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Non Protein Calorie: Nitrogen Ratio (NPC/N) as a Determinant of Clinical Outcome in Critically Illness

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Abstract

Aim: To test the hypothesis of Non protein Calorie: Nitrogen Ratio (NPC/N) as a determinant of clinical outcome in critical illness.

Methods: All consecutive patients with esophageal cancer admitted to ICU were enrolled.

Collected data:

1) Demographics, age, sex, height, body weight and BMI at admission, CCI, blood loss, and operation time,

2) Laboratory, CRP,

3) Nutritional, energy and protein intake, NPC/N,

4) Outcomes, and the Length of Stay (LOS) in ICU, highest CRP, and total insulin dose.

Analysis 1: All patients were divided into two groups by median values of energy, protein and NPC/N. Outcome parameters were compared between the two groups.

Analysis 2: All patients were divided into two groups by NPC/N < vs. ≥ 150 and other cutoff values. All collected data were compared between the two groups.

Analysis 3: Multiple logistic regression analysis was conducted to draw an Odds Ratio (OR) for each variable to predict a shorter LOS in ICU.

Results: 69 out of 91 patients were analyzed.

Result 1: Subjects with protein intake <0.48 g/kg/day showed a significantly shorter LOS in ICU (4.0 vs. 5.0, p=0.011).

Result 2: Subjects with NPC/N ≥ 150 showed a significantly shorter LOS in ICU (p=0.034).

Result 3: daily protein intake and NPC/N were determinants of clinical outcome (OR=0.005, 0.967, respectively).

Conclusion: We concluded that NPC/N could be identified as a determinant of clinical outcome when it is set at 150. From the analysis of all consecutive patients after esophageal surgery, we conclude that NPC/N can be identified as a determinant of clinical outcome when it is set at 150.

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Introduction

The nutritional supports for the critically ill adult patients in Intensive Care Unit (ICU) have been an issue to discuss. This issue consists of delivered nutrients of timing, route and their composition in term of improving clinical outcomes. There might at least been two modalities dealing nutrition,

energy and protein. First, regarding energy for ICU patients, guideline proposed by Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) (SCCM/A.S.P.E.N.) has stated that 100% of target (25 kcal/kg/day-30 kcal/kg/day) calculated by a simplistic weight-based equation of must be used to determine energy requirement for ICU patients as an expert consensus (A3b: quality of evidence level, very low) [1]. Contrary to this, the guideline written by the European Society for Clinical Nutrition and Metabolism (ESPEN) has recommended that hypocaloric nutrition (below 70% estimated needs) should be preferred for the first week in ICU (Recommendation 19: strong consensus, 95% agreement:) [2]. Among these, one concern is the low evidence of these recommendations. In addition, more importantly in clinical practice, these statements for energy provision seem inconsistent.

Second, moving to protein provision in ICU setting, differently from energy statement, two guidelines above mentioned for protein provision stated similar. For instance, SCCM/A.S.P.E.N. guideline has stated based on weight-based equation that protein requirement is expected to be in the range of 1.2 g/kg to 2.0 g/kg actual body weight per day (C4: quality of evidence, very low). Similarly, ESPEN also recommends that 1.3 g/kg/ day protein equivalent per day can be delivered progressively during critical illness (Recommendation 22: level of evidence, strong consensus (91% agreement)). However, recent meta-analysis study found that two arms with higher *vs.* lower protein intake (1.02 g/kg/day *vs.* 0.67 g/kg/day, respectively) did not show a relationship a mean protein delivery and mortality in ICU (i2=50.18%, p=0.433) [3]. However, these two guidelines added important issues from aspect of clinical practice. The latter, ESPEN guideline carefully added that Randomized Control Trials (RCTs) are less conclusive and they introduce an adverse event of renal failure after increasing dose of protein and that high protein administration does not always improve clinical outcomes [4]. Nevertheless, the former, SCCM/A.S.P.E.N. guideline importantly added that enteral formula are not easily met by provision of routine enteral formulation in which non protein calorie: nitrogen [NPC: N] is higher than needed. More recent two articles showed a more extreme results that less amounts of protein provision were associated with an earlier discharge from ICU and lower mortality at 6-month later [5,6]. From results of reviewing two guidelines, recent meta-analysis and studies seem to recommend extremely opposite of protein provision. As such, from standing point of view to protein provision especially in ICU setting, we hypothesized that NPC/NAS combinational index of energy and protein might be a determinant of clinical outcome, rather than estimating energy or protein intake separately. To test this hypothesis, we studied whether does exist or not an association of NPC/N of nutritional support in ICU with clinical outcomes in patients admitted to ICU after radical surgery of esophageal cancer.

Aim

To test hypothesis that Non Protein Calorie: Nitrogen Ratio (NPC/N) as the determinant of clinical outcome in critically illness.

Method

Patient enrollment

The present study was conducted by retrospective chart review in a single hospital. All consecutive patients with esophageal cancer, who admitted to an Intensive Care Unit (ICU) between 1st January and 31st December 2014 after radical surgery, were enrolled. The exclusion criteria were as the followings: 1) length of stay in ICU<2 days, 2) patients who did not undergo radical surgery, such as endoscopic submucosal and/or mucosal dissection, or palliative operation, 3) missing collected data mentioned below.

Table 1: Demographics of all subjects.

	Total (n=69)
Demographic	
Age, Years	67 (60, 70)
Gender (male, %)	54/69 (78%)
Anthoropometric parameters	
Weight, kg	57.2 (50.5, 64.6)
BMI, Kg/m^2	21.6 (19.4, 23.2)
Com Orbidity	
CCI	0 (0, 1)

IQR: Interquatile Range Data are presented as median and interquatile abbreviation; BMI: Body Mass Index; CCI: Charlson Comorbidity Index

Methods

After all patients were divided into two groups by each median values of nutrition intake described below, primary and secondary outcome parameters were compared between two groups. Approval for the study was obtained from Ethical Committee of Osaka International Cancer Institute (approval number: 1611259187). Given the nature of this study, the requirement for informed consent was considered unnecessary.

Collected data

All collected data from patients were as the follows: 1) Demographics, including age, sex, height, body weight, and Body Mass Index (BMI) measured at admission, Charlson Comorbidity Index (CCI) score as indicator of comorbidities severity (a comorbidities index including hypertension, diabetes, dyslipidemia, cerebrovascular disease, and 15 other diseases), blood loss (ml) and operation time (minutes) as integrity of operative stress, 2) Laboratory parameters, including C-Reactive Protein (CRP) measured during staying in ICU, 3) Nutritional parameters, including daily energy and protein intake during stay in ICU for each patient, and all parameters were expressed in daily average amounts per pre-operative body weight (kcal/kg/day and g/kg/day, respectively). Moreover, to estimate an impact of NPC/N on outcome, NPC/N of each subject was also calculated [7,8]. The details for calculating method of NPC/N was written elsewhere, 4) Outcome parameters, including the length of stay in ICU as the primary outcome, and highest CRP and total insulin doses for each patient during stay in ICU.

Analysis 1

Dividing all patients into two groups by each median value of the following nutritional parameters: daily energy, protein intake and NPC/N during ICU-stay, the primary and secondary outcome parameters were compared between two groups.

Analysis 2

To test hypothesis that cutoff point of NPC/N is a determinant of clinical outcome in patients with post-operative esophageal cancer, all patients were divided into two groups by NPC/N< *vs.* ≥ 150 (125, 140, 160, 175), all collected data were compared between two groups. For instance, when NPC/N set at 150, two groups whose NPC/N<150 *vs.* ≥ 150 showed significant difference in outcome parameter, 150 could be recognized as cutoff point of NPC/N to differentiate patients

Table 2: Comparison of demographics and outcome parameters between two groups according to their NPC/N< *vs.* ≤ NPC: at three different NPC/N (140, 150, 160).

NPC/N	140			150			160		
Group	<140	140 ≤	p	<150	150 ≤	p	<160	160 ≤	p
Subjects number		28	38		30	36			
BMI Kg/m^2	21.6 (19.6, 23.2)	21.4 (19.8, 24.3)	0.716	21.7 (19.8, 23.1)	21.4 (19.8, 24.3)	0.817	21.6 (19.9, 23.1)	21.6 (19.4, 24.4)	0.715
Com Orbidity- CCI	0 (0, 1.25)	0 (0, 1)	0.415	0 (0, 1)	0 (0, 1)	0.427	0 (0, 1)	0 (0, 1)	0.852
Nutrition									
Energy	16.0 (12.8, 19.7)	11.1 (8.7, 15.0)	0.025	17.1 (13.2, 19.6)	12.7 (9.6, 16.2)	0.007	17.2 (13.2, 19.68)	11.6 (9.5, 15.6)	0.001
Protein	0.92 (0.69, 1.00)	0.29 (0.16, 0.40)	0	0.87 (0.68, 0.98)	0.36 (0.17, 0.44)		0.83 (0.68, 0.98)	0.34 (0.17, 0.44)	0
NPC/N	88.5 (73.9, 101.8)	226.9 (201.8, 332.4)	0	98.2 (74.4, 106.1)	206.5 (173.2, 290.3)	0	93.5 (75.0, 112.5)	206.5 (1777.7, 317.1)	0
Primary outcome Length of stay in ICU, days	5.0 (4.0, 6.0)	4.0 (3.0, 4.0)	0.41	5.0 (4.0, 6.0)	4.0 (3.0, 5.0)		5.0 (4.0, 6.0)	4.0 (3.0, 5.0)	0.003
Secondary outcome Highest CRP, mg/dl	13.2 (10.2, 18.4)	14.8 (12.7, 19.1)	0.259	13.9 (10.4, 19.2)	13.7 (12.0, 19.1)	0.671	13.4 (9.9, 19.4)	13.9 (12.5, 18.7)	0.572
Total insulin dose. unit	0	0	0.236	0 (0, 0.75)	0	0.02	0	0	0.044

Data are presented as median and interquatile range (iqr) for continuous variables.
Mann-Whitney U test was used for continuous data.
Abbreviation: BML: Body Mass Index; CCI: Charlson Comorbidity Index

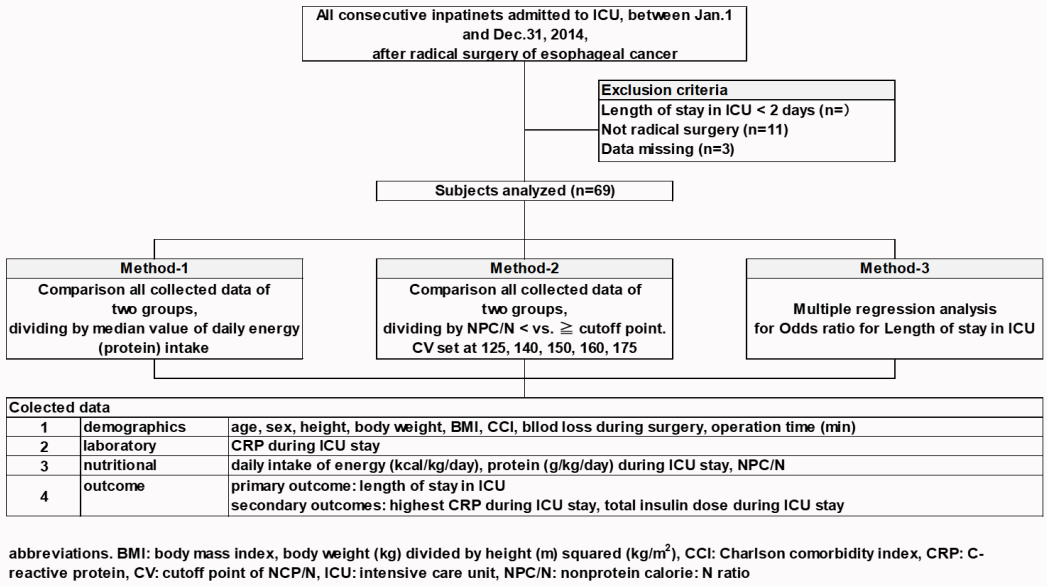

Figure 1: The flow chart of the study.

who could have better outcome and who does not. As such, NPC/N could be utilized as determinant factor of clinical outcome. In this matter, NPC/N ratio analyses were conducted with NPC/N set at 175, 160, 150, 140, 125, or continued until finding cutoff point if necessary.

Analysis 3

Giving a primary outcome parameter shows significant difference, multiple logistic regression analysis was conducted using the length of stay in ICU set as primary outcome as dependent variable to draw Odds Ratio (OR) for each variable, such as daily average energy and protein intake, NPC/N.

Statistical analyses

The outcome parameters in the two groups were divided into different categories and compared using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Odds Ratio (OR) and 95% Confidence Interval (CI) were obtained by multiple logistic regression analysis. All analyses were performed using SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA), and significance was examined at P<0.05.

Results

In total, 91 patients were enrolled. Excluding 22 patients were according to above mentioned exclusion criteria, the remaining 69 patients preceded to further analyses (analysis -1.1, -1.2, - 2 and -3: (Figure 1)). In these analyses, all collected data in two groups was compared. All demographics did not show significant differences. Each median value was as the follows: 14.30 kcal/kg, 0.48 g/kg, and 160, for daily energy, protein, and NPC/N ratio, respectively.

Results -1: Results of analysis-1

Using these cutoff points to divide all subjects, comparing primary

and secondary outcomes in two groups for analysis 1.2 for protein intake analysis, subject with protein intake <0.48 g/kg/day showed significantly shorter LOS than subject with ≥ 0.48 g/kg protein intake (4.0 *vs.* 5.0 days, p=0.011), whereas analysis 1.1 for energy intake did show no significant differences in outcome parameters.

Results -2: Results of analysis-2

When all subjects was divided into two groups with NPC/N setting at 160 and 150, groups whose NPC/N>160 or 150 showed significantly shorter LOS and less amount of insulin dose during their staying in ICU than subjects whose NPC<160 or 150 (4.0 *vs.* 5.0 days, p=0.003: 0.0 *vs.* 0.0 Units of insulin, p=0.044, respectively). Then, to determine cutoff point of NPC/N ratio to predict better outcomes, the additional further comparisons of collected data were continued with NPC/N setting at 140, 130, continuously until significant difference disappears. As the result, NPC/N could be set at 150, because significance was disappeared when NPCN was set at 140 and smaller (Table 1, 2). From these results, when cutoff point of NPC/N set at 150, subjects whose NPC/N ≥ 150 showed significantly shorter length of stay in ICU (p=0.034).

Results -3: Results of analysis-3

A daily protein intake (g/kg/day) and NPC/N were both determinant of clinical outcome, where each odds ratio was 0.005 (0.000–0.185, p=0.004) and 0.967 (0.950–0.984, p=0.000) (Table 3).

Discussion

Non protein Calorie/Nitrogen ratio (NPC/N) as a Determinant of Clinical Outcome in Critically ill patients from our observational results, NPC/N ratio set ≥ 150 seems associated with shorter length of stay in ICU in surgical patients with post-operative esophageal cancer. This cutoff point is very similar to that of ordinary diets, ranging from 150 to 200. This 150 of NPC/N might be able to use a cutoff point to discriminate pat8nets in ICU who have better clinical outcome. In other words, an optimal NPC/N set at 150 or more might be considered to be associated with better clinical outcome, such as shorter stay in ICU. The reason why critical patients with NPC/N ≥ 150is associated with better outcome the higher NPC/N is identical to the following three situations: (1) less nitrogen administration, (2) more NPC, or (3) both simultaneously. In the first situation, less nitrogen might be related fewer occurrences of renal injuries especially in severe stress, including hypotension and lower renal circulation. In the second situation, NPC nutrients involve carbohydrate, sugar and fat. In general, serum cortisol level seems associated with lipolysis in adipose tissues [9]. Contrary to this observation, another reported that enhancing of serum fatty acids level is associated not only with lipolysis in subcutaneous tissues, but with the other several factors, including effect of therapeutic agents, such as nor epinephrine and adrenergic agents [10]. In general, the resulting metabolic stress is characterized by glycolysis, lipolysis, and proteolysis [11]. The matter is which is oxidized more under critically illness, sugar *vs.* lipid. To some extents, there is report that the rate of glucose administration commonly used during critically ill patients does not suppress endogenous glucose production or net protein loss, but markedly stimulates *de novo* lipogenesis and CO_2 production. Increasing the proportion of fat may be beneficial, provided that lipid emulsion has no adverse effects. In this context, fat rather than sugar seems optimal to administer as NPC in critically illness [12]. However, as scientific studies regarding exogenous administered energy-producing nutrients and their oxidization are insufficient to draw definitive conclusions.

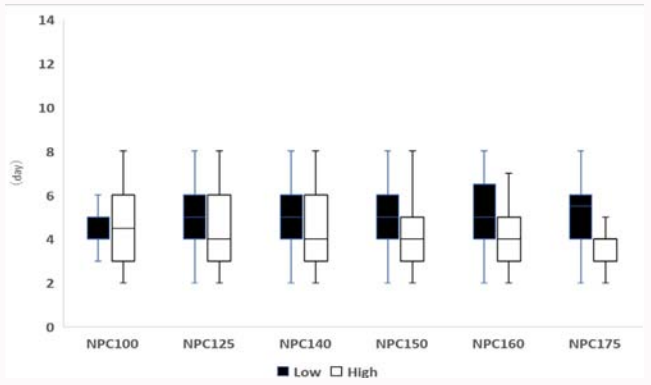

Figure 2: Comparisons of the length of stay in ICU between two groups: NPC < *vs.* ≤ 100, 125,140, 150, 160, and 175. * p<0.05, *vs.* High NPC group.

Table 3: The results of multiple logistic regression analysis to draw Odds Ratio (OD) of shorter length of stay in ICU ≤ 4 days.

	Dependent Variable	
Independent Variable	Adjusted OR (95% CI)	p value
Protein Intake	0.005 (0-0.185)	0.004
NPC/N	0.967(0.950-0.984)	0

X^2

Discriminatory median rate 86.4%

Abbreviations: NPC/N: Non protein calorie/Nitrogen Ratio

Less protein seems associated with better outcome. This might be explained by the phenomenon that normalized amount of protein might insult renal function to lead to renal insufficiency as aforementioned. Summing up energy NPC and protein matters simultaneously, higher NPC/N than 150 could be associated with better outcomes in critically ill settings as the present study showed. Additionally, although patients whose length of stay in ICU did not show more severe surgical stress from operation time and blood loss during surgery, and moreover their BMI were similar, their post-operative reactions to surgical stress might be enhanced more. However, as these factors to explain the reason from the aspects of stress responses including inflammatory cytokine or predisposal status as frailty [13,14], the further additional researches must be necessary to answer.

Much or Less, How much is protein intake associated with better outcome? The present study showed that post-operative esophageal patients managed with daily protein intake <0.48 g/kg of body weight showed a significantly shorted length of stay in ICU after radical surgery. This result might be inversely interpreted that larger amount of protein or nitrogen could be associated with poor outcome in stressed patients with critically illness.

The severely stresses patients have, the more a protein-sparing effect through the stimulation of protein synthesis is expected to occur [15]. However, the clinical outcome is not always consistent and the results seem controversial. Several studies have encourage to administer protein >1.2 g/kg/day to obtain a protein-sparing effect [16], and added a question how much increase protein requirement must be increase with patients in catabolic critical illness [17]. To contrary, most recently published two articles both concluded the same conclusion that lower protein intake in patients in medical ICU showed an earlier discharge from ICU [5,6]. The latter article showed divided ICU patients into septic and non-septic and conclude non-septic patients fed with protein intake <0.8 g/kg/day, compared

with 1.2 g/kg/day during both the first 3 and 4-7 days, showed significantly lower 6-month mortality (OR=0.8, p=0.005: 0.64, p=0.025, respectively) [18]. Similarly to this, the same authors also concluded that patients fed with <0.5 g/kg/day protein during the first 3 days showed significantly high survival rate during 6-month follow-up [19]. An anabolic resistance must also be considered in critically ill catabolic status. Moreover, dietary protein restriction under catabolic disarrangement is reported to associate with autophagy and nitrogen loss acceleration [19]. From these observations, administered protein has possibilities to enhance catabolic changes and lead to raise urea products in circulating blood. Instead cumulative energetic studied as above mentioned; there might be still necessary to study how much and when to administer protein to maximize nutritional effects on outcomes. To answer to these questions, the further large randomized studied must be necessary.

Is enteral route for protein administration optimal under critically ill setting? Another concern is whether energy-producing nutrients administered through enteral route could be utilized as energy sources. If not, as far as enteral route could be utilized after stress insults are setting down, there might be possibility that enterally administered nutrients could not used for energy and protein synthesis. The article regarding a study of protein balance in critically illness might be able to answer this clinical question [20]. The authors observed amino acid dynamics in patients in critically illness using stable-isotope-labeled Phenylalanine (Phe) and tyrosine tracers, with carefully designed and consented from anticipates. Then, they observed that the splanchnic extraction fraction and the availability of dietary Phe in arterial plasma were low. In addition, the authors also added the result that the net protein balance was improved in patients with parenteral amino acid supplement [21]. These observations could be interpreted that enterally administered amino acids seem less available in critically ill setting and that these trends might be improved by parenteral amino acid administration. Additionally, another study, in which the authors also utilized the similar isotope-labeling amino acid methodology, a positive balance for patients in ICU administered through enterally and parenterally and amino acids kinetics. As their results, amino acids given *via* enterally route patients with amino acid supplemented parenterally showed a significant improvement in whole-body net protein balance. Summing up these two studies, we could realize at least the following two notices. First, the enterally administered amino acids could not utilize to achieve a positive net protein balance. Second, parenteral route for amino acid supplementation might have a possibility to achieve a positive protein net balance. The amino acids or protein administration seems essential adding to its amount in critically ill settings.

Strength and Limitations

To our knowledge, this is the first to propose NPC/N as the determinant of the clinical outcome with the observational results. In clinical setting, NPC/N might be re-identified as compositional co-factor with the other nutrients, timing, and nutritional route.

This study warrants several limitations. First, the study design was retrospective and not randomly allocated to enroll subjects. As its effects, relatively large number of subjects was excluded and analyzable number of subjects was limited. Second, the number of subjects was also limited to draw a definitive conclusion. The larger number of subjects must be necessary in further clinical trials. Third, serum amino acid profile has never been measured. To discuss a glutamine deficiency in critically ill status, these profiling seems necessary. Fourth, although enhancing an importance of NPC/N ratio in critically ill settings, its ceiling number or upper limit has not been known because of limited number of subjects. TO make clear whether the ceiling upper limits of NPC/N ratio exist or not, wider range of energy and protein amount intake must be scheduled in prospective study fashion.

Conclusion

From the results of the present study analyzing data of consecutive all patients after esophageal surgery, it is concluded that NPC/N could be identified as the determinant of clinical outcome when set at 150.

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