How does adequacy of caloric and protein intake associate with the clinical outcomes in critically ill adults of high nutritional risk?

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Background: Nutritional therapy forms an important part of management among critically ill patients. The modified NUTrition Risk in the Critically Ill (mNUTRIC) score is one of the nutrition evaluation tools developed especially for this special group of patients. This study aims to examine any associations between nutritional adequacy and various clinical outcomes among critically ill adult patients of high nutritional risk in Hong Kong.

Methods: This was a retrospective single-centered cross-sectional study conducted in a mixed medical-surgical adult Intensive Care Unit (ICU) of Queen Elizabeth Hospital, a 2,000-bed major acute public hospital in Hong Kong. All patients admitted between January and December 2017 who fulfilled the exclusion criteria, had an mNUTRIC score of 5 to 9, and had at least three nutrition evaluable days were recruited. Based on their caloric and protein adequacy, they were divided into low (both were less than two thirds), medium (either was two thirds or more) and high (both were two thirds or more) nutritional subgroup. Associations with mortality and other clinical outcomes were examined.

Results: Among 215 patients analysed, majority (70.7%) had low nutritional adequacy (caloric adequacy 38.7%±13.7%, protein adequacy 39.7%±17.3%). The all-cause 60-day mortality did not differ significantly among the three nutritional subgroups, and it had no significant association with different levels of nutritional adequacy. Those in the high nutritional subgroup were significantly more likely to have prolonged mechanical ventilation of 7 days or more (58.6% *vs.* 78.6% *vs.* 85.7%, P<0.005) and the strength of association was moderate (Cramer's V =0.23).

Conclusions: Critically ill patients of high nutritional risk were often given a low level of nutritional support during the acute phase of ICU care. There was no significant difference in all-cause 60-day mortality or correlation with different levels of nutritional adequacy. The chance of prolonged mechanical ventilation was significantly higher among those of high nutritional adequacy with a moderate strength of association.

Keywords: Enteral nutrition; parenteral nutrition; intensive care

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Introduction

Background

For years, there have been numerous debates about different aspects of nutritional support among critically ill patients—from timing of initiation, route and dose of artificial nutrition; to the optimal rate of progression toward nutritional goal and individualization of nutritional strategies in special subgroups (1-3). There are currently four international guidelines to address these aspects (4-7) yet the level of evidence varies and they mostly comprise observational studies or expert opinion. What is certain though is that critically ill patients deserve special attention on nutritional therapy as they experience a series of metabolic adaptations in response to the acute physiological stress. While these responses are thought to provide evolutionary advantage in overcoming survivable insults, if prolonged and exaggerated they become self-destructive and cause secondary metabolic damage (8,9).

In one review article, the prevalence of malnutrition among critically ill patients reaches nearly 80%. Such problem is notoriously associated with poor clinical outcomes (10). Ironically, majority of the critically ill patients fail to receive adequate nutritional intake (11). While meeting caloric target appears an instinct (12), recent attention has been on the role of protein in mitigating acute illnesses and hastening long-term recovery (2,13,14). Given the complexity of nutritional intervention in critical care, nutritional risk assessment is proposed as a routine to guide subsequent nutritional strategy (15).

Owing to the limitations in obtaining detailed weight and diet history, and accurate anthropometric data among critically ill patients, a novel nutritional assessment tool called NUTrition Risk in the Critically Ill (NUTRIC) score was developed by Heyland *et al.* in 2011 (16) and was subsequently validated for use in different populations including Chinese (17-19). Being fast and pragmatic, and with a good discriminating value, it is increasingly being utilized around the world (20).

The NUTRIC score combines prehospitalization parameter (age), acute starvation status (prehospital admission duration), acute [interleukin (IL)-6] and chronic inflammatory parameters (No. of comorbidities), and severity of illness [Acute Physiology and Chronic Health Evaluation (APACHE)-II; and Sequential Organ Failure Assessment (SOFA) scores] on ICU admission to identify patients at risk of developing adverse outcomes and who may otherwise benefit from aggressive nutrition therapy. Without using IL-6 values, it is called modified NUTRIC (mNUTRIC) score. A total score of 0 to 4 correspond to low nutritional risk whereas 5 to 9 correspond to high nutritional risk. *Table 1* shows the variables and point distribution of the mNUTRIC scoring system.

Various studies have shown that provision of greater caloric and protein intake to the high-risk critically ill patients confer outcome benefit in terms of mortality and morbidity (18,19,21). Conversely, these patients are more likely to experience harm if there is inadequate nutritional support (22). However, this has not been proven in our local population.

Study objective and hypothesis

This is the first study in Hong Kong which aims to examine the association between nutritional adequacy and all-cause 60-day mortality among critically ill adult patients of high nutritional risk admitted to a local ICU of a tertiary hospital. In addition, it also investigates the association of caloric and protein adequacy with other patient-oriented outcomes including renal support and mechanical ventilation. We hypothesized that in high-risk ICU patients (represented by an mNUTRIC score of 5 to 9), prescribing more of both calories and protein at two thirds or more of their respective target is associated with decreased mortality and morbidities.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jeccm-20-135).

Methods

Study design and patient selection

This is a retrospective single-centered cross-sectional study conducted in a 24-bed medical and surgical adult ICU of a tertiary hospital in Hong Kong (Queen Elizabeth Hospital, Kowloon). All patients admitted from January to December 2017 were screened to minimize selection bias. They were excluded if they meet any of the following: length of stay in ICU for less than 72 hours; admitted after elective surgery as they were likely to have received nutritional screening and supplemental nutritional support preoperatively; pregnant at the time of ICU admission; data were incomplete to calculate mNUTRIC score; did not receive any artificial nutrition for the first 12 days of ICU admission; had repeated ICU admissions within the same

Table 1 Modified Nutrition Risk in the Critically Ill scoring system (adapted with permission from the Canadian Critical Care Nutrition website: www.criticalcarenutrition.com)

Variable	Range	Points
Age	<50	0
	50 to <75	1
	≥75	2
APACHE-II	<15	0
	15 to <20	1
	20 to 28	2
	≥28	3
SOFA	<6	0
	6 to <10	1
	≥10	2
No. of co-morbidities†	0 to 1	0
	≥2	1
Days from hospital to ICU admission	0 to <1	1
	≥1	1

†, including myocardial, vascular, pulmonary, neurologic, endocrine, renal, gastrointestinal, cancer/immune, psychological, musculoskeletal, substance use and miscellaneous. APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; SOFA, sequential organ failure assessment.

hospitalization episode; had repeated hospitalization within 1 year; or with major burns due to local referral policy. Among the remaining ones who were eligible, patients with high mNUTRIC of 5 to 9 were recruited, and those who had at least three nutrition evaluable days were selected and categorized into low, medium and high nutritional subgroup according to their caloric and protein adequacy. *Figure 1* illustrates the process of patient selection.

Data collection

There was no intervention in this observational study. All nutritional therapies were at the discretion of the attending clinicians. Patient's information including baseline and nutritional characteristics were retrieved from the Computer Information System, Hospital Authority Clinical Management System and electronic Patient Record. Clinical outcomes were analysed up to 60 days counting from the date of ICU admission. Investigators involved in the procedure of data collection were primed and the chance for information bias was deemed minimal.

Independent variables

Baseline characteristics

Table 2 shows the definitions for specific terms used in the current study. Apparent body weight, although less accurate than anthropometric measurement, is a practical and common way of weight estimation in ICU. When compared to derived values, visual estimation by trained personnel allows a closer approximation to patient's actual body weight especially those of extreme body sizes. It is thought to give a more realistic estimation of the nutritional requirement. Other baseline characteristics collected were age, sex, body mass index (BMI), APACHE-II and SOFA scores, days in hospital prior to ICU admission, number of co-morbidities if any.

Nutritional characteristics

The period of nutrition evaluable days is believed to represent the acute phase of nutritional status among the critically ill as most patients would only start oral diet after stabilization and shortly before transfer to general ward. The total amount of calories and protein prescribed were calculated by multiplying the volume of artificial nutrition given both enterally and parenterally by the energy (in kcal) and protein (in g) content per 1 mL of standard formula. Caloric intake from dextrose solution and propofol (if more than 200 mg per hour over 24 hours) were also taken into account. "Prescribed" but not the "actual" amount of artificial nutrition absorbed by the patient was considered due to practical reason in this study.

The goal caloric intake was based on the Harris-Benedict predictive equation taking into account the most significant stress factor and activity factor. On the other hand, a goal protein intake of 1.2 g/kg/day is being adopted according to the latest guidelines and consensus (4,7,23,24). Taking two thirds as the lower threshold of caloric and protein adequacy (12), three nutritional subgroups were derived: low (both <2/3), medium (either ≥2/3) and high (both ≥2/3). There was limited access to indirect calorimetry in our unit, and nitrogen balance measurement is not routinely performed.

Following data were also collected: time from ICU admission to start of nutritional support; initial route of nutritional support being enteral (versus parenteral); any major intra-abdominal or gastrointestinal (GI) system

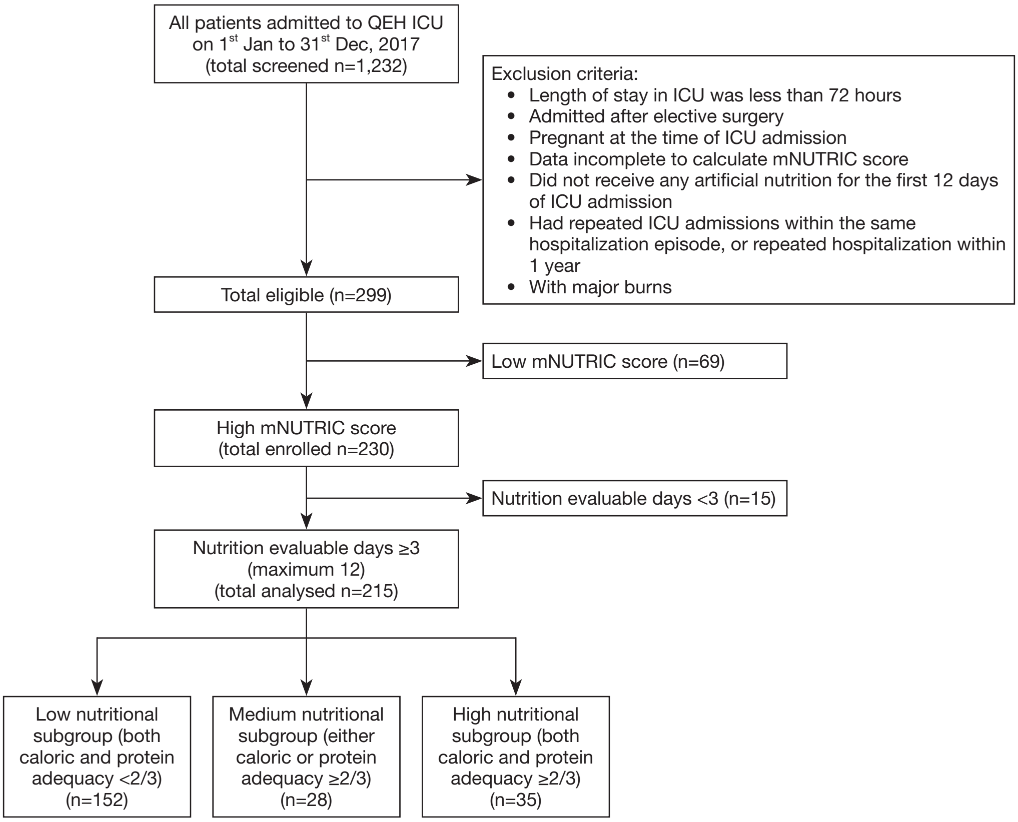

Figure 1 Process of patient selection.

related factors unfavourable for enteral feeding (such as paralytic ileus, intra-abdominal hypertension, mechanical intestinal obstruction, severe diarrhoea, major and/or active gastrointestinal bleeding, ischemic bowel, and recent bowel operation); and presence of GI intolerance (defined as gastric residual volume of 500 mL or more over 4 hours, or so documented in physician notes).

Dependent variables

The primary outcome was all cause 60-day in-hospital mortality since ICU admission. If a patient was discharged home or transferred to a private hospital before day 60, that patient would be considered alive on day 60. The secondary outcomes were: need of renal support (in any modalities of dialysis regardless of pre-existing end stage renal failure); presence of bloodstream infection from culture (excluding skin contaminants); need of hemodynamic support (either pharmacologically or mechanically, of any dose and any duration); need of mechanical ventilation (regardless of the cause and timing); and total duration of mechanical ventilation for 7 days or more.

Sample size

Assuming a medium effect size (Cohen's f =0.25) for the maximum reduction in 60-day mortality among high-mNUTRIC patients of different nutritional adequacies (18,19,21), a total sample size of at least 159 would allow a two-tailed significance level of 5% and statistical power of 80% using the G*power calculator (version 3.1.9.4; Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Considering possible dropout due to incomplete data (10%), minimal duration of nutrition evaluable days (5%), and loss to follow-up as a result of short ICU stay (10%), 212 patients were to be enrolled in this study.

Statistical analysis

Results were presented as mean ± standard deviation (SD) for continuous variables and frequency (percent) for categorical variables. For the overall comparison of

Table 2 Terms and definitions

Terms	Definitions
Low nutritional risk or low-mNUTRIC group	An mNUTRIC score of 0 to 4
High nutritional risk or high-mNUTRIC group	An mNUTRIC score of 5 to 9
Apparent body weight	Patient's body weight estimated visually by trained nurses on ICU admission
Nutrition evaluable days	Number of days prior to (but not including) the date of permanent progression to oral intake, discharge or death since admission to ICU (maximum 12 days)
Prescribed caloric intake	Average amount of calories prescribed via enteral and parental route per apparent body weight per nutrition evaluable day, in kcal/kg/day
Prescribed protein intake	Average amount of protein prescribed via enteral and parental route per apparent body weight per nutrition evaluable day, in g/kg/day
Goal caloric intake	Equals to patient's total daily energy expenditure as estimated by the Harris-Benedict equation, in kcal/kg/day
Goal protein intake	Equals to 1.2 g/kg/day
Caloric adequacy	Ratio of prescribed to goal caloric intake, in %
Protein adequacy	Ratio of prescribed to goal protein intake, in %
Low nutritional subgroup (abbreviated as both <2/3), low nutritional adequacy, or low nutritional support	Both caloric and protein adequacy are less than two thirds
Medium nutritional subgroup (abbreviated as either ≥2/3), medium nutritional adequacy, or medium nutritional support	Either caloric or protein adequacy is two thirds or more
High nutritional subgroup (abbreviated as both ≥2/3), high nutritional adequacy, or high nutritional support	Both caloric and protein adequacy are two thirds or more

the baseline and nutritional characteristics, and clinical outcomes among the three nutritional groups, a one-way analysis of variance (ANOVA) was used. Bonferroni's post hoc analysis with correction was used for multiple between-group comparisons of the continuous variables that showed a significant difference in the overall comparison. For the comparison of categorical variables, Pearson's Chi-square test or Fisher's exact test was used. The overall and risk-free survivals up to 60 days were calculated using the Kaplan-Meier method, and differences were compared using the log-rank test. Cox regression models were performed using multivariate analysis in order to illustrate the relationship between nutritional adequacy and all-cause 60-day mortality. Adjustment was done according to individual risk factors and potential confounders.

Cramer's V with chi-square was used to find out any correlation between different levels of nutritional adequacy and secondary outcomes, and to ascertain the strength of the differences in the variables.

A P value of <0.05 was considered statistically significant. All analyses were done using a statistical software package STATA (version 14.2; StataCorp., College Station, TX, USA).

Ethical principle

This study was conducted in accordance to the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Committee (Kowloon Central/Kowloon East) of Hospital Authority (Ref.: KC/KE-20-0194/ER-4). Individual consent for this retrospective analysis was waived.

Results

Patient characteristics

Table 3 shows the overall and subgroup patient characteristics. A total of 1,232 patients were screened and

Table 3 Patient characteristics

Variable	Total (n=215)	Nutritional subgroup			P value
		Low (n=152)	Medium (n=28)	High (n=35)	
Baseline characteristics					
Age (years)	64.4±14.0	63.4±14.2	61.6±14.0	71.0±11.1	<0 .01†‡
Male sex, n (%)	70 (32.6)	54 (35.5)	7 (25.0)	9 (25.7)	0.39
BMI (kg/m^2)	25.4±4.4	25.6±4.5	24.6±3.3	25.0±4.9	0.47
Severity of illness					
APACHE II score	27.0±8.1	27.7±8.2	26.2±8.7	24.8±7.0	0.14
SOFA score	13.2±3.2	13.6±3.3	12.5±3.1	12.1±2.6	0.02†
No. of days in hospital prior to ICU admission	3.5±6.2	3.0±5.1	4.2±6.1	5.2±9.7	0.14
No. of co-morbidities >2, n (%)	145 (67.4)	103 (67.8)	18 (64.3)	24 (68.6)	0.95
Diabetes mellitus	62 (28.8)	46 (30.3)	8 (28.6)	8 (22.9)	0.75
Hypertension	120 (55.8)	82 (54.0)	14 (50)	24 (68.6)	0.24
IHD/ACS	25 (11.6)	17 (11.2)	4 (14.3)	4(11.4)	0.89
ESRF	11 (5.1)	9 (5.9)	2 (7.1)	0 (0)	0.26
COAD	13 (6.1)	7 (4.6)	2 (7.1)	4 (11.4)	0.23
Malignancy	33 (15.4)	22 (14.5)	3 (10.7)	8 (22.9)	0.38
Cirrhosis	5 (2.3)	4 (2.6)	0 (0)	1 (2.9)	1.00
Nutritional characteristics					
mNUTRIC score	6.5±1.2	6.5±1.2	6.4±1.1	6.7±1.3	0.43
Nutritional adequacy					
Caloric (%)	48.8±21.1	38.7±13.7	63.6±9.9	80.8±14.5	<0.001†‡§
Protein (%)	51.8±25.0	39.7±17.3	71.5±9.5	88.4±13.3	<0.001†‡§
Time from ICU admission to start of nutritional support (hours)	35.1±28.5	40±30.2	28.0±20.8	19.3±17.5	<0.001†
Initial route of nutritional support being enteral, n (%)	169 (78.6)	128 (84.2)	20 (71.4)	21 (60.0)	<0.01†
Presence of major intra-abdominal or GI related factors unfavourable for enteral feeding, n (%)	72 (33.5)	47 (30.9)	8 (28.6)	17 (48.6)	0.12
Presence of GI intolerance, n (%)	76 (35.4)	53 (34.9)	11 (39.3)	12 (34.3)	0.90
Total No. of nutrition evaluable days	8.8±3.0	8.5±3.1	9.5±2.8	9.6±2.5	0.05

†, P<0.05 for the comparison of high versus low nutritional subgroup; ‡, P<0.05 for the comparison of high versus medium nutritional subgroup; §, P<0.05 for the comparison of medium versus low nutritional subgroup. APACHE II, Acute Physiology And Chronic Health Evaluation II; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; ESRF, end stage renal failure; GI, gastrointestinal; ICU, intensive care unit. IHD/ACS, ischemic heart disease/acute coronary syndrome; mNUTRIC, Modified Nutrition Risk in Critically Ill Score; SOFA, sequential organ failure assessment.

215 patients were analysed. Most (70.7%) of the patients belonged to the low nutritional subgroup. Patients with high nutritional adequacy were significantly older (63.4±14.2 *vs.* 61.6±14.0 *vs.* 71.0±11.1 years, P<0.01) while those with low nutritional adequacy were significantly more ill as suggested by the SOFA score (13.6 ± 3.3 *vs.* 12.5±3.1 *vs.* 12.1±2.6, P=0.02) although the absolute difference is small and the APACHE-II scores did not differ significantly among the

Table 4 Mortality and length of stay outcomes

Variable	Total (n=215)	Nutritional subgroup			P value
		Low (n=152)	Medium (n=28)	High (n=35)	
Mortality, n (%)					
ICU	47 (21.9)	33 (21.7)	6 (21.4)	8 (22.9)	1.00
60-day	81 (37.7)	57 (37.5)	11 (39.3)	13 (37.1)	0.98
Length of stay (days)					
ICU	13.4±11.4	12.5±10.8	14.3±12.4	16.3±12.5	0.19
Hospital	38.5±34.8	36.1±33.8	38.2±31.9	49±39.9	0.14

ICU, intensive care unit; LOS, length of stay.

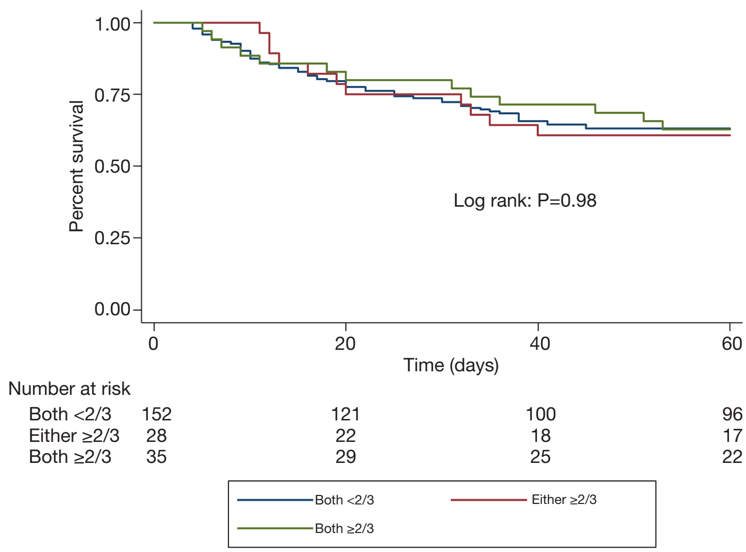

Figure 2 Kaplan-Meier curves for overall and risk-free survival up to 60 days after Intensive Care Unit admission.

three subgroups. Otherwise, the three nutritional subgroups were similar in their baseline characteristics.

As for the nutritional characteristics, the high nutritional subgroup was significantly more likely to receive early nutritional support when compared to low nutritional subgroup (time from ICU admission to start of nutritional support =40±30.2 *vs.* 28.0±20.8 *vs.* 19.3±17.5 hours, P<0.001). The difference in mean time for initiation of artificial nutrition between the two subgroups was about one day. On the other hand, the low nutritional subgroup was significantly more likely to start nutrition via the enteral route when compared to high nutritional subgroup (84.2% *vs.* 71.4 % *vs.* 60%, P<0.01).

Clinical outcomes

Primary and other relevant outcomes

Table 4 shows the mortality and length of stay outcomes, and *Figure 2* illustrates the Kaplan-Meier curves up to 60 days after ICU admission. There was no significant difference in all-cause 60-day mortality among the three nutritional subgroups, with an overall rate of 37.7% (81/215). Other relevant clinical outcomes including ICU mortality (21.9% for all), ICU length of stay (13.4±11.4 days for all) and hospital length of stay (38.5±34.8 days for all) also did not differ among the three nutritional subgroups.

Table 5 shows the results of Cox regression models for

Table 5 Cox regression models for 60-day mortality

Nutritional subgroup	n	60-day mortality, n (%)	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)			
					Model 1†	P value	Model 2‡	P value
Low	152	57 (37.5)	Reference	–	Reference	–	Reference	–
Medium	28	11 (39.3)	1.04 (0.55–1.99)	0.90	1.07 (0.56–2.07)	0.83	1.11 (0.56–2.20)	0.78
High	35	13 (37.1)	0.97 (0.53–1.78)	0.93	1.12 (0.59–2.13)	0.73	1.17 (0.59–2.35)	0.65

†, adjusted for age, BMI, baseline APACHE-II score, presence of at least two co-morbidities, and total No. of nutrition evaluable days; ‡, additionally adjusted for time from ICU admission to start of nutritional support, initial route of nutritional support being enteral, and presence of major intra-abdominal or GI related factors unfavourable for enteral feeding. CI, confidence interval; HR, hazard ratio.

Table 6 Secondary outcomes

Variable	Total (n=215)	Nutritional subgroup			P value	Cramer's V
		Low (n=152)	Medium (n=28)	High (n=35)		
Need of renal support, n (%)	105 (48.8)	82 (53.9)	10 (35.7)	13 (37.1)	0.07	0.16‡
Presence of bloodstream infection, n (%)	83 (38.6)	62 (40.8)	13 (46.4)	8 (22.9)	0.10	0.15‡
Need of hemodynamic support, n (%)	187 (87)	130 (85.5)	24 (85.7)	33 (94.3)	0.37	0.10‡
Need of mechanical ventilation, n (%)	211 (98.1)	148 (97.4)	28 (100)	35 (100)	0.43	0.09
MV for ≥7 days, n (%)	141 (65.6)	89 (58.6)	22 (78.6)	30 (85.7)	<0.005†	0.23§

†, P<0.05 for the comparison of high versus low nutritional subgroup; ‡, weak association; §, moderate association. MV, mechanical ventilation.

all-cause 60-day mortality. Taking the low nutritional subgroup as reference, the hazard ratios of both medium and high nutritional subgroups did not reach statistical significance, whether adjusted or unadjusted.

Secondary outcomes

Table 6 shows the secondary outcomes and their correlation with different levels of nutritional adequacy. Almost all patients required mechanical ventilatory support (98.1%) and a substantial proportion of them required hemodynamic support (87%). Those of high nutritional adequacy were significantly more likely to have prolonged mechanical ventilation (58.6% *vs.* 78.6% *vs.* 85.7%, P<0.005) and the strength of association was moderate (Cramer's V =0.23). There appeared a trend towards a greater need of renal support in the low nutritional subgroup (53.9% *vs.* 35.7% *vs.* 37.1%, P=0.07) although the strength of association was weak (Cramer's V =0.16).

Table 7 shows the results of a post hoc multivariate analysis for prolonged mechanical ventilation. Among the three nutritional subgroups, the adjusted OR for high nutritional adequacy was up to 7.26 and was statistically significant (P=0.03, 95% CI 1.24–42.57). However, the 95% CI was wide suggesting the possibility of a false positive result. A dose-response analysis was technically difficult considering the categorical nature of the variables and the small sample size of the study.

Discussion

In our current study, the all-cause 60-day mortality did not differ significantly among the three nutritional subgroups, and it had no significant association with different levels of nutritional adequacy. The chance of prolonged mechanical ventilation was significantly higher among those of high nutritional support with a moderate strength of association. This is contrary to the common belief that more nutrition is universally better for patients at risk of malnutrition although it echoes with the finding from some of the latest study.

Indeed, current opinion on the dose and timing of nutritional therapy in the critically ill is dividing (1,3,25). Although a number of studies suggest a dose-related beneficial relationship between the amount of calories and/or protein and mortality outcome especially in patients

Table 7 Post hoc multivariate analysis for prolonged mechanical ventilation

Nutritional subgroup	n	MV for ≥7 days, n (%)	Adjusted OR† (95% CI)	P value
Low	152	89 (58.6)	Reference	–
Medium	28	22 (78.6)	2.54 (0.49–13.21)	0.27
High	35	30 (85.7)	7.26 (1.24–42.57)	0.03

†, adjusted for age, BMI, baseline APACHE-II score, presence of at least two co-morbidities, and total No. of nutrition evaluable days, time from ICU admission to start of nutritional support, initial route of nutritional support being enteral, and presence of major intra-abdominal or GI related factors unfavourable for enteral feeding. CI, confidence interval; MV, mechanical ventilation; OR, odds ratio.

of high nutritional risk, all are observational in nature and some are single-centered with small sample sizes (12,13,18,19,21,22). Lee *et al.* prospectively observed within a mixed Asian cohort that when stratified according to nutritional risk, the mortality of patients with high nutritional risk did not significantly differ among those who received both ≥2/3 and either ≥2/3 compared with both <2/3 of energy and protein prescription (26). This was similar to the finding of our study. However, caution should be exercised when interpreting results from a single-centered observational study which in itself has limited generalizability.

Of note, randomized controlled data have demonstrated that near-target caloric intake in a mixed cohort of ICU patients actually do more harm (27), and a J-shaped relationship between caloric and survival in critically ill patients was being proposed (28). Such divergent results may be partly explained by the heterogeneity in the methodological characteristics of nutrition-related research studies. This is further hindered by the fact that even within the same critically ill population, their metabolic response and therefore clinical consequences to exogenous nutrients may be different, not to mention that the nutritional status of an individual patient will likely change as the clinical course unfolds.

This leads to the question of how one metabolically responds to critical illness. A classical description would be the "ebb and flow" phases first proposed by Sir Cuthbertson in year 1942 (29). It is characterized by firstly a hypometabolic and later a hypermetabolic period as a metabolic adaptation to acute physiological insult or stress. As catabolism becomes uncontrolled and resistance to anabolic signals develops, there appears an alteration in the energy expenditure and loss of control of energy substrate use by their availability (8). Besides aggressive treatment of underlying pathologies, energy expenditure-guided nutrition therapy may be helpful in correcting the unwanted metabolic reactions and meeting the energy requirement in midst of the unavoidable mobilization of endogenous substrates (9,30).

The latest European clinical practice guideline described the different stages of critical illness as acute early (ICU day 1 to 2), acute late (ICU day 3 to 7), and recovery phase (ICU day 7 and beyond) (7). In one of the latest enteral nutrition trials randomizing 3,957 patients, augmented energy delivery (about 30 kcal/kg ideal body weight/day) in the early phase of illness was not shown to improve mortality or any secondary clinical outcomes (31) albeit criticism on the possibility of refeeding syndrome in the intervention group. Worse outcome was also found in the early parenteral nutrition group in The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically ill Patients (EPaNIC) trial, the largest nutrition trial in critical illness (32). Notably, initial underfeeding during critical illness is not encouraged by the current literature (33-35). By recruiting patients with at least three nutrition evaluable days and limiting the duration to twelve days after ICU admission, our study effectively covered the initial period of ICU stay where the impact of nutrition therapy caused the greatest concern.

In our cohort of critically ill patients with high baseline nutritional risk, the high nutritional subgroup received almost 90% of goal calories and protein in the early course of ICU stay while the low nutritional subgroup received slightly more than a third. Whether this constitutes a higher risk of refeeding syndrome and therefore a higher prevalence of prolonged mechanical ventilation among those with high nutritional support remains arguable. Since ours is an observational study which made no attempt to influence the practice of nutrition prescription, there were only a limited number of patients of whom the caloric and protein adequacy differed in opposite directions (either was two thirds or more). It would be interesting to study the significance of energy to protein ratio in feeding the critically ill patients as more evidence is pointing towards the importance of protein rather than caloric intake during the acute phase of critical illness (13,36,37).

Since this was a retrospective single-centered observational study, no causal relationship could be established and the generalizability was limited. However, considering that this was the first local study examining the associations between nutritional adequacy and various clinical outcomes particularly focusing on critically ill adult patients of high nutritional risk, it was hypothesis-generating. Considering the non-randomisation nature of this study, potential confounders were included in the regression models to reduce bias. The goal caloric intake for individual patient was estimated by a predictive equation in this study with its inherent inaccuracy (3). At the time when data collection was done for this study, the use of indirect calorimeter was just started in our unit and was only done in selected patients. However, it is worth mentioning that although current guidelines recommend the use of indirect calorimetry to guide nutritional target (4,7), no existing data have shown its use to be more superior when compared to predictive equations in improving clinical outcomes. In conducting future local research, it would be meaningful to study the impact of nutritional therapy at different stages of critical illness (including post-ICU discharge period) with repeated assessment of patient's nutritional requirement using standardized method and to look for the effects (as well as side effects) of nutritional interventions.

Conclusions

This was the first local study in Hong Kong examining the associations between nutritional adequacy and clinical outcomes among critically ill adult patients of high nutritional risk. These patients were often given a low level of nutritional support during the acute phase of ICU stay. The all-cause 60-day mortality did not differ significantly among the three nutritional subgroups, and it had no significant association with different levels of nutritional adequacy. The chance of prolonged mechanical ventilation was significantly higher among those of high nutritional support with a moderate strength of association although the possibility of a false positive result could not be entirely ruled out. Large-scale prospective randomized-controlled studies with energy-expenditure guided nutritional provision are solicited to substantiate the optimal nutritional therapy for this special group of ICU patients.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance to the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Committee (Kowloon Central/Kowloon East) of Hospital Authority (Ref.: KC/KE-20-0194/ER-4). Individual consent for this retrospective analysis was waived.

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