Clinical Nutrition

Early Enteral Feeding with High-Protein Formulas Improves APACHE II and NUTRIC Score Compared to Oligomeric Formula and 5% Dextrose Solution

--Manuscript Draft--

Manuscript Number:	
Article Type:	Randomized Control Trials
Keywords:	critical ill; early enteral feeding; high-protein formula
Corresponding Author:	Agussalim Bukhari, M.D., M.Med., Ph.D. Universitas Hasanuddin Fakultas Kedokteran Makassar, South Sulawesi INDONESIA
First Author:	Agussalim Bukhari, M.D., M.Med., Ph.D.
Order of Authors:	Agussalim Bukhari, M.D., M.Med., Ph.D.
	Nurpudji A. Taslim, M.D., M.P.H., Dr.
	Suryani As'ad, M.D., M.Sc., Dr.
	Haerani Rasyid, M.D., M.H., Dr.
	Faisal Muchtar, M.D., M.H.
	Aminuddin Aminuddin, M.D., M.Nut.&Diet., Ph.D
	Umrayani Umrayani, M.D.
	Rosdiana Syahruddin, M.D.
	Christina Rusli, M.D.
Abstract:	Background & aims Critically ill patients are physiologically unstable, often have complex hypermetabolic responses to trauma. These patients are facing a high risk of death, multi-organ failure, and prolonged ventilator use. Nutrition is one of therapy for critical illness, however, patients often experience malnutrition caused by disease severity, delays in feeding, and miscalculation of calorie needs. This study aims to evaluate clinical improvement in critically ill participants that were given 3 kinds of early enteral feeding formulas, which were control (5% Dextrose), high-protein polymeric formula, and oligomeric formula.Methods A total of 55 critically ill participants admitted to the intensive care unit (ICU) between October 2017 – March 2018 and assigned in this controlled trial. Early enteral feeding was initiated within 24-48 hours after ICU admission. Each enteral feeding group was categorized to traumatic brain injury (TBI) or non-TBI. The primary endpoints were changes in white blood cell count, Acute Physiologic and Chronic Health Evaluation (APACHE) II score, and Nutrition Risk in the Critically Ill (NUTRIC) score from baseline to day 3.Results Baseline characteristics were similar between control (n=22), high-protein polymeric (n=19), and oligomeric (n=14) groups. There were significant decreases for white blood cell count (13262.5±6963.51 to 11687.5±7420.92; p=0.041), APACHE II score (17.33±3.31 to 13.83±1.95; p=0.007), and NUTRIC scores changes (3.08±1.44 to 1.92±1.00; p=0.022) in non-TBI participants receiving high-protein polymeric compared those in control or oligomeric participants. But there is no significant clinical improvement amongst the groups in TBI participants. Conclusions. Non-TBI participants benefit from early enteral feeding with high-protein polymeric formula.
Opposed Reviewers:	

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-4
	2b	Specific objectives or hypotheses	2-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5-6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	17
	13b	For each group, losses and exclusions after randomisation, together with reasons	17
Recruitment	14a	Dates defining the periods of recruitment and follow-up	17
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17-23
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	24-27
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Manuscript

Click here to access/download
ICMJE Conflict of Interest
coi_disclosure Agussalim Bukhari.pdf

Early Enteral Feeding with High-Protein Formulas Improves APACHE II and NUTRIC Score Compared to Oligomeric Formula and 5% Dextrose Solution

Agussalim Bukhari[1], Nurpudji A. Taslim[1], Suryani As'ad[1], Haerani Rasyid[1,2], Aminuddin[1], Faisal Muchtar[3], Christina Rusli[4], Rosdiana R.[4], and Umrayani[4]

[1] *Department of Nutritional Sciences, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[2] *Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[3] *Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[4] *Clinical Nutrition Specialist Program, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

Address correspondence to:

Agussalim Bukhari

Department of Nutritional Science

Faculty of Medicine, Hasanuddin University

5th floor, Jl. Perintis Kemerdekaan Km 11

Makassar 90245

South Sulawesi, Indonesia

Telephone: +62 812-2570-4670

Email: agussalim.bukhari@med.unhas.ac.id

Background & aims. Critically ill patients are physiologically unstable, often have complex hypermetabolic responses to trauma. These patients are facing a high risk of death, multi-organ failure, and prolonged ventilator use. Nutrition is one of therapy for critical illness, however, patients often experience malnutrition caused by disease severity, delays in feeding, and miscalculation of calorie needs. This study aims to evaluate clinical improvement in critically ill participants that were given 3 kinds of early enteral feeding formulas, which were control (5% Dextrose), high-protein polymeric formula, and oligomeric formula.

Methods. A total of 55 critically ill participants admitted to the intensive care unit (ICU) between October 2017 – March 2018 and assigned in this controlled trial. Early enteral feeding was initiated within 24-48 hours after ICU admission. Each enteral feeding group was categorized to traumatic brain injury (TBI) or non-TBI. The primary endpoints were changes in white blood cell count, Acute Physiologic and Chronic Health Evaluation (APACHE) II score, and Nutrition Risk in the Critically Ill (NUTRIC) score from baseline to day 3.

Results. Baseline characteristics were similar between control (n=22), high-protein polymeric (n=19), and oligomeric (n=14) groups. There were significant decreases for white blood cell count (13262.5±6963.51 to 11687.5±7420.92; p=0.041), APACHE II score (17.33±3.31 to 13.83±1.95; p=0.007), and NUTRIC scores changes (3.08±1.44 to 1.92±1.00; p=0.022) in non-TBI participants receiving high-protein polymeric compared those in control or oligomeric participants. But there is no significant clinical improvement amongst the groups in TBI participants. ***Conclusions***. Non-TBI participants benefit from early enteral feeding with high-protein polymeric formula.

Keywords critical ill, early enteral feeding, high-protein formula

INTRODUCTION

Notwithstanding under "proper" hospital care, approximately 40% of patients admitted to the hospital are malnourished at admission. Malnutrition is correlated with many adverse outcomes, such as immune system depression, diminished healing process, muscle wasting, prolonged length of stay, increased morbidity and mortality which lead to higher early re-admission rates and healthcare expenses. Critically ill patients often have various degrees of inflammation which results in an increased in energy expenditure and protein catabolism, but reduced energy and protein intake. Regardless of the patient's pre-existing malnutrition, every patient has a highly variable metabolic and immune response to injury or illness which might be attenuated by proper nutrition therapy (1–8).

Enteral nutrition (EN) is one approach to modulating inflammation and coagulation in critically ill patients, which has been correlated with beneficial outcomes such as reduced infectious complications, fewer organ failures, and reduced mortality. Although there is a general acceptance of early EN, only a few studies have approached the specific timing, volume, and formula type of tube feeds in critically ill patients population and fewer still have studied the effects on inflammation (8–10).

The expert committee of ESPEN suggested that hemodynamically stable critically ill patients should be fed early within 24-48 hours of patient's admission using an appropriate amount of feed, but there are no data showing improvement in relevant outcome parameters using early EN in these patients. This means a better understanding of managing inflammation in ICU patients could provide better-targeted care and help prevent malnutrition, morbidity, and mortality (3,11).

Compromised GI tract is one of inhibiting factors in critically ill patients which makes them generally susceptible to over-feeding and under-feeding (12,13). Such conditions make the patients to be fasted or given 5% dextrose for quite a long time, hence pointing to energy deficiency in these patients.

Many enteral formulations exist for the nourishment of the malnourished or at-risk patients, but most studies have failed to recognize their benefit. Nutritional guidelines suggest using polymeric formula when initiating enteral feeding in critically ill patients. In most cases, the given amount of protein is not adequate, although several studies have shown that low protein intakes can be related to adverse clinical outcomes (11,12,14,15).

There is limited evidence for applying oligomeric formulas in the ICU. This formula is slightly more expensive than polymeric formula, but data indicate that they are better tolerated by compromised GI tracts patients because these peptides are water-soluble and readily absorbed by the intestine and metabolized by the liver. Because it is partially digested, greater nutrient delivery may be obtained and reduced the degree of regurgitation, gastric emptying times, and gagging while improving tolerance. As a result, they have fewer gastrointestinal complications, improved visceral protein levels, and decreased rates of mortality (15–17).

There is no specific ICU nutritional score has been validated thus far. NUTRIC score was associated with mortality and nutritional support might lower mortality in patients with a high NUTRIC score (>5) (14,18).

We conducted this trial to compare the effects of different early enteral feeding formulas on inflammatory markers, NUTRIC score, length of stay, and mortality in critically ill patients.

MATERIALS AND METHODS

Study population and design.

This was a controlled clinical trial, conducted in the adult ICU participants of Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from October 2017 to March 2018. This study included 55 participants aged older than 18 years and with stable hemodynamic values. The exclusion criteria were gastrointestinal resection, contraindications for enteral feeding, history of diabetes or chronic kidney disease, receiving parenteral nutrition, severe intolerance for enteral nutrition or formula, gastric residual volume > 250 ml/4 hours. Informed consent was obtained from participants family members.

Participants were consecutively assigned to either the control group receiving dextrose 5%, high-protein polymeric formula (Peptisol®) group (22.4% protein from total calorie), or the oligomeric (Peptamen®) formula group (16.2% protein from total calorie). All participants were initiated on enteral feeding, as early as possible (within 24-48 hours) after intensive care unit (ICU) admission. Participants in the control group were given 5% dextrose as a starting regimen and were continued with other types of feeding regimen based on anesthesiologist instruction. Participants in the high-protein polymeric diet or oligomeric enteral nutrition group were given a feeding regimen which administered as boluses via a nasogastric tube. A total of 5 aliquots were administered at 4-hourly intervals in a daily feeding period of 24 hours, with the participant positioned 30° head-up.

Critically ill participants who completed the intervention period were analyzed based on the diagnoses categories of traumatic brain injury (TBI) and non-TBI.

Anthropometry and Laboratory Measurements.

Upon first 24 hours ICU admission, anthropometric data were collected including age, gender, height (participant in the supine position), ideal body weight (IBW), Mid-Upper-Arm Circumference (MUAC), and primary admission diagnosis (TBI or non-TBI). Severity-of-illness scores and laboratory assessment were conducted on 24 hour from admission and on day 3, which included: biochemical variables such as platelets, white blood cells, lymphocytes, serum creatinine levels, blood urea nitrogen (BUN) levels, albumin, serum potassium levels, serum sodium levels, serum pH, partial pressure of carbon dioxide, and partial pressure of oxygen (PO2), Acute Physiology and Chronic Health Evaluation II score (APACHE II score), Sequential Organ Failure Assessment score (SOFA score), Nutrition Risk in the Critically Ill score (NUTRIC score).

Calculation of nutritional goals and protein intake.

The daily calorie and protein prescriptions were calculated from standard recommendations (calories 25-30 kcal/kg/d, proteins 1.2-2 g/kg/d). A meticulous record of the calories and protein of intake was maintained for 3 days follow up.

Study end points.

Our primary outcomes were changes in laboratory values and nutritional indicators from baseline to day 3.

Statistical analysis.

The statistical package SPSS version 24 was used for the statistical analysis. All values are expressed as the means ± standard deviation. The changes between pre and post intervention were assessed using paired *t*-test or Wilcoxon signed-rank test. Differences of mean values between the 3 groups were compared using the Anova or Kruskal-Wallis test. A *p*-value <0.05 was considered statistically significant. To interpret the magnitude of effect, Cohen's d effect sizes (±95% confidence limits) were estimated using a purpose-built spreadsheet, with effect size thresholds set at <0.20, >0.50, >0.80, >1.20, >2.0 for trivial small, moderate, large, very large, huge, respectively.

The study was approved by the Faculty of Medicine, Hasanuddin University Ethics Committee.

RESULTS

The anthropometric profile and baseline characteristics of the study population are depicted in Table 1 and Table 2. During the study period, we screened 411 participants who were admitted to the ICU, 298 participants were excluded from our trial mostly due to participant's mortality. A total of 113 participants included in our trial were randomly assigned to either the control (5% dextrose), high-protein polymeric or oligomeric groups. We also separated our participants based on their diagnosis, which were Traumatic Brain Injury (TBI) and non-TBI participants. Participants in the control group were given 5% dextrose as a starting feeding regimen and were continued with other types of feeding regimen based on anesthesiologist's instruction. Whereas participants in the high-protein polymeric group or oligomeric group were given a total of 5 aliquots feeding regimen via a nasogastric tube, which were administered at 4-hourly intervals. We had 48 drop-out participants during our 3 days follow-up and a total of 55 participants were included in our statistical analysis comprising both male (53%) and female (47%) subjects. Twenty-two participants were included in the control group (5 participants were diagnosed with TBI and 17 participants were diagnosed with non-TBI), 19 participants in the high-protein polymeric formula group (7 participants were diagnosed with TBI and 12 participants were diagnosed with non-TBI), and 14 participants in the oligomeric formula group (4 participants were diagnosed with TBI and 10 participants were diagnosed with non-TBI).

At the time of ICU admission, the participants which were in the condition of malnutrition based on the TLC examination (19). In the TBI group were 6 participants in the category of severe malnutrition and 11 participants in the category of mild malnutrition. Whereas in the non-TBI group, 19 participants were included in the category of severe malnutrition and 19 participants were included in the category of mild malnutrition. Based on patient's MUAC examination, we divided our participants in the TBI group as 2 participants were included in the category of severe malnutrition, 1 patient was included in the category of moderate malnutrition, 4 participants were included in the category of mild malnutrition, and 10 participants were included in the category of good nutrition. In the group diagnosed with non-TBI 1 participant was in the category of severe malnutrition, 2 participants were in the category of moderate malnutrition, 7 participants were in the category of mild malnutrition, and 28 participants were included in the category of good nutrition.

Before we began the intervention, a risk assessment for malnutrition was conducted to our participants based on the NUTRIC score for each participant in the TBI or non-TBI groups. The participants in this study were more dominated by participants with NUTRIC score 0-5, and hence it was included in the category of mild risk of malnutrition. Whereas for the result for serum albumin levels before the intervention, we found that the majority of our patients were in hypoalbuminemia state. Most of the participants did not have any comorbid or only had 1 comorbid, both in the TBI and non-TBI groups.

There were several variations in the duration of administration of 5% dextrose that we observed in our study's participants. In the TBI group, there were 2 participants who were given 5% dextrose for 1 day, 1 participant who was given 5% Dextrose for 2 days, and 2 participants who were given 5% Dextrose during the 3 days of our observation in the ICU. Whereas in the non-TBI group there were 2 participants who were given regular food from the beginning of entry into the ICU, 10 participants were given 5% dextrose for 1 day, 2 participants were given 5% dextrose for 2 days, and 3 participants were given 5% dextrose for 3 days.

Both of TBI and non-TBI groups who were given early enteral feeding with 5% Dextrose obtained significantly lowest amount of energy and protein intake compared to the high-protein polymeric formula group and the oligomeric formula group (Table 3, Fig. 2, Fig. 3, Fig. 4, and Fig. 5). In contrast, there was no significant different in energy intake between the high-protein polymeric and the oligomeric formula groups. However, protein intake was higher in high-protein polymeric formula group than those in oligomeric and control groups (Table 3, Fig. 4, and Fig. 5)

There was no difference in mean white blood cells between pre and post-intervention for each TBI group (Table 4). Whereas for the non-TBI group, the result showed that there was a significant decrease (1575±10320,86) in white blood cells between the pre intervention and post intervention in the non-TBI group who received the intervention of high-protein polymeric formulas with Cohen's d effect sizes = 3.40 (huge).

The effect of early enteral feeding on the change in APACHE II score showed that there was no significant decrease between the pre and post-intervention in the TBI group that given 5% Dextrose (1,2±3,90) and high-protein polymeric formula (0,14±4,49), but there was a significant increase in the group given an oligomeric formula (3,2±2,49) with Cohen's d effect sizes = 1.4 (very large). In the non-TBI group, it can be interpreted that there was no significant difference in mean APACHE II score between the pre and post intervention in the control (0,59±6,61) and the oligomeric formula (1,67±3,57) group, but there was a significant decrease (3,5±3,66) in the APACHE II score in the group given high-protein polymeric formula with Cohen's d effect sizes = 2.5 (huge) (Table 4).

The results of statistical tests for the TBI group conducted to assess the effect of early enteral feeding on changes in NUTRIC score revealed no significant difference in NUTRIC scores between pre and post intervention for all groups. On the other hand, there was no significant difference in NUTRIC score between pre and post-intervention in the non-TBI group who received 5% Dextrose (0,29± 1,69) and oligomeric formula (0,22± 1,39) intervention, but there was a significant decrease (1,17± 1,40) in NUTRIC scores between pre and post in the non-TBI group who received high-protein polymeric formula interventions with Cohen's d effect sizes = 2.6 (huge) (Table 4).

TBI participants who received high-protein polymeric formula and control groups in the non-TBI participants had the shortest ICU length of stay and hospital length of stay (Table 5). There was no significant difference in mortality percentage between TBI and non-TBI groups (Table 6)

DISCUSSION

The definition of energy requirements is the amounts of macronutrients and micronutrients which are needed to balance energy expenditure. It is used to maintain reserve, normal metabolic and physiologic functions. Nutritional care in the intensive care unit (ICU) poses a challenge to the clinicians because the patient manifest hypermetabolism, proteolysis with nitrogen loss and accelerated gluconeogenesis and glucose utilization. The degree of metabolic response to assault depends on the length and severity of insult and is mediated through the release of cytokines and counterregulatory hormones. Other factors that influence metabolic needs during acute illness are mechanical ventilation, administration of vasoactive or sedative agents, type of disease, the severity of illness, nutritional state before ICU admission, and comorbidities of the patient (20).

Guidelines recommend to give 20–25 kcal/kg/day in the acute phase and 25–30 kcal/kg/day in the recovery phase for most critically ill patient. Protein requirements are higher than normal due to loss of total body protein, which is inevitable in the first days of ICU, even with an aggressive nutritional approach, primarily due to the catabolism of muscle. For non-previously malnourished patient, it is recommended to provide 0.20–0.25 g/ kg/day of nitrogen (1.3–1.5 g proteins/kg ideal body weight/day or 1.2–2.0 g/ kg actual body weight/day) and it can be increased to 0.35 g/kg/day (2.2 g/kg ideal body weight/day) of nitrogen in case of previous malnutrition or significant catabolism (20,21). Although early enteral nutrition in critically ill patients with clear liquid diet (5% dextrose) as their initiation food has been used, more recent guidelines recommended the use of full liquid diet (22).

Head-injured patient frequently have increases in metabolic rate and protein catabolism that elevate nutritional needs. Energy expenditure may increase until 200 % from normal values but factors such as delayed gastric emptying, interruptions to feeding due to fasting for medical procedures, and accidental removal of feeding tubes prevent the provision of adequate nutrition. This induce up to 30 % loss of body weight and signs of malnutrition in about 2/3 of patients two months after hospital admission (23–25). In TBI patients, the nutrition goals were to reach 35 – 45 calories/kilogram and a protein intake of 2 – 2.5 grams/kilogram on day one or as soon as possible. Adequate calories are required to prevent malnutrition and to improve healing and recovery. The brain functions as the regulator for metabolic activity leads to a complex milieu of metabolic alterations in TBI consisting of hormonal changes, aberrant cellular metabolism, and a vigorous cerebral and systemic inflammatory response in an effort to liberate substrate for injured cell metabolism. The degree of the hypermetabolic state is equal to the severity of injury and motor dysfunction (23,26). In our study, there are some expected clinical effects in the non-TBI group due to the more appropriate nutritional therapy accomplishment which helps to decrease the inflammation process, especially in the group which was given high-protein polymeric formula. The results of this study also found that the non-TBI group that did not receive appropriate therapy (control group) had an increased risk of malnutrition.

In the ICU, complete blood count, various biochemical tests, and inflammatory markers are a routine test which performed on patient upon their admission. A follow-up test is generally coordinated based on the patient's clinical characteristics and the underlying disease. (25) Thrombocytopenia is one of the most common laboratory abnormalities in critically ill patient, with the incidence ranging from 13-60%. It can be a result of increased platelet destruction, hemodilution process, platelet sequestration, or decreased production. Many previous studies have reported that thrombocytopenia in ICU is associated with prolonged hospital stay and reduced survival. APACHE II score which is the most commonly used prognostic score in ICU patient does not include platelet count and albumin levels (27). The platelet counts and lymphocyte count are parts of complete blood count (CBC) analysis. Platelet-to-lymphocyte ratio (PLR) can be used as an inflammatory marker. It has been found to be predictive of the prognoses of patient with diverse inflammatory and ischemic conditions, such as various cardiovascular diseases, and chronic inflammatory disease, and tumors. A positive monotonic association between a high PLR and a poor prognosis for these diseases has been reported. Significance of PLR examination has also been developed for inflammatory status in critically ill patient. It does not require additional tests or costs as they are calculated from the hemogram, which makes it cost-effective and easy to be applied to virtually all patient (28–32).

In both TBI and non-TBI groups, we observed that there was a relationship between some inflammatory markers (serum albumin levels, IL-6, and PLR). Albumin serum level is inversely proportional to the results of IL-6 and PLR. However, due to the limited number of samples in this study, further research is needed. To our knowledge, this is the first study to examine the relationship of PLR with intervention of early enteral feeding. Therefore, further research is still needed to assess the correlation between PLR and food intake in critically ill patient.

The results of the non-TBI group study were similar to those in respiratory ICU patient conducted in India. The enteral nutrition was initiated within the first 24- 48 hours following the admission and was advanced toward a goal over the next 48-72 hours. Their goals for a daily basis were 25%, 50% 75%, and 100%. They used both commercial and home-based formulas. The mortality rate was improved significantly from a 25% mortality rate to a 15% mortality rate APACHE score (33). This finding confirms that adequate nutritional support at the right time not only reduces the participant's length of stay, ventilator support days but also improves the overall nutritional status of the patient. Proper nutrition also has proven to reduce the mortality risk of patient (34).

In contrast to the non-TBI group, there was an increasing tendency of the NUTRIC score for the TBI group after feeding administration, which is different from the existing literature results (35). TBI group tended to have higher energy and protein needs than the non-TBI group, hence calorie and protein achievement in this group was lower.

The limitations of this study is that the calculation of calorie need was based on weight estimation, and not indirect calorimetry as a gold standard. We also did not assess the adequacy of protein intake using the more precise method of urine urea nitrogen. Observation time was limited due to participant's short ICU's length of stay.

In conclusion, non-TBI patient benefit from high-protein polymeric early enteral feeding than oligomeric or 5% Dextrose. By given this formula, the patient had decreased of white blood cells count, APACHE II score, and NUTRIC score.

Acknowledgments

We are indebted to the patient who participated in this study and to the intensive care unit personnel. We also would like to express our appreciation for Peptamen® provided by Nestle. Gratitude is extended to the Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

Statement of authorship

A.B., N.A.T., S.A., H.R., A., F.M. developed the study design and strategy of the research project. AB was the lead study physician and contributed together with C.R., U., and R.R. to the data acquisition and analysis. A.B., N.A.T., S.A., H.R., A., F.M., C.R., R.R., and U. were involved in interpretation of the data. A.B. drafted the manuscript and S.A., H.R., A., and F.M. critically revised it.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this paper. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this publication.

Funding sources

This study was partially funded by Institute of Research and Community Service, Hasanuddin University, Makassar, Indonesia and the Indonesian Ministry of Research, Technology, and Higher Education under WCU Program managed by Institut Teknologi Bandung.

REFERENCES

1. Chase C. Hansen MBA SDM. Nutrition in the intensive care unit. Southwest Respir Crit Care Chronicles [Internet]. 2015;3(10):10–6. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-0032871676&partnerID=40&md5=5b1a6add87924fb361ae915e3627575d
2. Sharma K, Mogensen KM, Robinson MK. Pathophysiology of Critical Illness and Role of Nutrition Pathophysiology of Critical Illness. Nutr Clin Pract. 2019;34(1):12–22.
3. Mohammad S, Mousavi H, Ostadrahimi A, Safaiyan A, Hashemzadeh S, Salehpour F. Effects of four different enteral feeding methods on tumor Necrosis Factor- α (TNF- α) and high sensitive C-Reactive Protein (hs-CRP) in critically Ill Patients : double blinded , randomized controlled trial. Prog Nutr 2016; 2016;18(3):236–41.
4. Padilla PF, Martínez G, Vernooij RW, Urrútia G, Figuls MR i, Cosp XB. Early versus delayed

enteral nutrition support for critically ill adults (Protocol). 2016;(9).

5. Oliveira NS, Caruso L, Bergamaschi DP, Cartolano F de C, Soriano FG. Impact of the adequacy of energy intake on intensive care unit mortality in patients receiving enteral nutrition. Rev Bras Ter Intensiva. 2011;23(2):183–9.
6. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: Prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health. 2011;8(2):514–27.
7. Bhurayanontachai R, Sa-nguansai S. Change of serum prealbumin levels and serum protein markers between egg white powder and casein protein additives in standard enteral feeding formulas in critically ill patients with acute respiratory failure. J Intensive Care [Internet]. 2016;4(32):1–8. Available from: http://dx.doi.org/10.1186/s40560-016-0157-0
8. Hegazi RA, Wischmeyer PE. Clinical review: Optimizing enteral nutrition for critically ill patients--a simple data-driven formula. Crit Care [Internet]. 2011 [cited 2018 Aug 7];15(6):234. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22136305
9. Bastarache JA, Ware LB, Girard TD, Wheeler AP, Rice TW. Markers of Inflammation and Coagulation may be Modulated by Enteral Feeding Strategy. JPEN J Parenter Enter Nutr. 2012;36(6):732–40.
10. Fremont RD, Rice TW. How soon should we start interventional feeding in the ICU? Curr Opin Gastroenterol [Internet]. 2014 [cited 2017 Sep 8];30(2):178–81. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4006101&tool=pmcentrez&rendertype=abstract
11. Ogasawara T, Matsuda S, Kato S, Tanaka K, Yano T, Marui S, et al. Early Enteral Nutrition Using Oligomeric Formula in Mechanically Ventilated , Critically Ill Patients : A Randomized Control Trial. J Hum Nutr food Sci. 2014;2:1–5.
12. Hasanloei MAV, Vahabzadeh D, Shargh A, Atmani A, Osalou RA. Clinical Nutrition ESPEN Original article A prospective study of energy and protein intakes in critically ill patients. Clin Nutr ESPEN [Internet]. 2018;23:162–6. Available from: https://doi.org/10.1016/j.clnesp.2017.10.007

13. Curry AS, Chadda S, Danel A, Nguyen DL. Early introduction of a semi-elemental formula may be cost saving compared to a polymeric formula among critically ill patients requiring enteral nutrition : a cohort cost – consequence model. Clin Outcomes Res. 2018;10:293–300.
14. Tignanelli CJ, Cherry-Bukowiec J. Hospital Based Nutrition Support : A Review of the Latest Evidence. J Clin Nutr Diet. 2017;3(3):22.
15. Sioson MS, Martindale R, Abayadeera A, Abouchaleh N, Aditianingsih D, Bhurayanontachai R, et al. Clinical Nutrition ESPEN Nutrition therapy for critically ill patients across the Asia Pacific and Middle East regions : A consensus statement. Clin Nutr ESPEN [Internet]. 2018;24:156–64. Available from: https://doi.org/10.1016/j.clnesp.2017.11.008
16. Alexander DD, Bylsma LC, Elkayam L, Nguyen DL, Alexander DD, Bylsma LC, et al. Nutritional and health benefits of semi-elemental diets : A comprehensive summary of the literature. World J Gastrointest Pharmacol Ther. 2016;7(2):306–19.
17. Kumpf VJ, Aguilar-nascimento JE De, Graf JID, Hall AM, Mckeever L, Steiger E, et al. ASPEN-FELANPE Clinical Guidelines : Nutrition Support of Adult Patients With Enterocutaneous Fistula. J Parenter Enter Nutr. 2016;20(10).
18. Singer P, Reintam A, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr [Internet]. 2019;38(1):48–79. Available from: https://doi.org/10.1016/j.clnu.2018.08.037
19. Cereda E, Pusani C, Limonta D, Vanotti A. The Association of Geriatric Nutritional Risk Index and Total Lymphocyte Count with Short-Term Nutrition-Related Complications in Institutionalised Elderly. J Am Coll Nutr. 2008;27(3):406–13.
20. Ichai C, Quintard H, Orban J-C. Metabolic Disorders and Critically Ill Patients From Pathophysiology to Treatment. Springer International Publishing AG; 2018.
21. 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: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enter Nutr. 2016;40(2):159–211.

22. Padar M, Uusvel G, Starkopf L, Starkopf J, Reintam Blaser A. Implementation of enteral feeding protocol in an intensive care unit: Before-and-after study. World J Crit Care Med [Internet]. 2017;6(1):56. Available from: http://www.wjgnet.com/2220-3141/full/v6/i1/56.htm

23. Sakine Mazaherpur, Khatony A, Abdi A, Pasdar Y, Najafi F. The Effect of Continuous Enteral Nutrition on Nutrition Indices, Compared to the Intermittent and Combination Enteral Nutrition in Traumatic Brain Injury Patients. J Clin Diagnostic Res [Internet]. 2016;10(10):JC01–5. Available from: http://jcdr.net/article_fulltext.asp?issn=0973-709x&year=2016&volume=10&issue=10&page=JC01&issn=0973-709x&id=8625

24. Chapple LS, Chapman MJ, Lange K, Deane AM, Heyland DK. Nutrition support practices in critically ill head-injured patients: a global perspective. Crit Care [Internet]. 2016;20(1):6. Available from: http://ccforum.com/content/20/1/6

25. Masha'al DA. The Change in Nutritional Status in Traumatic Brain Injury Patients : A Retrospective Descriptive Study. University of South Florida; 2016.

26. Metzger K. Nutrition Therapy for Patients with Traumatic Brain Injury in the Military. IomEdu [Internet]. 2009;1–7. Available from: http://www.iom.edu/~/media/Files/Activity Files/Nutrition/TBINutrition/Metzger 12-17-10 PrePub.pdf

27. Yildiz A, Yigit A, Ramazan A. The Impact of Nutritional Status and Complete Blood Count Parameters on Clinical Outcome in Geriatric Critically Ill Patients. J Clin Med Res. 2018;10(7):588–92.

28. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol [Internet]. 2015;(June 2012):606–13. Available from: http://www.gnresearch.org/doi/10.5935/abc.20150126

29. Liu WY, Lin SG, Wang LR, Fang CC, Lin YQ, Braddock M, et al. Platelet-To-lymphocyte ratio: A novel prognostic factor for prediction of 90-day outcomes in critically ill patients with diabetic ketoacidosis. Med (United States). 2016;95(4):1–7.

30. Zheng CF, Liu WY, Zeng FF, Zheng MH, Shi HY, Zhou Y, et al. Prognostic value of platelet-

to-lymphocyte ratios among critically ill patients with acute kidney injury. Crit Care. 2017;21(1):1–11.

31. Yildiz A, Yigit A, R. A, Benli. The prognostic role of platelet to lymphocyte ratio and mean platelet volume in critically ill patients. Eur Rev Med Pharmacol Sci [Internet]. 2018;22(8):2246–52. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L622016164%0Ahttp://dx.doi.org/10.26355/eurrev-201804-14811

32. Alexander N. Reference Values of Neutrophil-Lymphocyte Ratio , Platelet-Lymphocyte Ratio and Mean Platelet Volume in Healthy Adults in North Central. J Blood Lymph. 2016;6(1):1–4.

33. Mary Larancia A, Gayathri G, Hemamalini AJ. Adequacy of Nutritional Support to Critically Ill Patients Requiring Ventilator Support in Intensive Care Unit and Its Correlation with Outcomes. Int J Food Nutr Sci. 2013;2(3).

34. Wang W-N, Yang M-F, Wang C-Y, Hsu C-Y, Lee B-J, Fu P-K. Optimal Time and Target for Evaluating Energy Delivery after Adjuvant Feeding with Small Bowel Enteral Nutrition in Critically Ill Patients at High Nutrition Risk. Nutrients. 2019;11(645):1–10.

35. 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 [Internet]. 2011;15:R268. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3388687&tool=pmcentrez&rendertype=abstract

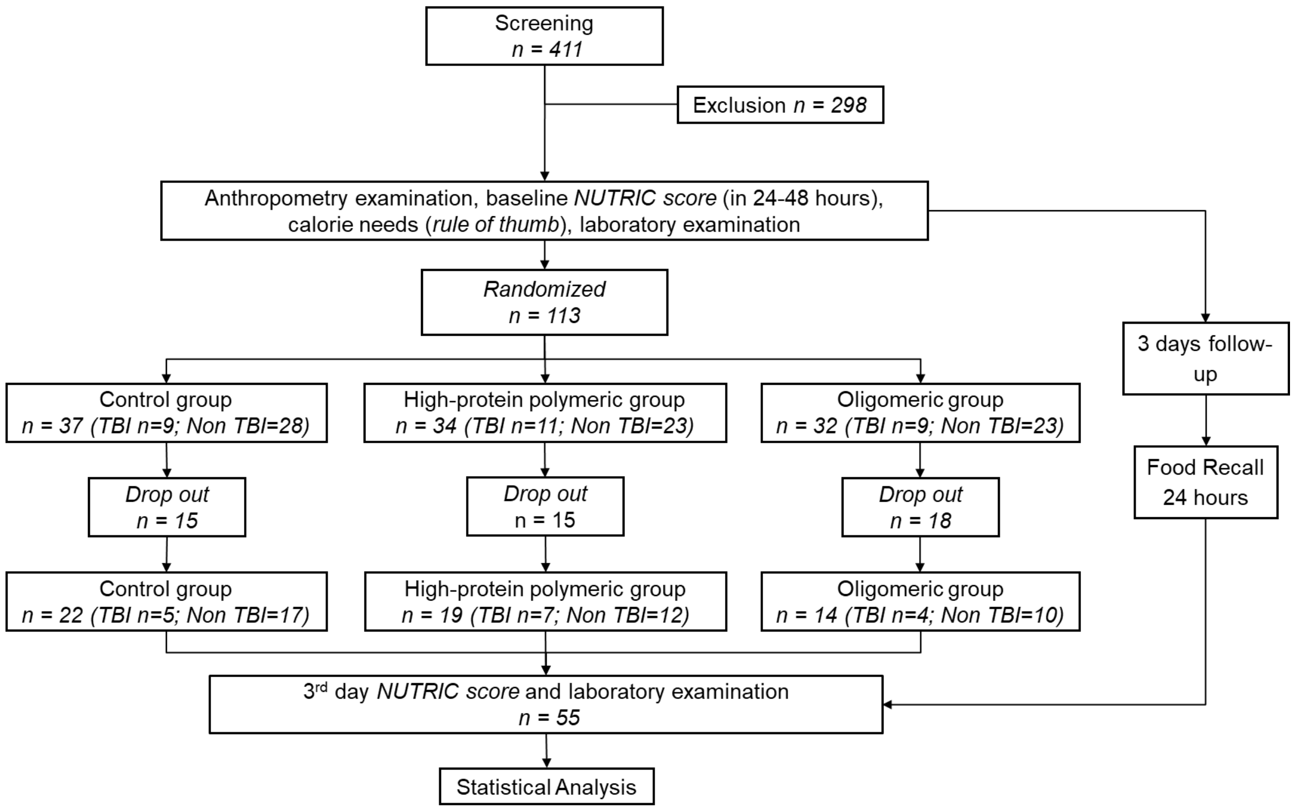

Fig. 1. Flow chart of the study population.

Table 1. Anthropometric profile

	TBI							NON TBI						
	Control		High Protein Polymeric		Oligomeric		*p-value*	Control		High Protein Polymeric		Oligomeric		*p-value*
	mean	SD	mean	SD	mean	SD		mean	SD	mean	SD	mean	SD	
Age	29.4	5.73	38.29	18.35	41.6	20.11	0.490*	55.41	15.47	50.25	15.92	42.44	20.27	0.249
Height	159.4	7.50	163.29	9.83	161.2	5.22	0.715*	157.35	4.89	156.08	8.15	160.06	7.54	0.406
IBW	56.76	5.07	59.27	6.87	56.2	3.90	0.371**	52.55	4.09	52.48	5.44	55.26	6.26	0.528
MUAC	23.7	5.67	24.86	5.18	28.06	5.33	0.429*	25.62	3.25	25.53	2.83	26.28	6.10	0.900

Abbreviations: TBI: Traumatic Brain Injury; IBW: Ideal Body Weight; MUAC: Mid Upper Arm Circumference.

In the TBI group, the mean age of patients was younger compared to the non-TBI group. For the characteristics of body height, we also found that the average TBI group was higher than the non-TBI group. For the characteristics of upper arm circumference (MUAC), the average MUAC of TBI group who got 5% Dextrose and protein-high polymeric formula was smaller than the non-TBI group, but for the TBI group who got oligomeric formula, the average MUAC was greater than non-TBI group. In the measurement of ideal body weight in each group, it was found that the TBI group was bigger than the non-TBI group.

Table 2. Baseline characteristics

		TBI						NON TBI					
		Control		High Protein Polymeric		Oligomeric		Control		High Protein Polymeric		Oligomeric	
		n	%	n	%	n	%	n	%	n	%	n	%
TLC	< 900	2	40.0%	2	28.6%	2	40.0%	10	58.8%	4	33.3%	5	55.6%
	< 1500	3	60.0%	5	71.4%	3	60.0%	7	41.2%	8	66.7%	4	44.4%
MUAC	< 19	1	20.0%	1	14.3%	0	0.0%	0	0.0%	0	0.0%	1	11.1%
	19-21,9	0	0.0%	1	14.3%	0	0.0%	1	5.9%	0	0.0%	1	11.1%
	22-23	2	40.0%	1	14.3%	1	20.0%	4	23.5%	3	25.0%	0	0.0%
	>23	2	40.0%	4	57.1%	4	80.0%	12	70.6%	9	75.0%	7	77.8%
NUTRIC Score	0-4	5	100.0%	7	100.0%	4	80.0%	16	94.1%	12	100.0%	9	100.0%
	≥ 5	0	0.0%	0	0.0%	1	20.0%	1	5.9%	0	0.0%	0	0.0%
Albumin	≥3,5	1	20.0%	1	14.3%	1	20.0%	5	29.4%	3	25.0%	3	33.3%
	< 3,5	4	80.0%	6	85.7%	4	80.0%	12	70.6%	9	75.0%	6	66.7%
Comorbid	0-1	5	100.0%	6	85.7%	4	100.0%	16	94.1%	11	91.7%	10	100.0%
	> 1	0	0.0%	1	14.3%	0	0.0%	1	5.9%	1	8.3%	0	0.0%

Abbreviations: TBI: Traumatic Brain Injury; TLC: Total Lymphocyte Count; MUAC: Mid Upper Arm Circumference; NUTRIC Score: Nutrition Risk in Critically ill Score; n: number of patients included in analysis.

Table 2 shows the assessment of the malnutrition for the patients in this study at ICU admission based on TLC and MUAC, the risk of malnutrition while being treated in ICU based on NUTRIC scores, serum albumin levels, and comorbidity in each TBI or non-TBI group.

Table 3. Feeding Profile

		TBI							NON TBI						
		Control		High Protein Polymeric		Oligomeric		*p-value*	Control		High Protein Polymeric		Oligomeric		*p-value*
		mean	SD	mean	SD	mean	SD		mean	SD	mean	SD	mean	SD	
Energy (kcal)	Day 1	15.41	21.16	447.43	283.51	448.00	422.52	0.017*	98.02	160.82	310.00	217.28	313.18	240.15	0.039*
	Day 2	377	324.65	710.71	284.26	842.60	369.48	0.094	336.42	260.21	634.33	212.21	672.78	214.17	0.001*
	Day 3	595.65	498.70	1200.51	259.37	1046.34	143.99	0.020*	569.04	333.14	1054.63	387.42	901.17	251.13	0.001*
	Total	988.06	765.33	2358.65	714.57	2336.94	891.93	0.019*	1003.48	583.08	1998.96	684.16	1887.12	598.72	0.000*
Protein (g)	Day 1	0	0	22.91	15.96	16.96	14.35	0.023*	2.78	8.60	15.78	12.88	11.71	9.30	0.003**
	Day 2	20.72	19.56	39.76	15.86	32.92	13.49	0.176	19.56	15.02	32.16	11.79	27.59	11.28	0.048*
	Day 3	36.40	29.23	71.36	16.91	43.91	5.64	0.017*	32.94	23.06	54.94	18.60	40.99	16.24	0.041*
	Total	57.12	44.65	134.03	42.58	93.79	26.65	0.016*	55.28	35.87	102.88	37.47	80.29	29.38	0.004*

Abbreviations: TBI: Traumatic Brain Injury.

In this study, for the early enteral feeding treatment group we used high-protein polymeric and oligomeric formula which were given with daily basis goals of 30%, 50%, and 70% from calorie needs.

Fig. 2. Daily intake in TBI Patients (kcal)

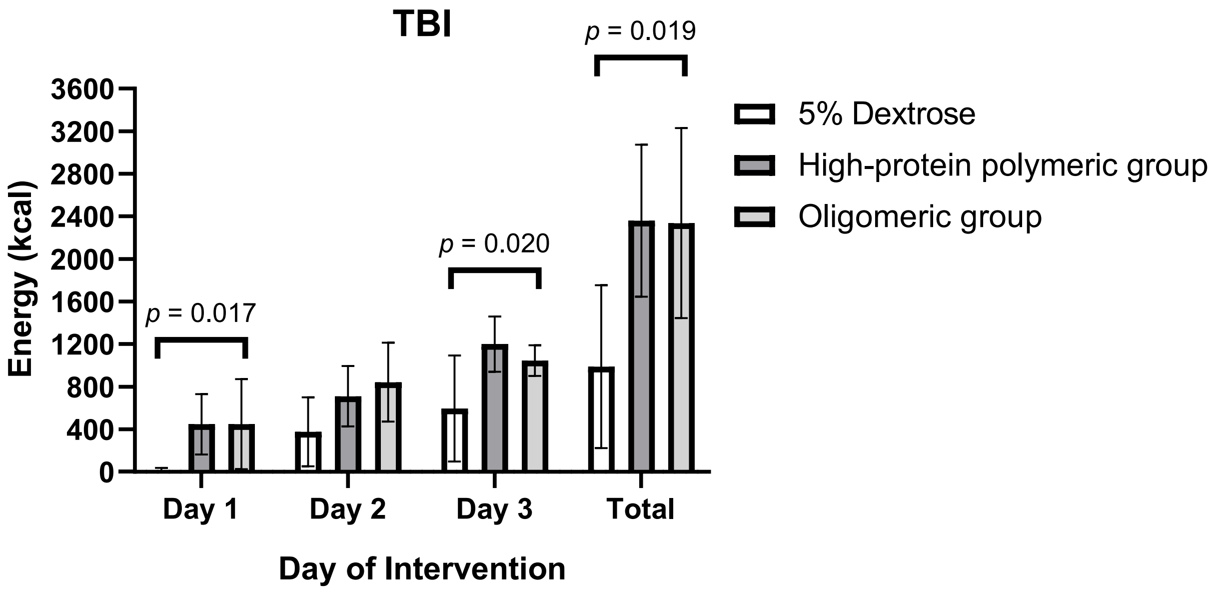

Fig. 3. Daily Intake in Non-TBI Patients (kcal)

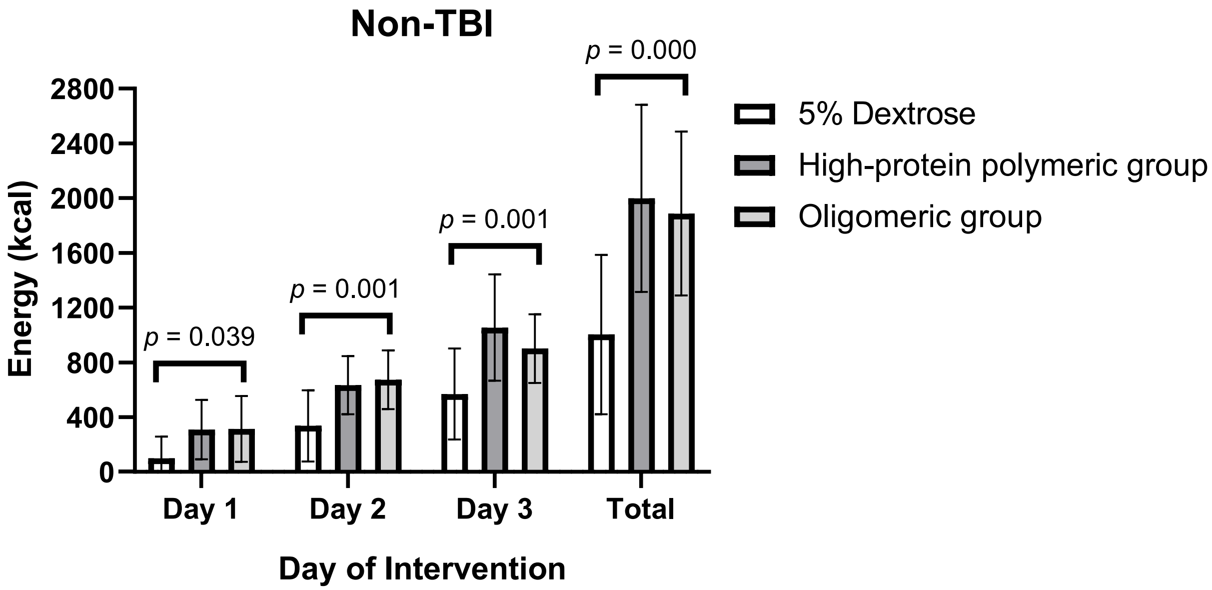

Fig. 4. Daily Protein intake in TBI patients (g)

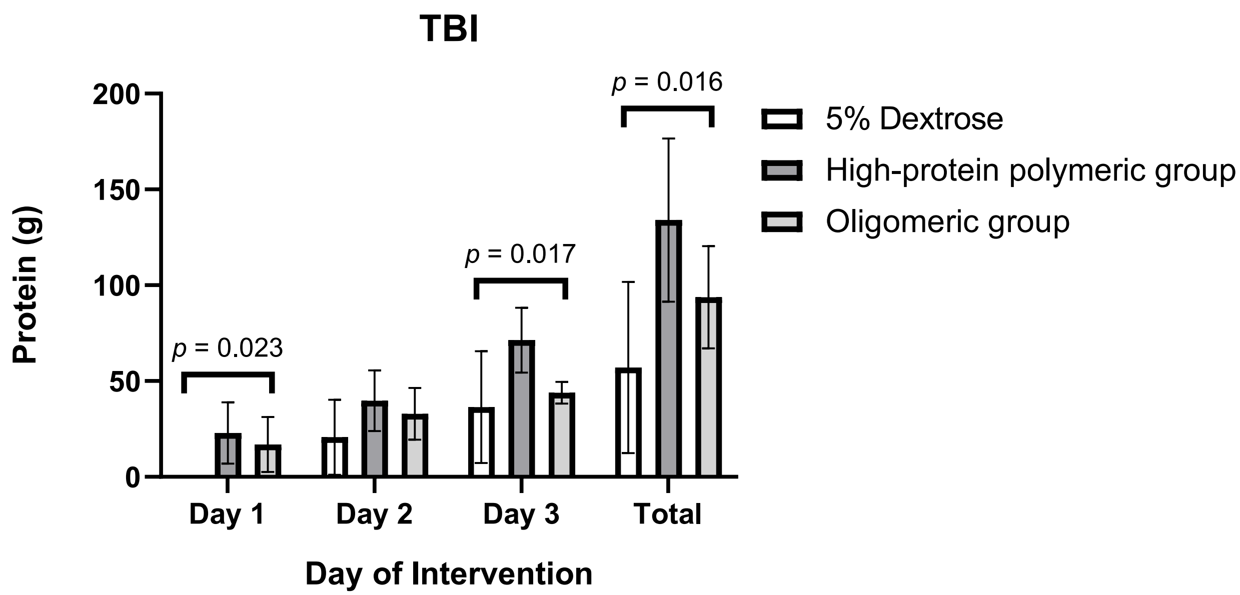

Fig. 5. Daily Protein intake in non-TBI patients (g)

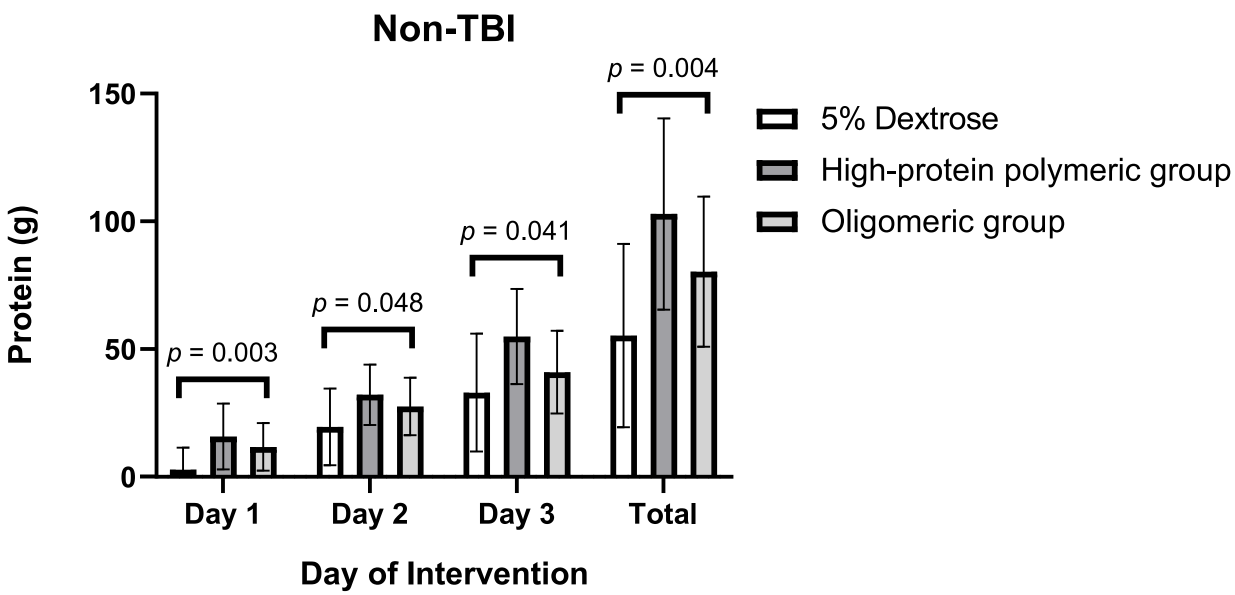

Table 4. Laboratory and scoring system results at baseline and at day 3 after initiating enteral nutrition

Parameter		TBI									NON TBI								
		Control			High Protein Polymeric			Oligomeric			Control			High Protein Polymeric			Oligomeric		
		mean	SD	*p-value*	mean	SD	*p-value*	mean	SD	*p-value*	mean	SD	*p-value*	mean	SD	*p-value*	mean	SD	*p-value*
TLC	Baseline	982.40	378.17	0.596	1071.43	554.93	0.514	914.00	415.66	0.345	815.94	513.67	0.389	1228.25	695.28	0.113	838.00	337.40	0.314
	Day 3	1208.80	639.47		1203.86	675.36		1232.2	583.16		970.41	591.28		973.17	542.60		762.00	577.08	
Serum Albumin	Baseline	3.14	0.83	0.709	2.81	0.62	0.827	2.98	0.61	0.700	2.80	0.84	0.452	2.95	0.84	0.548	3.33	0.53	0.212
	Day 3	2.96	0.47		2.76	0.50		2.9	0.32		2.96	0.59		3.13	0.65		3.09	0.55	
PLR	Baseline	167.19	82.27	0.586	151.97	51.24	0.716	279.21	211.39	0.405	482.83	454.46	0.163	296.84	270.54	0.814	351.72	271.04	0.515
	Day 3	185.95	77.70		166.52	77.4		196.33	95.70		280.00	238.60		291.89	173.74		399.32	218.10	
WBC	Baseline	10320.00	2107.61	0.684	11671.43	4530.16	0.760	15080.00	5987.24	0.411	16323.53	8069.20	0.122	13262.50	6963.51	0.041*	11313.33	4061.60	0.094
	Day 3	12060.00	2364.95		11000.00	4105.69		13300.00	5257.38		12511.76	6058.35		11687.50	7420.92		9655.56	3022.05	
IL-6	Baseline	55.0	31.12	0.686	159.71	168.62	0.499	29.5	11.44	0.500	170.29	227.84	0.277	120.25	203.60	0.071	59.34	97.50	0.374
	Day 3	121.48	184.65		171.93	193.75		107.58	169.94		121.44	149.76		67.16	99.34		177.28	270.04	
APACHE II Score	Baseline	19.2	8.44	0.529	21.0	4.32	0.731	23.2	5.40	0.045*	16.12	6.30	0.718	17.33	3.31	0.007*	17.33	3.24	0.205
	Day 3	18.0	8.63		20.86	6.15		26.4	3.13		16.71	7.30		13.83	1.95		15.67	4.80	
SOFA Score	Baseline	4.6	2.19	0.670	4.43	0.79	0.34	4.2	1.10	1.000	3.18	2.01	0.405	4.00	2.66	0.075	3.44	2.46	0.907
	Day 3	4.2	2.17		5.29	2.36		4.2	1.92		3.82	3.15		2.50	1.98		3.56	2.46	
NUTRIC Score	Baseline	2.0	2.12	0.178	2.57	1.40	0.655	4.0	1.87	0.477	2.88	1.80	0.483	3.08	1.44	0.022*	3.22	1.48	0.645
	Day 3	2.4	2.3		2.86	2.27		4.4	1.52		3.18	2.04		1.92	1.00		3.00	1.87	

Abbreviations: TBI: Traumatic Brain Injury; TLC: Total Lymphocyte Count; PLR: Platelet to Lymphocyte Ratio; WBC: White Blood Cell; IL-6: Interleukine-6; APACHE II Score: Acute Physiology and Chronic Health Evaluation II Score; SOFA Score: Sequential Organ Failure Assessment Score; NUTRIC Score: Nutrition Risk in Critically ill Score.

From our results, we have found that there were no differences in the mean TLC, serum albumin, PLR, and SOFA scores between pre and post intervention in each intervention for the TBI and non-TBI groups.

Table 5. Length of Stay

Groups			ICU Length of Stay		Hospital Length of Stay	
		n	Mean	SD	Mean	SD
TBI	Control	3	35.33	52.58	46.33	60.50
	High Protein Polymeric	3	15.33	9.02	24.33	10.21
	Oligomeric	3	17.33	9.71	44.33	27.39
p-value			0.837		0.494	
NON TBI	Control	14	4.93	2.82	13.21	7.17
	High Protein Polymeric	10	7.60	6.20	16.60	9.35
	Oligomeric	8	6.00	3.51	17.38	6.95
p-value			0.402		0.361	

Abbreviations: TBI: Traumatic Brain Injury; ICU: Intensive Care Unit; n: number of patients included in analysis.

From the above data, we found that there was no significant difference between the length of stay in the ICU or in the hospital for each TBI and non-TBI group.

Table 6. Mortality Percentage

Hospital Mortality			Groups				
			Control	High Protein Polymeric	Oligomeric	n	*p-value*
TBI	Survive	n	3	3	3	9	0.574
		%	60.0%	42.9%	75.0%	56.3%	
	Non-survival	n	2	4	1	7	
		%	40.0%	57.1%	25.0%	43.8%	
NON TBI	Survive	n	14	9	8	31	0.889
		%	82.4%	75.0%	80.0%	79.5%	
	Non-survival	n	3	3	2	8	
		%	17.6%	25.0%	20.0%	20.5%	

From the above data, we found that there was no significant difference for hospital mortality in the TBI and non-TBI group.

FIGURE LEGENDS

Figure 1

To get a description of the inflammation process in our study patients, we initially planned several laboratory examinations, which were at admission time, on day 3, and day 7. However, due to the short duration of care in the ICU patients who were the subjects of our study, we only conducted an examination at the beginning of the patient's entry into the ICU and day 3.

Figure 2

There were significant differences in the amount of calorie intake in each intervention for the TBI and non-TBI groups.

Figure 3

Protein intake in the Dextrose 5% intervention group was the lowest compared to the group given high-protein and oligomeric polymeric formulas.

Early Enteral Feeding with High-Protein Formulas Improves APACHE II and NUTRIC Score Compared to Oligomeric Formula and 5% Dextrose Solution

Agussalim Bukhari[1], Nurpudji A. Taslim[1], Suryani As'ad[1], Haerani Rasyid[1,2], Aminuddin[1], Faisal Muchtar[3], Christina Rusli[4], Rosdiana R.[4], and Umrayani[4]

[1] *Department of Nutritional Sciences, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[2] *Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[3] *Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[4] *Clinical Nutrition Specialist Program, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

Address correspondence to:
Agussalim Bukhari
Department of Nutritional Science
Hasanuddin University Teaching Hospital 5th floor
Jl. Perintis Kemerdekaan Km 11
Makassar 90245
South Sulawesi, Indonesia
Telephone: +62 812-2570-4670
Email: agussalim.bukhari@med.unhas.ac.id

Background & aims. Critically ill patients are physiologically unstable, often have complex hypermetabolic responses to trauma. These patients are facing a high risk of death, multi-organ failure, and prolonged ventilator use. Nutrition is one of therapy for critical illness, however, patients often experience malnutrition caused by disease severity, delays in feeding, and miscalculation of calorie needs. This study aims to evaluate clinical improvement in critically ill participants that were given 3 kinds of early enteral feeding formulas, which were control (5% Dextrose), high-protein polymeric formula, and oligomeric formula.

Methods. A total of 55 critically ill participants admitted to the intensive care unit (ICU) between October 2017 – March 2018 and assigned in this controlled trial. Early enteral feeding was initiated within 24-48 hours after ICU admission. Each enteral feeding group was categorized to traumatic brain injury (TBI) or non-TBI. The primary endpoints were changes in white blood cell count, Acute Physiologic and Chronic Health Evaluation (APACHE) II score, and Nutrition Risk in the Critically Ill (NUTRIC) score from baseline to day 3.

Results. Baseline characteristics were similar between control (n=22), high-protein polymeric (n=19), and oligomeric (n=14) groups. There were significant decreases for white blood cell count (13262.5±6963.51 to 11687.5±7420.92; p=0.041), APACHE II score (17.33±3.31 to 13.83±1.95; p=0.007), and NUTRIC scores changes (3.08±1.44 to 1.92±1.00; p=0.022) in non-TBI participants receiving high-protein polymeric compared those in control or oligomeric participants. But there is no significant clinical improvement amongst the groups in TBI participants. ***Conclusions***. Non-TBI participants benefit from early enteral feeding with high-protein polymeric formula.

Keywords critical ill, early enteral feeding, high-protein formula

INTRODUCTION

Notwithstanding under "proper" hospital care, approximately 40% of patients admitted to the hospital are malnourished at admission. Malnutrition is correlated with many adverse outcomes, such as immune system depression, diminished healing process, muscle wasting, prolonged length of stay, increased morbidity and mortality which lead to higher early re-admission rates and healthcare expenses. Critically ill patients often have various degrees of inflammation which results in an increased in energy expenditure and protein catabolism, but reduced energy and protein intake. Regardless of the patient's pre-existing malnutrition, every patient has a highly variable metabolic and immune response to injury or illness which might be attenuated by proper nutrition therapy (1–8).

Enteral nutrition (EN) is one approach to modulating inflammation and coagulation in critically ill patients, which has been correlated with beneficial outcomes such as reduced infectious complications, fewer organ failures, and reduced mortality. Although there is a general acceptance of early EN, only a few studies have approached the specific timing, volume, and formula type of tube feeds in critically ill patients population and fewer still have studied the effects on inflammation (8–10).

The expert committee of ESPEN suggested that hemodynamically stable critically ill patients should be fed early within 24-48 hours of patient's admission using an appropriate amount of feed, but there are no data showing improvement in relevant outcome parameters using early EN in these patients. This means a better understanding of managing inflammation in ICU patients could provide better-targeted care and help prevent malnutrition, morbidity, and mortality (3,11).

Compromised GI tract is one of inhibiting factors in critically ill patients which makes them generally susceptible to over-feeding and under-feeding (12,13). Such conditions make the patients to be fasted or given 5% dextrose for quite a long time, hence pointing to energy deficiency in these patients.

Many enteral formulations exist for the nourishment of the malnourished or at-risk patients, but most studies have failed to recognize their benefit. Nutritional guidelines suggest using polymeric formula when initiating enteral feeding in critically ill patients. In most cases, the given amount of protein is not adequate, although several studies have shown that low protein intakes can be related to adverse clinical outcomes (11,12,14,15).

There is limited evidence for applying oligomeric formulas in the ICU. This formula is slightly more expensive than polymeric formula, but data indicate that they are better tolerated by compromised GI tracts patients because these peptides are water-soluble and readily absorbed by the intestine and metabolized by the liver. Because it is partially digested, greater nutrient delivery may be obtained and reduced the degree of regurgitation, gastric emptying times, and gagging while improving tolerance. As a result, they have fewer gastrointestinal complications, improved visceral protein levels, and decreased rates of mortality (15–17).

There is no specific ICU nutritional score has been validated thus far. NUTRIC score was associated with mortality and nutritional support might lower mortality in patients with a high NUTRIC score (>5) (14,18).

We conducted this trial to compare the effects of different early enteral feeding formulas on inflammatory markers, NUTRIC score, length of stay, and mortality in critically ill patients.

MATERIALS AND METHODS

Study population and design.

This was a controlled clinical trial, conducted in the adult ICU participants of Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from October 2017 to March 2018. This study included 55 participants aged older than 18 years and with stable hemodynamic values. The exclusion criteria were gastrointestinal resection, contraindications for enteral feeding, history of diabetes or chronic kidney disease, receiving parenteral nutrition, severe intolerance for enteral nutrition or formula, gastric residual volume > 250 ml/4 hours.

Participants were randomly assigned to either the control group receiving dextrose 5%, high-protein polymeric formula (Peptisol®) group (22.4% protein from total calorie), or the oligomeric (Peptamen®) formula group (16.2% protein from total calorie). All participants were initiated on enteral feeding, as early as possible (within 24-48 hours) after intensive care unit (ICU) admission. Participants in the control group were given 5% dextrose as a starting regimen and were continued with other types of feeding regimen based on anesthesiologist instruction. Participants in the high-protein polymeric diet or oligomeric enteral nutrition group were given a feeding regimen which administered as boluses via a nasogastric tube. A total of 5 aliquots were administered at 4-hourly intervals in a daily feeding period of 24 hours, with the participant positioned 30° head-up.

Critically ill participants who completed the intervention period were analyzed based on the diagnoses categories of traumatic brain injury (TBI) and non-TBI.

Anthropometry and Laboratory Measurements.

Upon first 24 hours ICU admission, anthropometric data were collected including age, gender, height (participant in the supine position), ideal body weight (IBW), Mid-Upper-Arm Circumference (MUAC), and primary admission diagnosis (TBI or non-TBI). Severity-of-illness scores and laboratory assessment were conducted on 24 hour from admission and on day 3, which included: biochemical variables such as platelets, white blood cells, lymphocytes, serum creatinine levels, blood urea nitrogen (BUN) levels, albumin, serum potassium levels, serum sodium levels, serum pH, partial pressure of carbon dioxide, and partial pressure of oxygen (PO2), Acute Physiology and Chronic Health Evaluation II score (APACHE II score), Sequential Organ Failure Assessment score (SOFA score), Nutrition Risk in the Critically Ill score (NUTRIC score).

Calculation of nutritional goals and protein intake.

The daily calorie and protein prescriptions were calculated from standard recommendations (calories 25-30 kcal/kg/d, proteins 1.2-2 g/kg/d). A meticulous record of the calories and protein of intake was maintained for 3 days follow up.

Study end points.

Our primary outcomes were changes in laboratory values and nutritional indicators from baseline to day 3.

Statistical analysis.

The statistical package SPSS version 24 was used for the statistical analysis. All values are expressed as the means ± standard deviation. The changes between pre and post intervention were assessed using paired *t*-test or Wilcoxon signed-rank test. Differences of mean values between the 3 groups were compared using the Anova or Kruskal-Wallis test. A *p*-value <0.05 was considered statistically significant.

The study was approved by the Faculty of Medicine, Hasanuddin University Ethics Committee.

RESULTS

The anthropometric profile and baseline characteristics of the study population are depicted in Table 1 and Table 2. During the study period, we screened 411 participants who were admitted to the ICU, 298 participants were excluded from our trial mostly due to participant's mortality. A total of 113 participants included in our trial were randomly assigned to either the control (5% dextrose), high-protein polymeric or oligomeric groups. We also separated our participants based on their diagnosis, which were Traumatic Brain Injury (TBI) and non-TBI participants. Participants in the control group were given 5% dextrose as a starting feeding regimen and were continued with other types of feeding regimen based on anesthesiologist's instruction. Whereas participants in the high-protein polymeric group or oligomeric group were given a total of 5 aliquots feeding regimen via a nasogastric tube, which were administered at 4-hourly intervals. We had 48 drop-out participants during our 3 days follow-up and a total of 55 participants were included in our statistical analysis comprising both male (53%) and female (47%) subjects. Twenty-two participants were included in the control group (5 participants were diagnosed with TBI and 17 participants were diagnosed with non-TBI), 19 participants in the high-protein polymeric formula group (7 participants were diagnosed with TBI and 12 participants were diagnosed with non-TBI), and 14 participants in the oligomeric formula group (4 participants were diagnosed with TBI and 10 participants were diagnosed with non-TBI).

At the time of ICU admission, the participants which were in the condition of malnutrition based on the TLC examination (19). In the TBI group were 6 participants in the category of severe malnutrition and 11 participants in the category of mild malnutrition. Whereas in the non-TBI group, 19 participants were included in the category of severe malnutrition and 19 participants were included in the category of mild malnutrition. Based on patient's MUAC examination, we divided our participants in the TBI group as 2 participants were included in the category of severe malnutrition, 1 patient was included in the category of moderate malnutrition, 4 participants were included in the category of mild malnutrition, and 10 participants were included in the category of good nutrition. In the group diagnosed with non-TBI 1 participant was in the category of severe malnutrition, 2 participants were in the category of moderate malnutrition, 7 participants were in the category of mild malnutrition, and 28 participants were included in the category of good nutrition.

Before we began the intervention, a risk assessment for malnutrition was conducted to our participants based on the NUTRIC score for each participant in the TBI or non-TBI groups. The participants in this study were more dominated by participants with NUTRIC score 0-5, and hence it was included in the category of mild risk of malnutrition. Whereas for the result for serum albumin levels before the intervention, we found that the majority of our patients were in hypoalbuminemia state. Most of the participants did not have any comorbid or only had 1 comorbid, both in the TBI and non-TBI groups.

There were several variations in the duration of administration of 5% dextrose that we observed in our study's participants. In the TBI group, there were 2 participants who were given 5% dextrose for 1 day, 1 participant who was given 5% Dextrose for 2 days, and 2 participants who were given 5% Dextrose during the 3 days of our observation in the ICU. Whereas in the non-TBI group there were 2 participants who were given regular food from the beginning of entry into the ICU, 10 participants were given 5% dextrose for 1 day, 2 participants were given 5% dextrose for 2 days, and 3 participants were given 5% dextrose for 3 days.

Both of TBI and non-TBI groups who were given early enteral feeding with 5% Dextrose obtained significantly lowest amount of energy and protein intake compared to the high-protein polymeric formula group and the oligomeric formula group (Table 3, Fig. 2, Fig. 3, Fig. 4, and Fig. 5). In contrast, there was no significant different in energy intake between the high-protein polymeric and the oligomeric formula groups. However, protein intake was higher in high-protein polymeric formula group than those in oligomeric and control groups (Table 3, Fig. 4, and Fig. 5)

There was no difference in mean white blood cells between pre and post-intervention for each TBI group (Table 4). Whereas for the non-TBI group, the result showed that there was a significant decrease

(1575±10320,86) in white blood cells between the pre intervention and post intervention in the non-TBI group who received the intervention of high-protein polymeric formulas.

The effect of early enteral feeding on the change in APACHE II score showed that there was no significant decrease between the pre and post-intervention in the TBI group that given 5% Dextrose (1,2±3,90) and high-protein polymeric formula (0,14±4,49), but there was a significant increase in the group given an oligomeric formula (3,2±2,49). In the non-TBI group, it can be interpreted that there was no significant difference in mean APACHE II score between the pre and post intervention in the control (0,59±6,61) and the oligomeric formula (1,67±3,57) group, but there was a significant decrease (3,5±3,66) in the APACHE II score in the group given high-protein polymeric formula (Table 4).

The results of statistical tests for the TBI group conducted to assess the effect of early enteral feeding on changes in NUTRIC score revealed no significant difference in NUTRIC scores between pre and post intervention for all groups. On the other hand, there was no significant difference in NUTRIC score between pre and post-intervention in the non-TBI group who received 5% Dextrose (0,29± 1,69) and oligomeric formula (0,22± 1,39) intervention, but there was a significant decrease (1,17± 1,40) in NUTRIC scores between pre and post in the non-TBI group who received high-protein polymeric formula interventions (Table 4).

TBI participants who received high-protein polymeric formula and control group's in the non-TBI participants had the shortest ICU length of stay and hospital length of stay (Table 5). There was no significant difference in mortality percentage between TBI and non-TBI groups (Table 6)

DISCUSSION

The definition of energy requirements is the amounts of macronutrients and micronutrients which are needed to balance energy expenditure. It is used to maintain reserve, normal metabolic and physiologic functions. Nutritional care in the intensive care unit (ICU) poses a challenge to the clinicians because the patient manifest hypermetabolism, proteolysis with nitrogen loss and accelerated gluconeogenesis and glucose utilization. The degree of metabolic response to assault depends on the length and severity of insult and is mediated through the release of cytokines and counterregulatory hormones. Other factors that influence metabolic needs during acute illness are mechanical ventilation, administration of vasoactive or sedative agents, type of disease, the severity of illness, nutritional state before ICU admission, and comorbidities of the patient (20).

Guidelines recommend to give 20–25 kcal/kg/day in the acute phase and 25–30 kcal/kg/day in the recovery phase for most critically ill patient. Protein requirements are higher than normal due to loss of total body protein, which is inevitable in the first days of ICU, even with an aggressive nutritional approach, primarily due to the catabolism of muscle. For non-previously malnourished patient, it is recommended to provide 0.20–0.25 g/ kg/day of nitrogen (1.3–1.5 g proteins/kg ideal body weight/day or 1.2–2.0 g/ kg actual body weight/day) and it can be increased to 0.35 g/kg/day (2.2 g/kg ideal body weight/day) of nitrogen in case of previous malnutrition or significant catabolism (20,21). Although early enteral nutrition in critically ill patients with clear liquid diet (5% dextrose) as their initiation food has been used, more recent guidelines recommended the use of full liquid diet (22).

Head-injured patient frequently have increases in metabolic rate and protein catabolism that elevate nutritional needs. Energy expenditure may increase until 200 % from normal values but factors such as delayed gastric emptying, interruptions to feeding due to fasting for medical procedures, and accidental removal of feeding tubes prevent the provision of adequate nutrition. This induce up to 30 % loss of body weight and signs of malnutrition in about 2/3 of patients two months after hospital admission (23–25). In TBI patients, the nutrition goals were to reach 35 – 45 calories/kilogram and a protein intake of 2 – 2.5 grams/kilogram on day one or as soon as possible. Adequate calories are required to prevent malnutrition and to improve healing and recovery. The brain functions as the regulator for metabolic activity leads to a complex milieu of metabolic alterations in TBI consisting of hormonal changes, aberrant cellular metabolism, and a vigorous cerebral and systemic inflammatory response in an effort to liberate substrate for injured cell metabolism. The degree of the hypermetabolic state is equal to the severity of injury and motor dysfunction (23,26). In our study, there are some expected clinical effects in the non-TBI group due to the more appropriate nutritional therapy accomplishment which helps to decrease the inflammation process, especially in the group which was given high-protein polymeric formula. The results of this study also found that the non-TBI group that did not receive appropriate therapy (control group) had an increased risk of malnutrition.

In the ICU, complete blood count, various biochemical tests, and inflammatory markers are a routine test which performed on patient upon their admission. A follow-up test is generally coordinated based on the patient's clinical characteristics and the underlying disease. (25) Thrombocytopenia is one of the most common laboratory abnormalities in critically ill patient, with the incidence ranging from 13-60%. It can be a result of increased platelet destruction, hemodilution process, platelet sequestration, or decreased production. Many previous studies have reported that thrombocytopenia in ICU is associated with prolonged hospital stay and reduced survival. APACHE II score which is the most commonly used prognostic score in ICU patient does not include platelet count and albumin levels (27). The platelet counts and lymphocyte count are parts of complete blood count (CBC) analysis. Platelet-to-lymphocyte ratio (PLR) can be used as an inflammatory marker. It has been found to be predictive of the prognoses of patient with diverse inflammatory and ischemic conditions, such as various cardiovascular diseases, and chronic inflammatory disease, and tumors. A positive monotonic association between a high PLR and a poor prognosis for these diseases has been reported. Significance of PLR examination has also been developed for inflammatory status in critically ill patient. It does not require additional tests or costs as they are calculated from the haemogram, which makes it cost-effective and easy to be applied to virtually all patient (28–32).

In both TBI and non-TBI groups, we observed that there was a relationship between some inflammatory markers (serum albumin levels, IL-6, and PLR). Albumin serum level is inversely proportional to the results of IL-6 and PLR. However, due to the limited number of samples in this study, further research is needed. To our knowledge, this is the first study to examine the relationship of PLR with intervention of early enteral feeding. Therefore, further research is still needed to assess the correlation between PLR and food intake in critically ill patient.

The results of the non-TBI group study were similar to those in respiratory ICU patient conducted in India. The enteral nutrition was initiated within the first 24- 48 hours following the admission and was advanced toward a goal over the next 48-72 hours. Their goals for a daily basis were 25%, 50% 75%, and 100%. They used both commercial and home-based formulas. The mortality rate was improved significantly from a 25% mortality rate to a 15% mortality rate APACHE score (33). This finding confirms that adequate nutritional support at the right time not only reduces the participant's length of stay, ventilator support days but also improves the overall nutritional status of the patient. Proper nutrition also has proven to reduce the mortality risk of patient (34).

In contrast to the non-TBI group, there was an increasing tendency of the NUTRIC score for the TBI group after feeding administration, which is different from the existing literature results (35). TBI group tended to have higher energy and protein needs than the non-TBI group, hence calorie and protein achievement in this group was lower.

The limitations of this study is that the calculation of calorie need was based on weight estimation, and not indirect calorimetry as a gold standard. We also did not assess the adequacy of protein intake using the more precise method of urine urea nitrogen. Observation time was limited due to participant's short ICU's length of stay.

In conclusion, non-TBI patient benefit from high-protein polymeric early enteral feeding than oligomeric or 5% Dextrose. By given this formula, the patient had decreased of white blood cells count, APACHE II score, and NUTRIC score.

Acknowledgments

We are indebted to the patient who participated in this study and to the intensive care unit personnel. We also would like to express our appreciation for Peptamen® provided by Nestle. Gratitude is extended to the Department of Anesthesiology, Intensive Care and Pain Management, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

Statement of authorship

A.B., N.A.T., S.A., H.R., A., F.M. developed the study design and strategy of the research project. AB was the lead study physician and contributed together with C.R., U., and R.R. to the data acquisition and analysis. A.B., N.A.T., S.A., H.R., A., F.M., C.R., R.R., and U. were involved in interpretation of the data. A.B. drafted the manuscript and S.A., H.R., A., and F.M. critically revised it.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this paper. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this publication.

Funding sources

This study was partially funded by Institute of Research and Community Service, Hasanuddin University, Makassar, Indonesia and the Indonesian Ministry of Research, Technology, and Higher Education under WCU Program managed by Institut Teknologi Bandung.

REFERENCES

1. Chase C. Hansen MBA SDM. Nutrition in the intensive care unit. Southwest Respir Crit Care Chronicles [Internet]. 2015;3(10):10–6. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-0032871676&partnerID=40&md5=5b1a6add87924fb361ae915e3627575d
2. Sharma K, Mogensen KM, Robinson MK. Pathophysiology of Critical Illness and Role of Nutrition Pathophysiology of Critical Illness. Nutr Clin Pract. 2019;34(1):12–22.
3. Mohammad S, Mousavi H, Ostadrahimi A, Safaiyan A, Hashemzadeh S, Salehpour F. Effects of four different enteral feeding methods on tumor Necrosis Factor- α (TNF- α) and high sensitive C-Reactive Protein (hs-CRP) in critically Ill Patients : double blinded , randomized controlled trial. Prog Nutr 2016; 2016;18(3):236–41.
4. Padilla PF, Martínez G, Vernooij RW, Urrútia G, Figuls MR i, Cosp XB. Early versus delayed enteral nutrition support for critically ill adults (Protocol). 2016;(9).
5. Oliveira NS, Caruso L, Bergamaschi DP, Cartolano F de C, Soriano FG. Impact of the adequacy of energy intake on intensive care unit mortality in patients receiving enteral nutrition. Rev Bras Ter Intensiva. 2011;23(2):183–9.

6. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: Prevalence, identification and impact on patients and the healthcare system. Int J Environ Res Public Health. 2011;8(2):514–27.

7. Bhurayanontachai R, Sa-nguansai S. Change of serum prealbumin levels and serum protein markers between egg white powder and casein protein additives in standard enteral feeding formulas in critically ill patients with acute respiratory failure. J Intensive Care [Internet]. 2016;4(32):1–8. Available from: http://dx.doi.org/10.1186/s40560-016-0157-0

8. Hegazi RA, Wischmeyer PE. Clinical review: Optimizing enteral nutrition for critically ill patients--a simple data-driven formula. Crit Care [Internet]. 2011 [cited 2018 Aug 7];15(6):234. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22136305

9. Bastarache JA, Ware LB, Girard TD, Wheeler AP, Rice TW. Markers of Inflammation and Coagulation may be Modulated by Enteral Feeding Strategy. JPEN J Parenter Enter Nutr. 2012;36(6):732–40.

10. Fremont RD, Rice TW. How soon should we start interventional feeding in the ICU? Curr Opin Gastroenterol [Internet]. 2014 [cited 2017 Sep 8];30(2):178–81. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4006101&tool=pmcentrez&rendertype=abstract

11. Ogasawara T, Matsuda S, Kato S, Tanaka K, Yano T, Marui S, et al. Early Enteral Nutrition Using Oligomeric Formula in Mechanically Ventilated , Critically Ill Patients : A Randomized Control Trial. J Hum Nutr food Sci. 2014;2:1–5.

12. Hasanloei MAV, Vahabzadeh D, Shargh A, Atmani A, Osalou RA. Clinical Nutrition ESPEN Original article A prospective study of energy and protein intakes in critically ill patients. Clin Nutr ESPEN [Internet]. 2018;23:162–6. Available from: https://doi.org/10.1016/j.clnesp.2017.10.007

13. Curry AS, Chadda S, Danel A, Nguyen DL. Early introduction of a semi-elemental formula may be cost saving compared to a polymeric formula among critically ill patients requiring enteral nutrition : a cohort cost – consequence model. Clin Outcomes Res. 2018;10:293–300.

14. Tignanelli CJ, Cherry-Bukowiec J. Hospital Based Nutrition Support : A Review of the Latest

Evidence. J Clin Nutr Diet. 2017;3(3):22.

15. Sioson MS, Martindale R, Abayadeera A, Abouchaleh N, Aditianingsih D, Bhurayanontachai R, et al. Clinical Nutrition ESPEN Nutrition therapy for critically ill patients across the Asia Pacific and Middle East regions : A consensus statement. Clin Nutr ESPEN [Internet]. 2018;24:156–64. Available from: https://doi.org/10.1016/j.clnesp.2017.11.008

16. Alexander DD, Bylsma LC, Elkayam L, Nguyen DL, Alexander DD, Bylsma LC, et al. Nutritional and health benefits of semi-elemental diets : A comprehensive summary of the literature. World J Gastrointest Pharmacol Ther. 2016;7(2):306–19.

17. Kumpf VJ, Aguilar-nascimento JE De, Graf JID, Hall AM, Mckeever L, Steiger E, et al. ASPEN-FELANPE Clinical Guidelines : Nutrition Support of Adult Patients With Enterocutaneous Fistula. J Parenter Enter Nutr. 2016;20(10).

18. Singer P, Reintam A, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr [Internet]. 2019;38(1):48–79. Available from: https://doi.org/10.1016/j.clnu.2018.08.037

19. Cereda E, Pusani C, Limonta D, Vanotti A. The Association of Geriatric Nutritional Risk Index and Total Lymphocyte Count with Short-Term Nutrition-Related Complications in Institutionalised Elderly. J Am Coll Nutr. 2008;27(3):406–13.

20. Ichai C, Quintard H, Orban J-C. Metabolic Disorders and Critically Ill Patients From Pathophysiology to Treatment. Springer International Publishing AG; 2018.

21. 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: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enter Nutr. 2016;40(2):159–211.

22. Padar M, Uusvel G, Starkopf L, Starkopf J, Reintam Blaser A. Implementation of enteral feeding protocol in an intensive care unit: Before-and-after study. World J Crit Care Med [Internet]. 2017;6(1):56. Available from: http://www.wjgnet.com/2220-3141/full/v6/i1/56.htm

23. Sakine Mazaherpur, Khatony A, Abdi A, Pasdar Y, Najafi F. The Effect of Continuous Enteral

Nutrition on Nutrition Indices, Compared to the Intermittent and Combination Enteral Nutrition in Traumatic Brain Injury Patients. J Clin Diagnostic Res [Internet]. 2016;10(10):JC01–5. Available from: http://jcdr.net/article_fulltext.asp?issn=0973-709x&year=2016&volume=10&issue=10&page=JC01&issn=0973-709x&id=8625

24. Chapple LS, Chapman MJ, Lange K, Deane AM, Heyland DK. Nutrition support practices in critically ill head-injured patients: a global perspective. Crit Care [Internet]. 2016;20(1):6. Available from: http://ccforum.com/content/20/1/6

25. Masha'al DA. The Change in Nutritional Status in Traumatic Brain Injury Patients : A Retrospective Descriptive Study. University of South Florida; 2016.

26. Metzger K. Nutrition Therapy for Patients with Traumatic Brain Injury in the Military. IomEdu [Internet]. 2009;1–7. Available from: http://www.iom.edu/~/media/Files/Activity Files/Nutrition/TBINutrition/Metzger 12-17-10 PrePub.pdf

27. Yildiz A, Yigit A, Ramazan A. The Impact of Nutritional Status and Complete Blood Count Parameters on Clinical Outcome in Geriatric Critically Ill Patients. J Clin Med Res. 2018;10(7):588–92.

28. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol [Internet]. 2015;(June 2012):606–13. Available from: http://www.gnresearch.org/doi/10.5935/abc.20150126

29. Liu WY, Lin SG, Wang LR, Fang CC, Lin YQ, Braddock M, et al. Platelet-To-lymphocyte ratio: A novel prognostic factor for prediction of 90-day outcomes in critically ill patients with diabetic ketoacidosis. Med (United States). 2016;95(4):1–7.

30. Zheng CF, Liu WY, Zeng FF, Zheng MH, Shi HY, Zhou Y, et al. Prognostic value of platelet-to-lymphocyte ratios among critically ill patients with acute kidney injury. Crit Care. 2017;21(1):1–11.

31. Yildiz A, Yigit A, R. A, Benli. The prognostic role of platelet to lymphocyte ratio and mean platelet volume in critically ill patients. Eur Rev Med Pharmacol Sci [Internet].

2018;22(8):2246–52. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L622016164%0Ahttp://dx.doi.org/10.26355/eurrev-201804-14811

32. Alexander N. Reference Values of Neutrophil-Lymphocyte Ratio , Platelet-Lymphocyte Ratio and Mean Platelet Volume in Healthy Adults in North Central. J Blood Lymph. 2016;6(1):1–4.

33. Mary Larancia A, Gayathri G, Hemamalini AJ. Adequacy of Nutritional Support to Critically Ill Patients Requiring Ventilator Support in Intensive Care Unit and Its Correlation with Outcomes. Int J Food Nutr Sci. 2013;2(3).

34. Wang W-N, Yang M-F, Wang C-Y, Hsu C-Y, Lee B-J, Fu P-K. Optimal Time and Target for Evaluating Energy Delivery after Adjuvant Feeding with Small Bowel Enteral Nutrition in Critically Ill Patients at High Nutrition Risk. Nutrients. 2019;11(645):1–10.

35. 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 [Internet]. 2011;15:R268. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3388687&tool=pmcentrez&rendertype=abstract

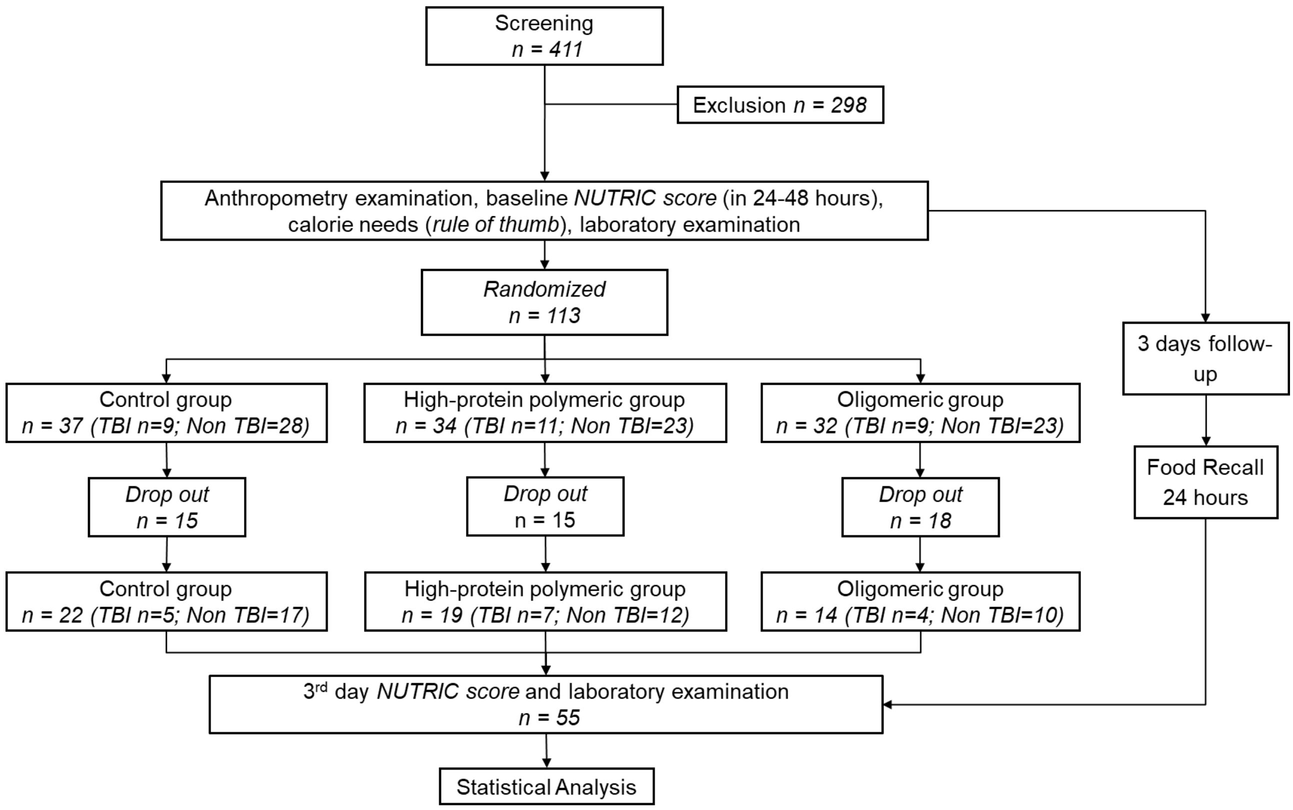

Fig. 1. Flow chart of the study population.

Table 1. Anthropometric profile

	TBI							NON TBI						
	Control		High Protein Polymeric		Oligomeric		*p-value*	Control		High Protein Polymeric		Oligomeric		*p-value*
	mean	SD	mean	SD	mean	SD		mean	SD	mean	SD	mean	SD	
Age	29.4	5.73	38.29	18.35	41.6	20.11	0.490*	55.41	15.47	50.25	15.92	42.44	20.27	0.249
Height	159.4	7.50	163.29	9.83	161.2	5.22	0.715*	157.35	4.89	156.08	8.15	160.06	7.54	0.406
IBW	56.76	5.07	59.27	6.87	56.2	3.90	0.371**	52.55	4.09	52.48	5.44	55.26	6.26	0.528
MUAC	23.7	5.67	24.86	5.18	28.06	5.33	0.429*	25.62	3.25	25.53	2.83	26.28	6.10	0.900

Abbreviations: TBI: Traumatic Brain Injury; IBW: Ideal Body Weight; MUAC: Mid Upper Arm Circumference.

In the TBI group, the mean age of patients was younger compared to the non-TBI group. For the characteristics of body height, we also found that the average TBI group was higher than the non-TBI group. For the characteristics of upper arm circumference (MUAC), the average MUAC of TBI group who got 5% Dextrose and protein-high polymeric formula was smaller than the non-TBI group, but for the TBI group who got oligomeric formula, the average MUAC was greater than non-TBI group. In the measurement of ideal body weight in each group, it was found that the TBI group was bigger than the non-TBI group.

Table 2. Baseline characteristics

		TBI						NON TBI					
		Control		High Protein Polymeric		Oligomeric		Control		High Protein Polymeric		Oligomeric	
		n	%	n	%	n	%	n	%	n	%	n	%
TLC	< 900	2	40.0%	2	28.6%	2	40.0%	10	58.8%	4	33.3%	5	55.6%
	< 1500	3	60.0%	5	71.4%	3	60.0%	7	41.2%	8	66.7%	4	44.4%
MUAC	< 19	1	20.0%	1	14.3%	0	0.0%	0	0.0%	0	0.0%	1	11.1%
	19-21,9	0	0.0%	1	14.3%	0	0.0%	1	5.9%	0	0.0%	1	11.1%
	22-23	2	40.0%	1	14.3%	1	20.0%	4	23.5%	3	25.0%	0	0.0%
	>23	2	40.0%	4	57.1%	4	80.0%	12	70.6%	9	75.0%	7	77.8%
NUTRIC Score	0-4	5	100.0%	7	100.0%	4	80.0%	16	94.1%	12	100.0%	9	100.0%
	≥ 5	0	0.0%	0	0.0%	1	20.0%	1	5.9%	0	0.0%	0	0.0%
Albumin	≥3,5	1	20.0%	1	14.3%	1	20.0%	5	29.4%	3	25.0%	3	33.3%
	< 3,5	4	80.0%	6	85.7%	4	80.0%	12	70.6%	9	75.0%	6	66.7%
Comorbid	0-1	5	100.0%	6	85.7%	4	100.0%	16	94.1%	11	91.7%	10	100.0%
	> 1	0	0.0%	1	14.3%	0	0.0%	1	5.9%	1	8.3%	0	0.0%

Abbreviations: TBI: Traumatic Brain Injury; TLC: Total Lymphocyte Count; MUAC: Mid Upper Arm Circumference; NUTRIC Score: Nutrition Risk in Critically ill Score; n: number of patients included in analysis.

Table 2 shows the assessment of the malnutrition for the patients in this study at ICU admission based on TLC and MUAC, the risk of malnutrition while being treated in ICU based on NUTRIC scores, serum albumin levels, and comorbidity in each TBI or non-TBI group.

Table 3. Feeding Profile

		TBI							NON TBI						
		Control		High Protein Polymeric		Oligomeric		*p-value*	Control		High Protein Polymeric		Oligomeric		*p-value*
		mean	SD	mean	SD	mean	SD		mean	SD	mean	SD	mean	SD	
Energy (kcal)	Day 1	15.41	21.16	447.43	283.51	448.00	422.52	0.017*	98.02	160.82	310.00	217.28	313.18	240.15	0.039*
	Day 2	377	324.65	710.71	284.26	842.60	369.48	0.094	336.42	260.21	634.33	212.21	672.78	214.17	0.001*
	Day 3	595.65	498.70	1200.51	259.37	1046.34	143.99	0.020*	569.04	333.14	1054.63	387.42	901.17	251.13	0.001*
	Total	988.06	765.33	2358.65	714.57	2336.94	891.93	0.019*	1003.48	583.08	1998.96	684.16	1887.12	598.72	0.000*
Protein (g)	Day 1	0	0	22.91	15.96	16.96	14.35	0.023*	2.78	8.60	15.78	12.88	11.71	9.30	0.003**
	Day 2	20.72	19.56	39.76	15.86	32.92	13.49	0.176	19.56	15.02	32.16	11.79	27.59	11.28	0.048*
	Day 3	36.40	29.23	71.36	16.91	43.91	5.64	0.017*	32.94	23.06	54.94	18.60	40.99	16.24	0.041*
	Total	57.12	44.65	134.03	42.58	93.79	26.65	0.016*	55.28	35.87	102.88	37.47	80.29	29.38	0.004*

Abbreviations: TBI: Traumatic Brain Injury.

In this study, for the early enteral feeding treatment group we used high-protein polymeric and oligomeric formula which were given with daily basis goals of 30%, 50%, and 70% from calorie needs.

Fig. 2. Daily intake in TBI Patients (kcal)

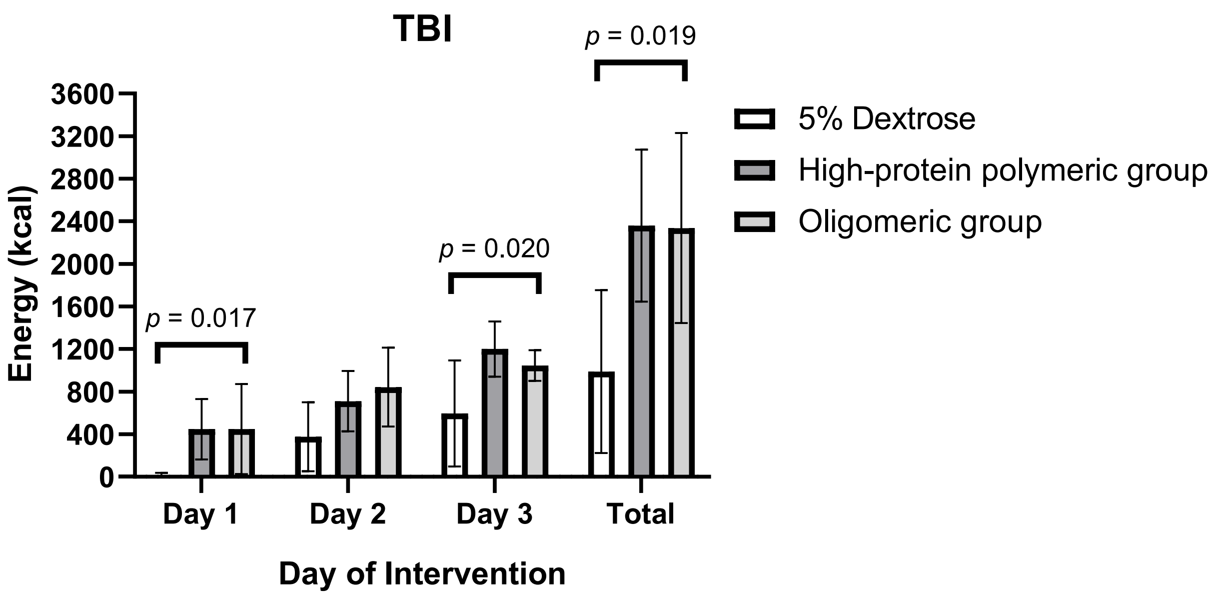

Fig. 3. Daily Intake in Non-TBI Patients (kcal)

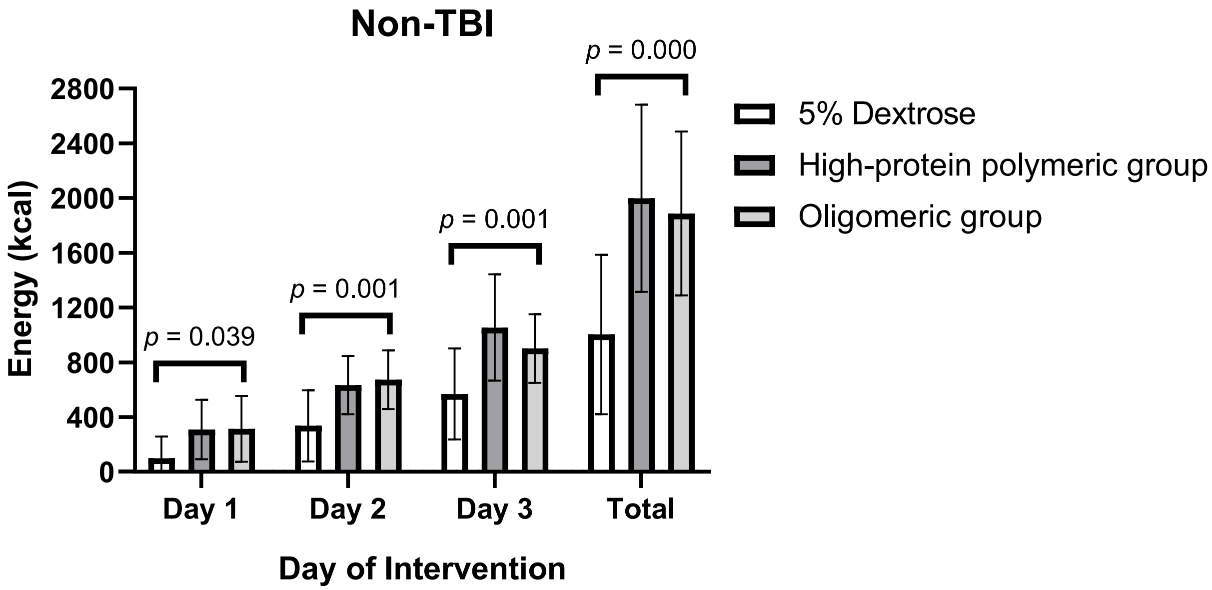

Fig. 4. Daily Protein intake in TBI patients (g)

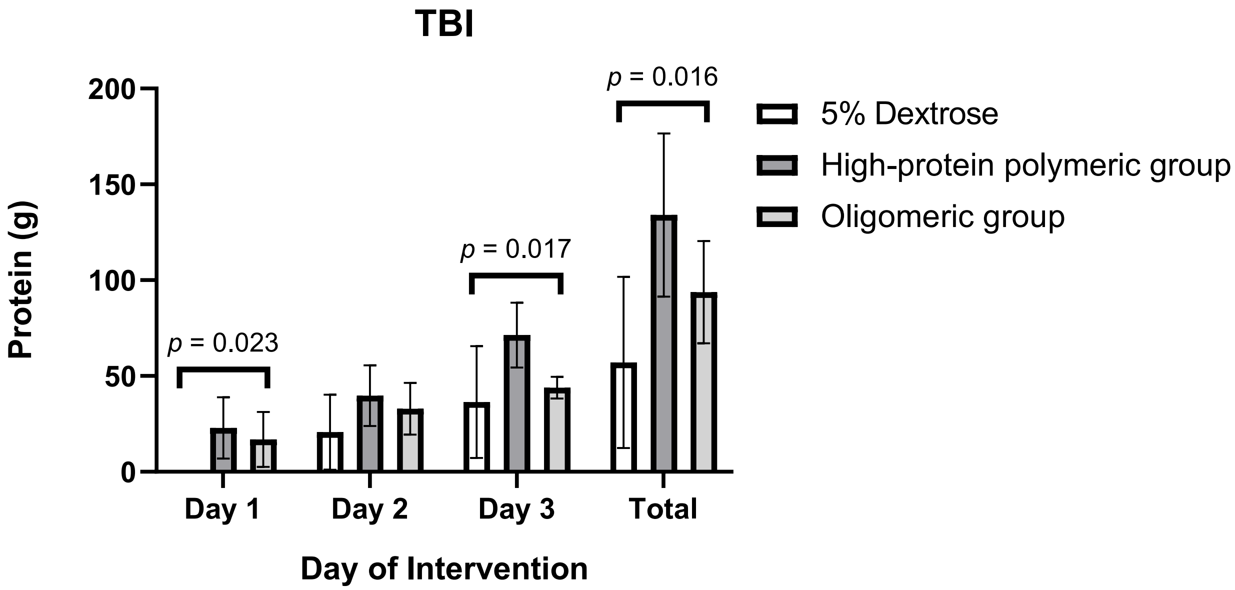

Fig. 5. Daily Protein intake in non-TBI patients (g)

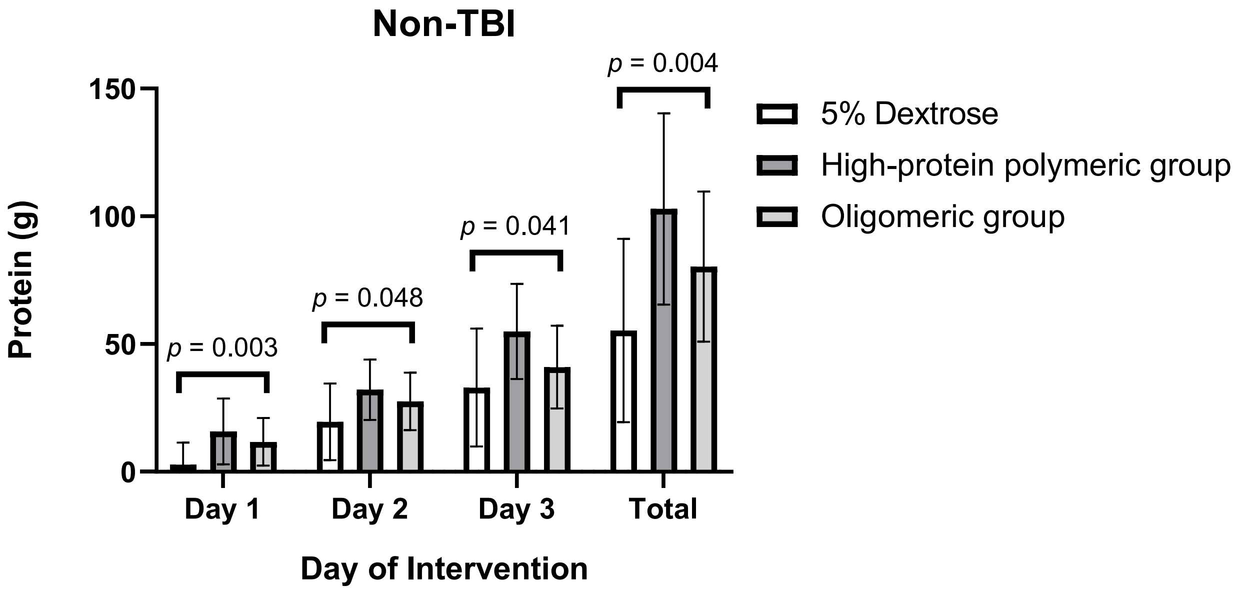

Table 4. Laboratory and scoring system results at baseline and at day 3 after initiating enteral nutrition

Parameter		TBI Control mean	SD	p-value	TBI High Protein Polymeric mean	SD	p-value	TBI Oligomeric mean	SD	p-value	NON TBI Control mean	SD	p-value	NON TBI High Protein Polymeric mean	SD	p-value	NON TBI Oligomeric mean	SD	p-value
TLC	Baseline	982.40	378.17	0.596	1071.43	554.93	0.514	914.00	415.66	0.345	815.94	513.67	0.389	1228.25	695.28	0.113	838.00	337.40	0.314
	Day 3	1208.80	639.47		1203.86	675.36		1232.2	583.16		970.41	591.28		973.17	542.60		762.00	577.08	
Serum Albumin	Baseline	3.14	0.83	0.709	2.81	0.62	0.827	2.98	0.61	0.700	2.80	0.84	0.452	2.95	0.84	0.548	3.33	0.53	0.212
	Day 3	2.96	0.47		2.76	0.50		2.9	0.32		2.96	0.59		3.13	0.65		3.09	0.55	
PLR	Baseline	167.19	82.27	0.586	151.97	51.24	0.716	279.21	211.39	0.405	482.83	454.46	0.163	296.84	270.54	0.814	351.72	271.04	0.515
	Day 3	185.95	77.70		166.52	77.4		196.33	95.70		280.00	238.60		291.89	173.74		399.32	218.10	
WBC	Baseline	10320.00	2107.61	0.684	11671.43	4530.16	0.760	15080.00	5987.24	0.411	16323.53	8069.20	0.122	13262.50	6963.51	0.041*	11313.33	4061.60	0.094
	Day 3	12060.00	2364.95		11000.00	4105.69		13300.00	5257.38		12511.76	6058.35		11687.50	7420.92		9655.56	3022.05	
IL-6	Baseline	55.0	31.12	0.686	159.71	168.62	0.499	29.5	11.44	0.500	170.29	227.84	0.277	120.25	203.60	0.071	59.34	97.50	0.374
	Day 3	121.48	184.65		171.93	193.75		107.58	169.94		121.44	149.76		67.16	99.34		177.28	270.04	
APACHE II Score	Baseline	19.2	8.44	0.529	21.0	4.32	0.731	23.2	5.40	0.045*	16.12	6.30	0.718	17.33	3.31	0.007*	17.33	3.24	0.205
	Day 3	18.0	8.63		20.86	6.15		26.4	3.13		16.71	7.30		13.83	1.95		15.67	4.80	
SOFA Score	Baseline	4.6	2.19	0.670	4.43	0.79	0.34	4.2	1.10	1.000	3.18	2.01	0.405	4.00	2.66	0.075	3.44	2.46	0.907
	Day 3	4.2	2.17		5.29	2.36		4.2	1.92		3.82	3.15		2.50	1.98		3.56	2.46	
NUTRIC Score	Baseline	2.0	2.12	0.178	2.57	1.40	0.655	4.0	1.87	0.477	2.88	1.80	0.483	3.08	1.44	0.022*	3.22	1.48	0.645
	Day 3	2.4	2.3		2.86	2.27		4.4	1.52		3.18	2.04		1.92	1.00		3.00	1.87	

Abbreviations: TBI: Traumatic Brain Injury; TLC: Total Lymphocyte Count; PLR: Platelet to Lymphocyte Ratio; WBC: White Blood Cell; IL-6: Interleukine-6; APACHE II Score: Acute Physiology and Chronic Health Evaluation II Score; SOFA Score: Sequential Organ Failure Assessment Score; NUTRIC Score: Nutrition Risk in Critically ill Score.

From our results, we have found that there were no differences in the mean TLC, serum albumin, PLR, and SOFA scores between pre and post intervention in each intervention for the TBI and non-TBI groups.

Table 5. Length of Stay

Groups		n	ICU Length of Stay Mean	ICU Length of Stay SD	Hospital Length of Stay Mean	Hospital Length of Stay SD
TBI	Control	3	35.33	52.58	46.33	60.50
	High Protein Polymeric	3	15.33	9.02	24.33	10.21
	Oligomeric	3	17.33	9.71	44.33	27.39
p-value			0.837		0.494	
NON TBI	Control	14	4.93	2.82	13.21	7.17
	High Protein Polymeric	10	7.60	6.20	16.60	9.35
	Oligomeric	8	6.00	3.51	17.38	6.95
p-value			0.402		0.361	

Abbreviations: TBI: Traumatic Brain Injury; ICU: Intensive Care Unit; n: number of patients included in analysis.

From the above data, we found that there was no significant difference between the length of stay in the ICU or in the hospital for each TBI and non-TBI group.

Table 6. Mortality Percentage

Hospital Mortality			Groups				
			Control	High Protein Polymeric	Oligomeric	n	*p-value*
TBI	Survive	n	3	3	3	9	0.574
		%	60.0%	42.9%	75.0%	56.3%	
	Non-survival	n	2	4	1	7	
		%	40.0%	57.1%	25.0%	43.8%	
NON TBI	Survive	n	14	9	8	31	0.889
		%	82.4%	75.0%	80.0%	79.5%	
	Non-survival	n	3	3	2	8	
		%	17.6%	25.0%	20.0%	20.5%	

From the above data, we found that there was no significant difference for hospital mortality in the TBI and non-TBI group.

FIGURE LEGENDS

Figure 1

To get a description of the inflammation process in our study patients, we initially planned several laboratory examinations, which were at admission time, on day 3, and day 7. However, due to the short duration of care in the ICU patients who were the subjects of our study, we only conducted an examination at the beginning of the patient's entry into the ICU and day 3.

Figure 2

There were significant differences in the amount of calorie intake in each intervention for the TBI and non-TBI groups.

Figure 3

Protein intake in the Dextrose 5% intervention group was the lowest compared to the group given high-protein and oligomeric polymeric formulas.

Christina Rusli
christina_rusli@yahoo.com
+ Add to contacts

Please find your galley proofs of your manuscript as attached files.
Please examine proofs very carefully because changes may be made by editor.
And English checker's comments and alternations are included in manuscript.

Please keep alterations to a minimum. Alterations from the original manuscript are not allowed in the proofs.
(Please write your corrections on the PDF proofs, or list them up in the e-mail message.
You do not need to revise Word file.)

Corrected proofs are to be send back by fax or e-mail as soon as possible
to:

JNSV staff
Center for Academic Publications Japan
2-4-16, Yayoi, Bunko-ku, Tokyo 113-0032, JAPAN
fax: +(81)-3-3817-5830
E-mail: jnsv_ed@capj.or.jp

They should be here by November 20.

Sincerely,

Admin JNSV
Journal of Nutritional Science and Vitaminology

Center for Academic Publications Japan
2-4-16 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

Tel. +81-3-3817-5821 Fax. +81-3-3817-5830
E-mail: jnsv_ed@capj.or.jp
https://mc.manuscriptcentral.com/jnsv

Christina Rusli
christina_rusli@yahoo.com
+ Add to contacts

The editorial team of the Journal of Nutritional Science and Vitaminology would like to thank you for your manuscript submission as part of your participation at the ACN 2019. We have received a great number of submissions, which has been reviewed by our editorial team. We are pleased to inform you that your manuscripts titled "Comparison of Different Early Enteral Feeding Formulas on Critically Ill Patients" and "Nutrition Therapy in Critically Ill Overweight Elderly Patient with Heart Failure, Myocardial Infarction, Pneumonia, and Chronic Kidney Disease" meets our selection criteria to be published in our special edition for the Asia Congress of Nutrition 2019.

I am attaching documents with some required edits that need to be applied to your manuscript before it's published. Please complete the following steps to revise your manuscript:

1. Revise your manuscript according to the reviewers's comments
2. Please activate Track Changes
3. Please follow the Author Guidelines for formatting the manuscript
4. Revised manuscript should be accompanied by a summary of your responses to the reviewers' comments. Please fill in your Response Form

You have 1 week to respond to this revision and resend the revised version of the manuscript and Response Form before 5th February, 2020.

Thank you for your kind attention

Kind regards,
Secretariat of ACN 2019

Download all attachments as a zip file

Please find your galley proofs of your manuscript as attached files.
Please examine proofs very carefully because changes may be made by editor.
And English checker's comments and alternations are included in manuscript.

Please keep alterations to a minimum. Alterations from the original manuscript are not allowed in the proofs.
(Please write your corrections on the PDF proofs, or list them up in the e-mail message.
You do not need to revise Word file.)

Corrected proofs are to be send back by fax or e-mail as soon as possible
to:

JNSV staff
Center for Academic Publications Japan
2-4-16, Yayoi, Bunko-ku, Tokyo 113-0032, JAPAN
fax: +(81)-3-3817-5830
E-mail: jnsv_ed@capj.or.jp

They should be here by November 20.

Sincerely,

Admin JNSV
Journal of Nutritional Science and Vitaminology

Center for Academic Publications Japan
2-4-16 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

Tel. +81-3-3817-5821 Fax. +81-3-3817-5830
E-mail: jnsv_ed@capj.or.jp
https://mc.manuscriptcentral.com/jnsv

Christina Rusli
christina_rusli@yahoo.com
+ Add to contacts