaluable days.

All data were collected using an electronic data capture system. Where possible categorical response field types were used to minimize the risk of data entry errors, while free text fields were kept at a minimal level. During the data entry procedures, pre-defined validation rules (such as accepted value range etc.) were installed to allow for basic data validation control. The amount of random missing data entries was reduced to a minimum, by including options related to the reasons for missing data, and data closure check-points were applied at defined intervals. Furthermore, each participating center was provided with an instruction sheet, containing detailed information regarding the survey-related case report forms and instructions on the data entry procedures.

2.4. Statistical analyses

The two primary predictor variables included the % of the energy and protein prescriptions received by either EN, PN, propofol or protein supplements, during all evaluable days. Associations between the % of prescription received during the evaluable days

and 60-day hospital mortality were modelled by logistic regression with the use of generalized estimating equations (GEE), to account for potential between-ICU heterogeneity. All models were controlled for admission type, age, APACHE II score, country region, and evaluable days, except for the final high-risk group (BMI < 20 kg/m² and reduced oral intake or prior weight loss) model which was only controlled for admission type and evaluable days (furthermore this final model used regular logistic regression rather than GEE), due to the small sample size. The logistic GEE models were applied with interaction terms, to assess whether the association between proportion of prescription received and mortality differed according to: a) LICU (<12 days vs. ≥12 days), b) BMI (BMI < 20 kg/m², 20 ≤ BMI < 35 kg/m² and BMI ≥ 35 kg/m²), and c) prior unintentional weight loss or reduced oral intake (both, either of the two, or neither). Within subgroup, estimates were obtained, and interaction terms were tested for statistical significance.

3. Results

As stressed in the CONSORT diagram [20] (Fig. 1), a total of 8052 patients during the years 2013 ($n = 4066$) and 2014 ($n = 3986$) were identified from the INS datasets, of which 326 (4%) had an unknown mNUTRIC score, 2973 (37%) had a NUTRIC score ≤4 and the remaining 5 (59%) had a mNUTRIC score of 5 or more. The current analysis includes the 2781 patients (48.6 ± 17.1 years old, 63% males) with a mNUTRIC score ≤4 and at least 3 evaluable nutrition days. Table 1 describes this subgroup's characteristics. Mean BMI of the sample was 26.8 ± 7.2 , with 9.6% of the patients having a BMI <20 kg/m². The majority (64%) had at least one comorbidity and 47% stayed in the ICU for a period exceeding 12 days. For 2091 patients (75%), a nutrition history was available and 20% of the patients either experienced unintentional weight loss during the last 3 months, or had reduced food intake over the past week, or both. The overall 60-day hospital mortality rate of our sample reached 15% (421/2781) and the median [Q1, Q3] LICU was 11.3 [6.3, 21.7] days. The median (range) evaluable nutrition days were 8.8 (3–12). Mean total percent of prescription received by either EN, PN, propofol or protein supplements during the first 12 evaluable days was $57.4 \pm 28.1\%$ for energy and $53.7 \pm 29.2\%$ for protein, and these were strongly correlated ($r = 0.90$) with each other. Among the 1224 patients with 12 evaluable nutrition days, the mean

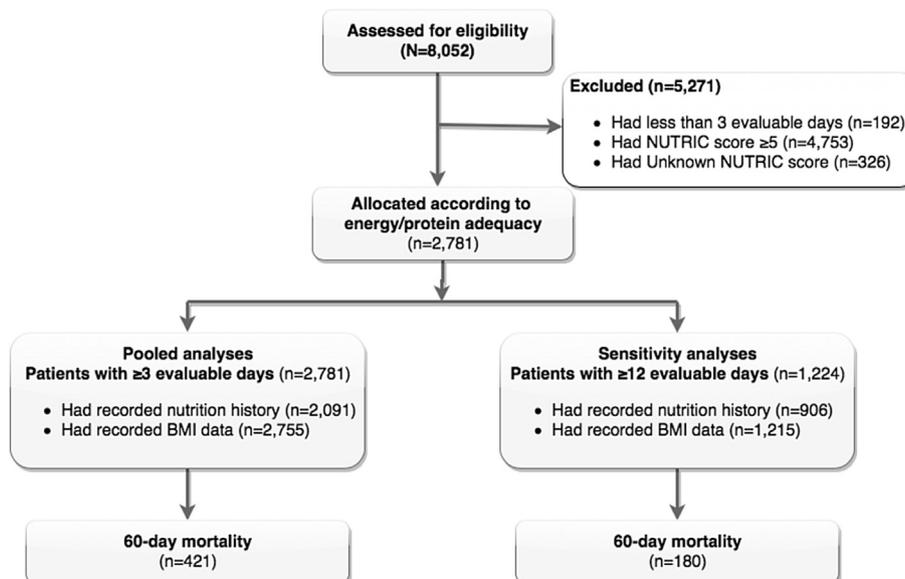


Fig. 1. Flow diagram of the study process.

percent of prescription received was $69.8 \pm 22.9\%$ for energy and $65.8 \pm 24.6\%$ for protein.

Results of the logistic regression models are presented in Table 2 (combined for energy and for protein). After controlling for evaluable days, admission type, age, APACHE II and region, for every 20% increase in the proportion of prescription received, the adjusted OR for 60-day hospital mortality was OR = 1.11 (95%CI: 1.00–1.23, $p = 0.05$) for energy and OR = 1.07 (95%CI: 0.98–1.17, $p = 0.15$) for protein, indicating evidence for lack of association between nutritional intake and mortality in the pooled patient sample. Furthermore, no association was observed between either energy, or protein intake and 60-day mortality in any of the subgroups analyzed. The lack of association remained even when energy was controlled for protein and vice versa.

The sensitivity analyses using only patients with 12 evaluable days are displayed on Table 3 (combined for energy and for protein). No significant associations were identified.

4. Discussion

Our study examined whether the provision of additional energy or protein – closer to the recommendations – would affect 60-day hospital mortality among the pooled low-NUTRIC cohort and amongst different subgroups of low-NUTRIC ICU patients. No significant associations between nutritional adequacy and 60-day hospital mortality were observed neither in the pooled sample, nor in any of the subgroups examined.

ICU underfeeding is a universal phenomenon, with more than half of all ICU patients worldwide being significantly underfed in terms of energy and protein during the first two weeks of ICU care [21]. To date, controversy exists concerning the optimal amount of nutrient prescription, leading to imprecise ICU therapy [22], with the uncertainty being corroborated by conflicting findings concerning the effects of increased energy and protein provision among undernourished patients [23]. Several studies have showed

Table 2
Association between caloric and protein adequacy in first 12 ICU days and 60-day hospital mortality in patients with NUTRIC score ≤ 4 who had at least 3 evaluable ICU days.

Subgroup	Deaths/n (mortality)	Caloric adequacy		Protein adequacy	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Overall	421/2781 (15%)	1.11 (1.00–1.23)	0.05	1.07 (0.98–1.17)	0.15
Days in ICU		(Interaction test $p = 0.87$)		(Interaction test $p = 0.60$)	
<12	246/1470 (17%)	1.09 (0.94–1.27)	0.27	1.03 (0.91–1.17)	0.64
≥ 12	175/1311 (13%)	1.10 (0.98–1.25)	0.11	1.08 (0.96–1.21)	0.20
Nutrition history variables ^a		(Interaction test $p = 0.05$)		(Interaction test $p = 0.10$)	
Both	35/166 (21%)	1.31 (0.99–1.74)	0.06	1.23 (0.94–1.61)	0.14
Either	54/253 (21%)	0.87 (0.71–1.06)	0.17	0.87 (0.70–1.06)	0.17
Neither	234/1672 (14%)	1.12 (0.97–1.29)	0.11	1.09 (0.95–1.24)	0.21
BMI		(Interaction test $p = 0.97$)		(Interaction test $p = 0.52$)	
<20 kg/m ²	48/265 (18%)	1.18 (0.94–1.48)	0.16	1.25 (0.99–1.58)	0.06
20–24.9 kg/m ²	157/1063 (15%)	1.12 (0.96–1.30)	0.15	1.04 (0.92–1.18)	0.54
25–34.9 kg/m ²	165/1136 (15%)	1.11 (0.96–1.28)	0.16	1.06 (0.93–1.21)	0.37
≥ 35 kg/m ²	45/291 (15%)	1.11 (0.85–1.44)	0.44	1.13 (0.89–1.43)	0.33
BMI <20 kg/m ² and reduced oral intake or prior weight loss	24/100 (24%)	0.94 (0.65–1.35)	0.72	1.06 (0.74–1.50)	0.76

Odds ratios estimate how much the odds of 60-day hospital mortality is multiplied per 20% increase in proportion of caloric prescription received by EN, PN or propofol. Estimates are from a logistic GEE model clustering by ICU and with factors controlling for: admission type, age, APACHE II score and region. The final model (BMI < 20 kg/m² with reduced oral intake or prior weight loss) only controls for admission type due to small numbers.

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; CI: Confidence Intervals; EN: Enteral Nutrition; GEE: Generalized Estimating Equation; ICU: Intensive Care Unit; OR: odds ratio; PN: Parenteral Nutrition.

^a Both refers to unintentional weight loss in the past 3 months and food intake decline over the past week due to loss of appetite. Either is one of the two previously mentioned conditions, and neither is neither condition.

Table 3
Associations between caloric and protein adequacy in the first 12 ICU days and 60-day hospital mortality, in patients with NUTRIC score ≤ 4 , who had at least 12 evaluable ICU days (sensitivity analysis).

Subgroup	Deaths/n (mortality)	Caloric adequacy		Protein adequacy	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Overall	180/1224 (15%)	1.06 (0.91–1.23)	0.46	1.01 (0.88–1.15)	0.91
Nutrition history variables ^a		(Interaction test $p = 0.42$)		(Interaction test $p = 0.73$)	
Both	18/74 (24%)	0.82 (0.53–1.27)	0.37	0.88 (0.62–1.26)	0.50
Either	19/93 (20%)	1.05 (0.70–1.60)	0.80	1.00 (0.66–1.51)	0.99
Neither	92/739 (12%)	1.13 (0.90–1.42)	0.31	1.05 (0.85–1.29)	0.68
BMI		(Interaction test $p = 0.24$)		(Interaction test $p = 0.09$)	
<20 kg/m ²	23/105 (22%)	1.34 (0.87–2.06)	0.18	1.45 (0.99–2.12)	0.06
20–24.9 kg/m ²	53/459 (12%)	1.16 (0.88–1.51)	0.29	1.04 (0.85–1.26)	0.72
25–34.9 kg/m ²	80/505 (16%)	0.88 (0.69–1.12)	0.31	0.84 (0.66–1.06)	0.14
≥ 35 kg/m ²	20/146 (14%)	1.22 (0.84–1.78)	0.29	1.16 (0.82–1.66)	0.40
BMI <20 kg/m ² and reduced oral intake or prior weight loss	12/37 (32%)	0.93 (0.54–1.59)	0.79	1.18 (0.67–2.08)	0.57

Odds ratios estimate how much the odds of 60-day hospital mortality is multiplied per 20% increase in proportion of caloric prescription received by EN, PN or propofol. Estimates are from a logistic GEE model clustering by ICU and with factors controlling for: admission type, age, APACHE II score and region. The final model (BMI < 20 kg/m²) with reduced oral intake or prior weight loss, only controls for admission type due to small numbers.

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; CI: Confidence Intervals; EN: Enteral Nutrition; GEE: Generalized Estimating Equation; ICU: Intensive Care Unit; OR: odds ratio; PN: Parenteral Nutrition.

^a Both refers to unintentional weight loss in the past 3 months and food intake decline over the past week due to loss of appetite. Either is one of the two previously mentioned conditions, and neither is neither condition.

that nutritional risk greatly determines the amount of energy and macronutrient requirements in the ICU. Among patients with high-NUTRIC scores, increased nutrition provision has been shown to effectively reduce mortality and time to discharge, in comparison to low-NUTRIC patients [7,9,11]. The PERMIT trial failed to show a positive effect of more nutrition in high NUTRIC patients [24]. On the other hand, in the TOP-UP pilot trial [25], a NUTRIC score subgroup analysis revealed a large positive treatment effect in high NUTRIC patients but it must be noted that neither group was powered to meaningfully look at clinical outcomes.

A recent meta-analysis [26] failed to conclude on the effect of prescribed hypocaloric feeding to mortality in hospital, in the ICU and at 30 days, as well as in length of hospital and ICU stay, infectious complications and the length of mechanical ventilation. They noted very low-quality evidence available and wide range of estimates for the above-mentioned parameters, included both appreciable benefits and harms.

Our study failed to demonstrate favourable outcomes with the provision of increased nutrition prescription among any of the examined low-NUTRIC patient groups. However, several methodological factors might have influenced the results. For instance, one should consider that nutritional assessment in the ICU entails several limitations. The calculation of energy requirements in the critically ill consists of a difficult process, since for 80% of the patients, predictive equations fail to match their actual needs [27]. This is why, the use of indirect calorimetry is suggested, in order to avoid overfeeding and its consequences [27]. As far as protein losses are concerned, although specific assays are needed for their determination [28], usually estimation of requirements is based on calculations.

Nutritional assessment is often imprecise in the ICU setting, and also nutrient requirements, physiological response to the exogenous nutrient provision, disease progress and outcome, greatly depend on the anabolic/catabolic state of each patient [23,28]. According to Wischmeyer [29], critical illness has distinct phases that should be used to guide treatment. Given that nutritional risk scores do not consider the anabolic/catabolic state of each patient, we are in need of additional markers in order to optimize nutritional strategy in each disease phase [23]. Therefore, in order to ameliorate outcomes, research, guidelines and step-by-step processes suggested for the provision of evidence-based care in the ICU, we must acknowledge that the dose, timing and combination of nutrient delivery should be tailored to disease phase. The four-days cutoff suggested in literature [28] does not always correspond to the exact transition from the acute to the chronic phase of metabolic response to critical illness and in the case of the present study, this might have resulted in insignificant findings.

Additionally, although mortality is the main endpoint of interest in ICU-based studies, multiple other clinical outcomes that were not controlled for in the study herein due to the retrospective design, might be improved from the provision of nutritional support among low-NUTRIC score patients. For instance, recent studies have showed that for every 25% increase in caloric provision in the first ICU week, an improvement in 3-month post-ICU physical quality of life scores (as measured by the SF-36) is observed and recovery is accelerated [16,30]. Additionally, greater protein and energy provision have been shown to accelerate time to discharge alive [9], whereas early nutrition has resulted in reduced duration of invasive ventilation [31].

A common problem in ICU-based studies is population heterogeneity [22]. Based on the heterogeneity observed in the ICU setting, a low malnutrition risk does not ensure that the patient will survive the ICU stay, since many patients in a rather benign state during admission might acutely progress to a more precarious disease status. Knowing that even low-NUTRIC score patients tend

to remain in the ICU for prolonged periods of time, have an increased mortality risk and experience several collateral malnutrition risk factors, withholding nutritional support among these patients would be precarious. After all, the NUTRIC score was developed to allocate patients who would benefit more from nutritional support, without any overall suggestion of withholding nutritional support among those exhibiting a low score.

Unfortunately, at the moment we are unable to predict which patients will prove to be of increased risk and demand extended LICU [29]. This is why, recommendations promoting trophic or permissive underfeeding during the first week among low-NUTRIC score patients, as the current ASPEN guidelines [15], might eventually harm ICU patients with prolonged LICU, and this harm will be evident when there will be not enough time to replenish the energy and protein deficit acquired during their first ICU week [6,16,29].

Our study revealed a trend towards elevated mortality per 20% increase in the provision of energy and/or protein prescription received in low NUTRIC patients. Similarly, a small observational study reported that when both energy and protein are provided at least at 2/3 of the prescribed amounts, a trend towards an increased 60-day mortality is observed among low-NUTRIC score patients [32], suggesting the need for iatrogenic underfeeding. When the two (energy and protein) were assessed separately, none appeared to affect mortality. However, the relatively small number of participants ($N = 154$) and the recruitment from a single ICU, although ensuring homogeneity of the sample and methodology used, do not allow for generalization of the results, especially considering that only patients with complications were being admitted in this specific ICU.

The results by Lee and associates [32] in conjunction to the positive trend between increased energy/protein provision and mortality noted in the results herein, could be indicative of undiagnosed refeeding syndrome among a large proportion of patients in both studies, irrespectively of the low nutritional risk of participants. It is known that during the early phase of critical illness, nutrient delivery may lead to the development of refeeding syndrome [23]. In these patients trophic underfeeding appears to be more effective in reducing mortality compared to standard caloric intake [33,34], but in the present study diagnosis of refeeding syndrome was not included in the exclusion criteria.

Several important issues arise from the findings herein. Firstly, with NUTRIC score being evaluated on the 3rd day of ICU admission (as is the suggestion of the authors of the NUTRIC score), a great number of patients allocated as low-risk are bound to transition to high-NUTRIC patients as they remain in ICU for more than 5–7 days. This is why, nutritional screening should be as frequent and accurate as possible. Disease and metabolic response to disease are dynamic processes dependent on various factors that should be recorded for the optimal provision of nutritional care.

As our data was collected over a period of 4 years, one good question whether any changes in the management of the ICUs since the start of collection of data could be able to change their interpretation. However, we cannot state whether clinically meaningful changes in the management of ICUs have taken place since that time as we have not conducted another International Survey since then.

The strengths of the present study include the use of a large sample and the application of robust statistical adjustments for different geographical settings, age groups and admission type. The large multicenter nature of the study enhances the generalizability of the findings. On the other hand, several limitations should be considered. Among the weaknesses of our study is that due to the pragmatic nature of this survey design, several known and unknown factors that may affect malnutrition and ICU mortality were not recorded, as they do not consist of standard procedures in most ICUs.

Factors, not accounted for in the present study, including recent ICU admission or transfer from another unit [29], presence and degree of cachexia and sarcopenia [30] have been shown to affect ICU mortality. It is highly likely that if these factors were recorded and controlled for, more significant results would have been revealed from the analyses.

Finally, as in all observational studies, causality cannot be assumed. Therefore, future research should consider providing different proportions of the prescribed amounts of energy and protein among subgroups of low-NUTRIC score patients, in order to test clinical outcomes.

Currently, research on the proper amount of nutrition provision in the ICU appears controversial, with the majority of relevant trials using heterogeneous or sicker patients. From the point of clinical practice, nutritional assessment with the use of the NUTRIC score should be performed on the 3rd day of ICU stay. The scientific evidence on how much nutritional support patients of lower nutritional risk need is limited and although such patients appear to attain better-projected clinical outcomes during admission, it is highly likely that we are not providing them with the best of care in terms of nutrition support. Given the morbidity and mortality even of low-NUTRIC patients, further exploration of the value of nutrition support is warranted.

5. Conclusion

Low-NUTRIC score patients experience extended LICU and significant mortality rates, while demonstrating a variety of malnutrition risk factors. Although no improvements in mortality were observed with increased nutritional intake, this should not be construed as a rationale for withholding artificial nutrition among these patients. Increased nutritional intake could still confer benefits in other clinical outcomes except mortality. Further exploration of the effects of nutritional support is warranted among more homogeneous samples of low-NUTRIC patients.

Ethics approval and consent to participate

This study was approved by the Health Research Ethics Board of the Queens University, in Ontario, Canada.

Funding

None.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MC and MGG and DKH wrote the manuscript. Additionally, AGD and DKH acquired the data, while AGD and EB performed the statistical analyses, and DKH conceived the study, supervised all procedures and designed the study. All authors participated in the interpretation of data, revision of the manuscript for important intellectual content and agreed to be accountable for all aspects of the work. The manuscript has been read and its submission approved by all co-authors.

Conflicts of interest

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Acknowledgements

The authors wish to thank all participating centers of INS2013 and INS2014 (Improving Nutrition Practices in the Critically Ill International Nutrition Surveys), as well as the patients and their caregivers.

References

- [1] Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. *J Parenter Enteral Nutr* 2017;41:744–58. <https://doi.org/10.1177/0148607115625638>.
- [2] White JV, Guenter P, Jensen G, Malone A, Schofield M, Academy of Nutrition and Dietetics Malnutrition Work Group, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Acad Nutr Diet* 2012;112:730–8. <https://doi.org/10.1016/j.jand.2012.03.012>.
- [3] Corkins MR, Guenter P, DiMaria-Ghalili RA, Jensen GL, Malone A, Miller S, et al. Malnutrition diagnoses in hospitalized patients. *J Parenter Enteral Nutr* 2014;38:186–95. <https://doi.org/10.1177/0148607113512154>.
- [4] Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med* 2011;37:601–9. <https://doi.org/10.1007/s00134-011-2146-z>.
- [5] Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *Am J Manag Care* 2013;19:121–8.
- [6] Heyland DK, Dhaliwal R, Wang M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally “at-risk” critically ill patient: results of an international, multicenter, prospective study. *Clin Nutr* 2015;34:659–66. <https://doi.org/10.1016/j.clnu.2014.07.008>.
- [7] Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care* 2011;15:R268. <https://doi.org/10.1186/cc10546>.
- [8] Patel C, Omer E, Diamond SJ, McClave SA. Can nutritional assessment tools predict response to nutritional therapy? *Curr Gastroenterol Rep* 2016;18:15. <https://doi.org/10.1007/s11894-016-0488-y>.
- [9] Compher C, Chittams J, Sammarco T, Nicolo M, Heyland DK. Greater protein and energy intake may be associated with improved mortality in higher risk critically ill patients: a multicenter, multinational observational study. *Crit Care Med* 2017;45:156–63. <https://doi.org/10.1097/CCM.0000000000002083>.
- [10] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med* 2009;35:1728–37. <https://doi.org/10.1007/s00134-009-1567-4>.
- [11] Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the “modified NUTRIC” nutritional risk assessment tool. *Clin Nutr* 2016;35:158–62. <https://doi.org/10.1016/j.clnu.2015.01.015>.
- [12] Özbilgin Ş, Hancı V, Ömür D, Özbilgin M, Tosun M, Yurtlu S, et al. Morbidity and mortality predictivity of nutritional assessment tools in the postoperative care unit. *Medicine (Baltimore)* 2016;95:e5038. <https://doi.org/10.1097/MD.0000000000005038>.
- [13] Mendes R, Policarpo S, Fortuna P, Alves M, Virella D, Heyland DK, et al. Nutritional risk assessment and cultural validation of the modified NUTRIC score in critically ill patients—a multicenter prospective cohort study. *J Crit Care* 2017;37:249. <https://doi.org/10.1016/j.jccr.2016.09.007>.
- [14] Kalaiselvan MS, Renuka MK, Arunkumar AS. Use of nutrition risk in critically ill (NUTRIC) score to assess nutritional risk in mechanically ventilated patients: a prospective observational study. *Indian J Crit Care Med* 2017;21:253–6. https://doi.org/10.4103/ijccm.IJCCM_24_17.
- [15] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. *J Parenter Enteral Nutr* 2016;40:159–211. <https://doi.org/10.1177/0148607115621863>.
- [16] Wei X, Day AG, Ouellette-Kuntz H, Heyland DK. The association between nutritional adequacy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: a multicenter cohort study. *Crit Care Med* 2015;43:1569–79. <https://doi.org/10.1097/CCM.0000000000001000>.
- [17] Kondrup J. Nutritional-risk scoring systems in the intensive care unit. *Curr Opin Clin Nutr Metab Care* 2014;17:177–82. <https://doi.org/10.1097/MCO.0000000000000041>.

- [18] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
- [19] Moreno R, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working group on sepsis related problems of the ESICM. *Intensive Care Med* 1999;25:686–96.
- [20] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet (London, England)* 2001;357:1191–4.
- [21] Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: what is “best achievable” practice? An international multicenter observational study. *Crit Care Med* 2010;38:395–401. <https://doi.org/10.1097/CCM.0b013e3181c0263d>.
- [22] Maslove DM, Lamontagne F, Marshall JC, Heyland DK. A path to precision in the ICU. *Crit Care* 2017;21:79. <https://doi.org/10.1186/s13054-017-1653-x>.
- [23] Arabi YM, Casaer MP, Chapman M, Heyland DK, Ichai C, Marik PE, et al. The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* 2017;43:1239–56. <https://doi.org/10.1007/s00134-017-4711-6>.
- [24] Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med* 2015;372:2398–408. <https://doi.org/10.1056/NEJMoa1502826>.
- [25] Wischmeyer PE, Hasselmann M, Kummerlen C, Kozar R, Kutsogiannis DJ, Karvellas CJ, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. *Crit Care* 2017;21:142. <https://doi.org/10.1186/s13054-017-1736-8>.
- [26] Perman MI, Ciapponi A, Franco JV, Loudet C, Crivelli A, Garrote V, et al. Prescribed hypocaloric nutrition support for critically-ill adults. *Cochrane Database Syst Rev* 2018;6:CD007867. <https://doi.org/10.1002/14651858.CD007867.pub2>.
- [27] Fraipont V, Preiser J-C. Energy estimation and measurement in critically ill patients. *J Parenter Enteral Nutr* 2013;37:705–13. <https://doi.org/10.1177/0148607113505868>.
- [28] Preiser J-C, van Zanten A, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care* 2015;19:35. <https://doi.org/10.1186/s13054-015-0737-8>.
- [29] Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. *Crit Care* 2015;19(Suppl. 3):S6. <https://doi.org/10.1186/cc14724>.
- [30] Paratz JD, Kenardy J, Mitchell G, Comans T, Coyer F, Thomas P, et al. IMPOSE (IMProving Outcomes after Sepsis)—the effect of a multidisciplinary follow-up service on health-related quality of life in patients postsepsis syndromes—a double-blinded randomised controlled trial: protocol. *BMJ Open* 2014;4:e004966. <https://doi.org/10.1136/bmjopen-2014-004966>.
- [31] Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition. *J Am Med Assoc* 2013;309:2130. <https://doi.org/10.1001/jama.2013.5124>.
- [32] Lee Z-Y, Noor Airini I, Barakatun-Nisak M-Y. Relationship of energy and protein adequacy with 60-day mortality in mechanically ventilated critically ill patients: a prospective observational study. *Clin Nutr* 2018;37:1264–70. <https://doi.org/10.1016/j.clnu.2017.05.013>.
- [33] Doig GS, Simpson F, Bellomo R, Heighes PT, Sweetman EA, Chesher D, et al. Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. *Intensive Care Med* 2015;41:1197–208. <https://doi.org/10.1007/s00134-015-3827-9>.
- [34] Marik PE, Hooper MH. Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. *Intensive Care Med* 2016;42:316–23. <https://doi.org/10.1007/s00134-015-4131-4>.