ORIGINAL ARTICLE

Comparative effect of protein dosage on nitrogen balance and health outcomes in critically ill patients

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Abstract

Objective: To compare the impact of two different doses of proteins on nitrogen balance and clinical outcomes in critically ill patients.

Method: The randomised clinical trial was conducted from November 2020 to May 2021 at the intensive care unit of Shifa International Hospital, Islamabad, Pakistan, and comprised critically ill adult patients of either gender at nutritional risk. They were divided into Group I receiving 1g per kilogramme body weight of protein, and Group II receiving 2g per kilogramme body weight of protein. Sequential Organ Failure Assessment scores were calculated for each case. Data was analysed using SPSS 23.

Results: Of the 88 patients, 45(51.13%) were in Group I; 28(62.2%) males and 17(37.8%) females with mean age 61±3.5 years. There were 43(48.86%) patients in Group II; 30(69.8%) males and 13(30.2%) females with mean age 64.4±11.6 years (p>0.05). There was no significant difference in nitrogen balance between the groups on day 1 (p=0.381). However, by the discharge day, nitrogen balance was significantly improved in Group II compared to Group I (p=0.001). There was a statistically weak negative relationship between nitrogen balance and Sequential Organ Failure Assessment score (r=-0.131). Nitrogen balance had no significant relationship with the number of ventilated days (r=-0.002), intensive care unit days (r=0.043) and length of hospital stay (r=0.089).

Conclusion: Nitrogen balance was significantly better in the critically ill patients who received 2g protein per kilogramme body weight compared to those receiving 1g protein per kilogramme body weight.

Clinical Trial Registration: ClinicalTrials.gov, NCT04468503.

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Introduction

A critical illness is a disease condition, either medical or surgical, that requires treatment in a critical care unit. Catabolism is a potentially fatal condition caused by serious tissue injury, which increases the demand for protein utilisation to facilitate rapid and appropriate healing of the tissues. Raised metabolic needs in intensive care unit (ICU) patients can cause a loss of lean body mass, leading to poor nutritional status. Appropriate nutrition support therapy may be necessary at this stage to improve health outcomes during a critical illness.[1]

During the metabolic breakdown phase of illness, protein serves as the fundamental source of energy. Critical illness is linked with catabolism and proteolysis, particularly in the skeletal muscles. The availability of amino acids in the blood circulation contributes to tissue anabolism as well as the synthesis of acute-phase proteins. Catabolism can also suppress immunity, which is further linked to increased mortality and slow recovery.[2] Increased protein consumption is thought to minimise the catabolic condition by providing adequate exogenous amino acids.[3]

The gluconeogenesis process, followed by proteolysis in critical illness, results in increased nitrogen excretion from the body. Nitrogen balance (NB) is one of the methods used for monitoring protein optimisation, which calculates the amount of nitrogen consumed from protein intake minus the amount of nitrogen losses.[4] NB is a good indicator of optimum protein intake and better health outcomes. However, there have been only a few large, randomised trials investigating NB-accommodated protein consumption in ICU patients.[5]

During critical illness, adequate amino acid supplementation may be necessary to prevent excessive proteolysis. Protein supplementation cannot completely stop catabolism, but it supports increased protein synthesis to compensate for some of the protein losses.[6] According to the current guidelines of the Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition, protein should be provided at a level of 1.2-2.0g/kg/day, with possibly higher amounts for obese

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patients or those with multiple traumas or burns.[7]

Various meta-analyses and recent randomised controlled trials (RCTs) have indicated that a hyper-calorie and hypo-protein diet increases the risk of complications in malnourished ICU patients.[8] Recent literature has reported the benefits of increasing protein for malnourished critically ill patients.[9] Numerous studies regarding protein recommendations for critically ill patients, and its association with NB have been conducted worldwide, but there is limited evidence comparing various protein dosages.[4] Particularly in Pakistan, there have been limited investigations, with no standard cut-off value. A cross-sectional, observational study was conducted in the ICU at a hospital, aiming to determine the protein intake of various groups in relation to NB.[10] However, until now, to our knowledge, no study has reported on the comparative effects of different protein dosages on NB and health outcomes in critically ill patients. The current study was planned to fill the gap in literature by comparing the impact of two different doses of proteins on NB and clinical outcomes in critically ill patients.

Patients and Methods

The single-blind randomised clinical trial was conducted from November 2020 to May 2021 at the Shifa International Hospital (SIH), Islamabad, Pakistan, and comprised critically ill patients at nutritional risk. The patients were divided into Group I receiving 1g/kg body weight of protein, and Group II receiving 2g/kg body weight of protein. The patients were kept blinded to their respective group.

After approval from the ethics review committee of SIH / Shifa Tameer-e-Millat University (STMU) and Shifa Clinical Research Centre, Islamabad, the study was conducted in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[11]

The sample size was determined using the World Health Organisation (WHO) calculator in the light of earlier studies[5,12,13] with 5% significance, indicating the acceptable probability of a Type I error. The power of the test was kept 80%, representing the likelihood of detecting a true effect if it exists. The standard deviation was,[8,9] the test value of the population mean for the low protein group was 9.7 and the anticipated population mean for the high protein group was 4.1. The sample size was inflated by 10%. A simple randomization technique was employed to assign eligible participants to either Group 1 or Group 2.

The study included critically ill adult patients of either gender who had been in ICUs, high-dependence units (HDUs) and step-down units (SDUs) for >48 hours and who were at nutritional risk, as assessed by Nutrition Risk in Critically ill (NUTRIC) score >3.[12] Patients under 18 years of age, those on physician-prescribed protein restrictions, or on ventilator support for >72 hours were excluded, and sp were patients with ICU stay <48 hours, and those expected to have life support withdrawn within 7 days.

Data was collected after taking informed consent from all the patients. the Acute Physiology and Chronic Health Evaluation (APACHE-II) score assessed disease severity, the Sequential Organ Failure Assessment (SOFA) score evaluated organ function, and NUTRIC score identified nutritional risk.[12]

Protein was administered through oral, enteral, or parenteral routes, adjusted to patients' tolerance and medical status. Protein sources included oral/tube feeds based on egg whites or supplements (Beneprotein Boost, Peptamen, Nova Source, Resource Optimum, Resource Diabetes), while parenteral administration used standard amino acid solutions (5% Aminoplasmol, 10% Aminoplasmol, 5% Aminovil, 10% Aminoluban, Nutriflex Tripple Chamber).

Aferm collecting demographic information as well as APACHE-II and NUTRIC scores, further data included Glasgow Coma Scale (GCS), renal function test and dietary assessments every 24 hours. Subsequently, SOFA score, urine urea nitrogen, C-reactive protein (CRP), albumin and liver function tests (LFTs) were measured every 72 hours. Lastly, a 30-day follow-up tracked mortality and re-hospitalisation.

Baseline characteristics, such as age, gender, body mass index (BMI), medical history, recent hospitalisation and smoking status, were extracted from the medical records. Initial APACHE-II and NUTRIC score screenings occurred within 24 hours of ICU admission. Daily data encompassed diagnosis category, vital signs and biochemical values. Dietary assessments were conducted and compared to ASPEN guidelines for recommended caloric intake (25-30kcal/kg/day).[13] Patients' actual caloric intake was monitored and contrasted with the guidelines. Urine urea nitrogen was measured for NB calculations [6] from 24-hour urine samples collected every 72 hours while in the ICU.

Data was analysed using SPSS 23. Data was expressed as mean±standard deviation or as frequencies and percentages, as appropriate. Kolmogorov-Smirnov test was used to assess data normality, validating the use of parametric statistical tests for further analysis. Independent sample t-test was used to compare NB in the groups. Paired t-test was used to compare the change in NB within the groups, while the relationship between NB and various clinical outcomes were determined using the Pearson correlation. $P<0.01$ was kept as the level of significance.

Results

Of the 376 patients screened, 88(23.4%) were included (Figure-1). Of them, 45(51.13%) were in Group I; 28(62.2%) males and 17(37.8%) females with mean age 61±3.5 years. There were 43(48.86%) patients in Group II; 30(69.8%) males and 13(30.2%) females with mean age 64.4±11.6 years (p>0.05). There were no significant differences between the groups at baseline (Table-1).

The mean calorie intake was 1755±273 and the mean protein intake was 88±32 (Table-2).

There was no significant difference in NB between the groups on day 1 (p=0.381). However, by the discharge day, NB was significantly improved in Group II compared to Group I (p=0.001) (Table-3, Figure-2).

There was a significant positive correlation of the length of

Table-1: Baseline characteristics of the patients.

Characteristics	Group I n (%)(n=45)	Group II n (%)(n=43)	Overall n (%)(n=88)	*p*-value
Mean Age (years)	61±3.5	64.4±11.6	62.7±12.6	>0.05
Gender				>0.05
Male	28 (62.2%)	30 (69.8%)	58 (65.9%)	
Female	17 (37.8%)	13 13 (30.2%)	30 (34.0%)	
Mean BMI	26.7 ± 4.8	27.0 ± 6.4	26.9 ± 5.6	>0.05
Diagnosis Category				
Respiratory	30 (66.7%)	27 (62.8%)	57 (61%)	>0.05
GI Disease	0 (0%)	2 (4.7%)	2 (2.3%)	
Nephrology	4 (8.9%)	2 (4.7%)	6 (6.8%)	
Neurology	3 (6.7%)	4 (9.3%)	7 (8%)	
CVD Disease	4 (8.9%)	2 (4.7%)	6 (6.8%)	
Other	4 (8.9%)	6 (14.0%)	10 (11%)	
Past Medical History				
>1 comorbids	32 (71.1%)	30 (69.8%)	62(70%)	>0.05
Nil	13 (28.9%)	13 (30.2%)	26(30%)	
Mean GCS	13.1 ± 2.3	13.7 ± 1.6	13.4 ± 2	>0.05
Smoking History	20 (44.4%)	16 (37.2%)	36 (40%)	>0.05
Mean Scores				
APATCHE Score	15.5±4	17.8±4.4	16.7±4.3	>0.05
NUTRIC Score	5.8±1.5	5.5 ±1.4	5.7±1.5	>0.05
SOFA Score	6.7±1.8	13.7±1.6	5.9±1.9	<0.001
Study Exit	30 (66.7%)	28 (65.1%)	58(65%)	>0.05
Mean Biochemical Variables Distribution				
Haemoglobin	11.8±2.9	12.1±2.9	--	>0.05
Haemoglobin A1c	7.6±2.7	6.9±2.3	--	
Magnesium	1.7±0.4	1.8±0.39	--	
Total Bilirubin	1.1±0.9	1.6±2.6	--	
Creatinine	2.4±2.1	1.8±1.5	--	
Albumin	2.9±0.5	2.9±0.63	--	
C-Reactive Protein	126.1±108.6	137.3±211.6	--	
White Blood Cells	16376.4±7915	15021.6±6379	--	
Nitrogen Balance	-8.6±4.4	-9.4±4.8	--	
Platelet	209333.3±105163	210444.1±98504	--	

BMI: Body mass Index, GI: Gastrointestinal, CVD: Cardiovascular diseases, GCS: Glasgow coma scale, APATCHE: Acute physiology and chronic health evaluation. NUTRIC: Nutrition risk in critically ill; SOFA: Sequential organ failure assessment, SD: Standard deviation.

Table-2: Caloric protein intake achieved by the patients.

Variable	Recommended Mean ±SD	Actual Intake in ICU Mean ±SD	% Intake of RDA
Energy (kcal/kg/day)	2150±208	1755±273	83
Protein (g/kg/day)	93.6±29	88±32	94

SD: Standard deviation, RDA: Recommended dietary allowance.

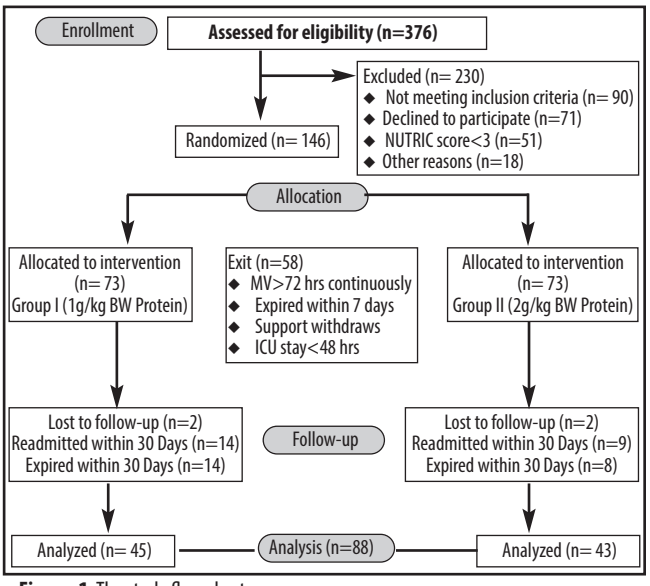

Figure-1: The study flow chart.
MV: Mechanical ventilation, ICU: Intensive care unit.

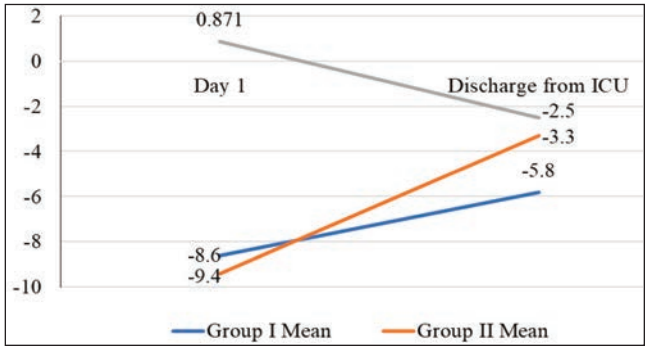

Figure-2: Comparison of nitrogen balance NB) at Day 1 and discharge from intensive care unit (ICU).

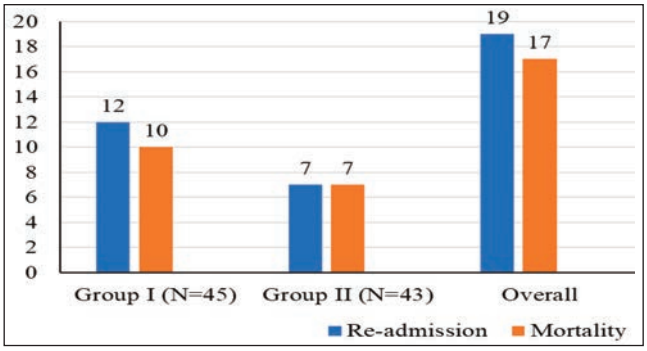

Figure-3: Follow-up after discharge from intensive care unit (ICU).

Table-3: Intergroup comparison of change in nitrogen balance (NB).

	Mean Nitrogen Balance		Paired Difference				*p*-value
	Day 1	At Discharge	SD	Std. Error Mean	95% Confidence Interval of the Difference		
					Lower	Upper	
Group I	-8.6	-5.8	3.9	0.58	-3.9	-1.606	<0.001
Group II	-9.4	-3.3	5.2	0.80	-7.8	-4.5	<0.001

* Significant at p<0.01; SD: Standard deviation.

Table-4: Correlational matrix between clinical outcomes and nitrogen balance (NB).

	Mean±SD	1	2	3	4	5
1. Length of ICU Stay	9.59±4.1	---	---	---	---	---
2. Length of MV Dependency	1.83±1.5	0.65**	---	---	---	---
3. Length of Hospital stay	13.94±5.3	0.88**	0.59**	---	---	---
4. SOFA score variation over time	-1.75±1.6	-0.75	-0.063	-0.155	---	---
5. Variation in NB	4.43±4.9	0.043	-0.002	0.089	-0.131	1

**. Correlation is significant at the 0.01 level (2-tailed); MV: Mechanical ventilation, SOFA: Sequential organ failure assessment, NB: Nitrogen balance, ICU: Intensive care unit, SD: Standard deviation.

hospital stay (LOS) with the length of ICU stay (r=0.88, p<0.001) and length of mechanical ventilation (MV) dependence (r=0.59, p<0.001) The improvement in NB showed a moderate negative correlation with LOS (r=-0.131, p<0.001). SOFA score variation over time displayed a moderate negative correlation with LOS (r=-0.75, p<0.001) and a weak negative correlation with length of MV dependence (r=-0.063, p=0.002) (Table-4).

Discussion

Positive association of clinical outcomes with improved protein intake in critically ill patients was observed, which inspired the current clinical trial to analyse the influence of two different protein prescriptions on NB and outcomes in critically ill patients.[15] All patients admitted to the ICU had negative NB, indicating the catabolic state, and none had positive NB in the current study. The findings were consistent with multiple similar trials that also reported negative NB in approximately 100% of critically ill patients.[14,15]

A recent RCT was compared two groups with 'standard' or 'high' protein supply (1.2g and 1.8g protein/kg body weight per day, respectively)[14] by medical nutrition treatment. In critically ill patients, studies have examined the hypothesis that higher total protein intake was linked to lower 90-day mortality and improved protein biomarkers, such as serum pre-albumin, serum transferrin, and 24-hour urinary urea nitrogen (UUN)[8,16] The trials indicated distinct clinical findings, but could not elaborate on the protein dosage to analyse which one was more potent.

Through the strategic use of supplementary protein feedings, patients' actual protein intake was elevated in the current study, reaching a commendable 94% of the recommended value. By incorporating supplementary protein feedings into the overall nutritional support plan, the study's positive outcomes underscore the significance of personalised and targetted interventions to enhance nutrition in ICUs. This proactive approach not only reflects the dedication of the healthcare team, but also emphasises the potential benefits of optimised protein intake in improving patient outcomes during their ICU stay.[17,18]

The findings of the current study confirmed that an increased protein intake was comparatively beneficial (p<0.001) in terms of improving NB compared to a low protein intake. This was in line with literature.[18] When comparing the effects of a protein-fortified diet and a standard diet with ICU protocol care on NB of critical care patients, a study noted a significant improvement in the protein-fortified diet group.[19]

All the critically ill patients in the current study were in the catabolic state (Figure-2), as indicated by negative NB regardless of their diagnoses. This was consistent with literature.[7]

In both the study groups, the mean NB at day 1 was higher than at discharge. This suggests that both groups experienced a decline in negative NB over time or improvement towards a positive value. The level of significance (p<0.001) indicated that the observed NB changes were unlikely to be due to random chance. The standard deviations (SDs) help understand the variability in NB measurements within each group. Higher SD values indicate more dispersion or spread of the data points around the mean. The 95% confidence intervals (CIs) of the difference indicated the range within which the researchers were 95% confident that the true difference in NB between day 1 and discharge happened to be significant.[18] Some recent studies reported similar findings.[18] As such, it is possible to hypothesise that high-protein medical nutrition therapy following the onset of trauma could effectively reduce endogenous proteolysis, thereby contributing to muscle mass preservation.[8]

In the current study, there was a significant relationship between NB and SOFA score (Table-4), which was in line with another observational study.[3] However, the study yielded inconclusive findings regarding the link between increased protein intake and clinical outcomes. RCTs comparing protein doses in ICU patients are limited, and vary greatly in their study designs and basic outcomes. These studies generally had relatively small differences in the amount of protein delivered to them. A systematic review of existing studies found no difference in mortality with increased protein consumption.[20]

However, the current study identified a link of protein

intake, LOS and ICU stay with MV support and mortality rate. This connection is particularly crucial for critically ill patients undergoing an extended ICU stay, such as those with multiple traumatic injuries. A high-protein diet is beneficial in critical illness, as it supports muscle mass preservation, and aids recovery. High-protein diet remains a valuable tool in managing muscle loss and promoting healing in clinical settings.[21] However, long-term research is needed in this regard. Future research needs to compare the quality and type of proteins that will incur better outcomes in critically ill patients.

Conclusion

Catabolism-induced muscle mass loss and loss of functional proteins are linked to poor outcomes in critically ill patients. Therefore, it is suggested that an adequate supply of protein should be included in a medical nutrition concept to improve positive NB.

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References

1. Sharma K, Mogensen KM, Robinson MK. Pathophysiology of Critical Illness and Role of Nutrition. Nutr Clin Pract 2019;34:12-22. doi: 10.1002/ncp.10232.
2. Hsu CC, Sun CY, Tsai CY, Chen MY, Wang SY, Hsu JT, et al. Metabolism of Proteins and Amino Acids in Critical Illness: From Physiological Alterations to Relevant Clinical Practice. J Multidiscip Healthc 2021;14:1107-17. doi: 10.2147/JMDH.S306350.
3. Arabi YM, Al-Dorzi HM, Sadat M. Protein intake and outcome in critically ill patients. Curr Opin Clin Nutr Metab Care 2020;23:51-8. doi: 10.1097/MCO.0000000000000619.
4. Singer P. Protein metabolism and requirements in the ICU. Clin Nutr ESPEN 2020;38:3-8. doi: 10.1016/j.clnesp.2020.03.026.
5. Danielis M, Lorenzoni G, Azzolina D, Iacobucci A, Trombini O, De Monte A, et al. Effect of Protein-Fortified Diet on Nitrogen Balance in Critically Ill Patients: Results from the OPINiB Trial. Nutrients 2019;11:972. doi: 10.3390/nu11050972.
6. Wang S, Zhao X, Wang Q, Wu Y, Xu J, Li R, et al. Impact of early enteral nutrition on ventilator associated pneumonia in intubated severe trauma patients: A propensity score-matched study. Front Nutr 2023;10:1172526. doi: 10.3389/fnut.2023.1172526.
7. Chatterjee R, Garg AK. Nutrition Delivery in Critically Ill Patients. In: Malbrain MLNG, Wong A, Nasa P, Ghosh S, eds. Rational Use of Intravenous Fluids in Critically Ill Patients. Cham, Switzerland: Springer Nature Switzerland GA, 2024; pp 275-92. Doi: 10.1007/978-3-031-42205-8.
8. Dresen E, Weißbrich C, Fimmers R, Putensen C, Stehle P. Medical high-protein nutrition therapy and loss of muscle mass in adult ICU patients: A randomized controlled trial. Clin Nutr 2021;40:1562-70. doi: 10.1016/j.clnu.2021.02.021.
9. De Waele E, Jakubowski JR, Stocker R, Wischmeyer PE. Review of evolution and current status of protein requirements and provision in acute illness and critical care. Clin Nutr 2021;40:2958-73. doi: 10.1016/j.clnu.2020.12.032.
10. Khan SA, Zahid M, Naqvi S, Kirmani M, Zaidi SK, Khalil H. Influence of Macronutrient Intake on Nitrogen Balance in Critically Ill Patients. Pak Armed Forces Med J 2015;65(Suppl 1):s31-4.
11. Rigutto-Farebrother J, Ahles S, Cade J, Murphy KJ, Plat J, Schwingshackl L, et al. Perspectives on the application of CONSORT guidelines to randomised controlled trials in nutrition. Eur J Nutr 2023;62:2319-32. doi: 10.1007/s00394-023-03137-5.
12. Kim TJ, Park SH, Jeong HB, Ha EJ, Cho WS, Kang HS, et al. Optimizing Nitrogen Balance Is Associated with Better Outcomes in Neurocritically Ill Patients. Nutrients 2020;12:3137. doi: 10.3390/nu12103137.
13. Palmer J. Enteral Feeding in Critically Ill Adults: An Evidenced Based Practice Update. [Online] 2023 [Cited 2025 March 17]. doi: 10.28971/532023PJ77. Available from URL: https://digitalcollections.ric.edu/record/1636?v=pdf
14. Berger MM, Reintam-Blaser A, Calder PC, Casaer M, Hiesmayr MJ, Mayer K, et al. Monitoring nutrition in the ICU. Clin Nutr 2019;38:584-93. doi: 10.1016/j.clnu.2018.07.009.
15. Li L, Li R, Wu Z, Yang X, Zhao M, Liu J, et al. Therapeutic strategies for critically ill patients with COVID-19. Ann Intensive Care 2020;10:45. doi: 10.1186/s13613-020-00661-z.
16. Arabi YM, Al-Dorzi HM, Mehta S, Tamim HM, Haddad SH, Jones G, et al. Association of protein intake with the outcomes of critically ill patients: a post hoc analysis of the PermiT trial. Am J Clin Nutr 2018;108:988-96. doi: 10.1093/ajcn/nqy189.
17. Rougier L, Preiser JC, Fadeur M, Verbrugge AM, Paquot N, Ledoux D, et al. Nutrition During Critical Care: An Audit on Actual Energy and Protein Intakes. JPEN J Parenter Enteral Nutr 2021;45:951-60. doi: 10.1002/jpen.1962.
18. van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. Crit Care 2019;23:368. doi: 10.1186/s13054-019-2657-5.
19. Tezze C, Sandri M, Tessari P. Anabolic Resistance in the Pathogenesis of Sarcopenia in the Elderly: Role of Nutrition and Exercise in Young and Old People. Nutrients 2023;15:4073. doi: 10.3390/nu15184073.
20. Devries MC, Sithamparapillai A, Brimble KS, Banfield L, Morton RW, Phillips SM. Changes in Kidney Function Do Not Differ between Healthy Adults Consuming Higher- Compared with Lower- or Normal-Protein Diets: A Systematic Review and Meta-Analysis. J Nutr 2018;148:1760-75. doi: 10.1093/jn/nxy197.
21. Moon J, Koh G. Clinical Evidence and Mechanisms of High-Protein Diet-Induced Weight Loss. J Obes Metab Syndr 2020;29:166-73. doi: 10.7570/jomes20028.

Author Contribution:

ZB: Concept, data curation, formal analysis, investigation, methodology, project administration, resources, software, visualisation, writing-original draft and final approval.

MS: Concept, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing, review, editing and final approval.

AH: Investigation, methodology, project administration and final approval.