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About the Journal

Clinical Science of Nutrition is an international, peer-reviewed, open access journal. It publishes research articles, reviews, case reports, and letters to the editor on all aspects of nutrition and dietetics.

Clinical Science of Nutrition is a triannual journal that is published in English in April, August, and December.

Abstracting and indexing

Clinical Science of Nutrition is covered in the following abstracting and indexing databases;

- TR-Index
- EBSCO
- Gale
- CNKI

Aims and Scope

The journal aims to contribute to the literature by publishing high impact content and become one of the leading publications of the field while functioning as an open discussion forum on significant issues of current interest. Clinical Science of Nutrition also aims to have significant input in emphasizing the increasing importance of clinical nutrition in Turkey and the region, identifying the effects of differences between societies on study results in a clearer way and converting clinical applications into scientific publications as well as forming a bridge between West and East.

The scope of Clinical Science of Nutrition includes original research articles, review articles, case reports, conference reports, and letters to the editor as well as editorials, abstracts from international and national congresses, panel meetings, conferences and symposia. As an online-only publication, in addition to traditional manuscript submissions, Clinical Science of Nutrition is also able to process video, audio and interactive software submissions. Authors are encouraged to submit their content in the most appropriate medium to best convey their findings to the audience of Clinical Science of Nutrition.

The journal covers all aspects of nutrition and dietetics including prevalence of malnutrition and its effects on clinical results; nutritional support and delivery methods and their advantages and disadvantages; nutritional support products and their side effects; immune system and nutritional support; ERAS protocol and nutritional support; home parenteral and enteral nutrition; nutrition support teams and their necessity, challenges and potential solutions of nutritional support.

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State of nutrition profession in Asian countries and its association with food security, anemia and stunting

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ABSTRACT

Background: The continent of Asia has a vast range of complex nutritional issues ranging from undernutrition and its consequences e.g. anemia, stunting, wasting etc. to overnutrition and its related diseases. Most of the strategies used to combat these health crises are aimed at reducing poverty, increasing food production, and fortifying food. Efforts for identifying sustainable solutions by using existing resources are rare. The reason may be limitations in finding appropriate professional expertise and human resources for these efforts.

Objective: This paper aims to estimate the nutrition profession competence in Asia and to explore its association with food security and the nutrition situation in Asia.

Methods: For comparing State of Nutrition Profession in various countries of Asia four indicators were used: Volume of relevant Research output, Quality of relevant research output, Higher Education opportunities in Nutrition and Country's Membership international nutrition organizations. Data available at relevant websites was used to collect information about these indicators and a composite index was developed to develop a single variable termed Nutrition Competence Index. Data for Gross Domestic Product (GDP) and Nutritional issues were obtained from the website of the World Bank, and data for food security from Impact Economist. Scale level data was transformed as ranks to represent the relative position of various countries in relation to the study variables. Associations between variables were assessed by studying correlations. Regression analysis was done to estimate the relative role of various indicators in determining the outcome.

Results: The study results indicate that the association between Nutrition research activity score and Food Affordability Score (r=.445, P=.038, n=20) and association between Nutrition Professional Activity Score and Food Availability Score (r=.557, P=.007, n=20) were statistically significant even after controlling for GDP. Similarly, Nutrition research activity scores were found significantly linked with rates of anemia under 5-year-old children (R2 = .52, F(5, 22) = 4.932, p = .004) and rates of stunting under 5-year-old children, (R2 = .58, F(5, 19) = 5.321, p = .003).

Conclusion: It is concluded from this study that Nutrition Competence has the potential to reduce the impact of GDP variations on food security and malnutrition globally, but its strength and utilization vary by continent, particularly in Asia.

Keywords: nutrition competence, GDP, food security, nutrition situation, nutritional issues

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Introduction

The realization of the importance of good nutrition as an essential factor for human health as well as sustainable development is increasing.[1] The FAO report published in 2019 "Food Security and Nutrition in the World: Safeguarding against Economic Slowdowns and Downturn" clearly demonstrated the association among countries economic status (as assessed by GDP per capita), food security and nutritional status of their populations.[2] It is obvious that the level of GDP translates into the personal income of the population, which is the main determinant of the degree to which the population's needs are satisfied and countries experiencing rapid GDP per capita growth have seen the greatest improvements in food security.[3] Unfortunately, the majority of people with food insecurity lives in the Asian regions.[4] A sharp increment in food security is observed in developing countries during the last 3 decades and it is alarming that highest number of undernourished people lives in Asia and this continent was a home to 55 percent (402 million) of the people in the world affected by hunger in 2022.[5,6] Malnutrition due to limited food availability reflected as stunting and anemia are highly prevalent in Asia.[7]

It is also noteworthy that in addition to the food access, diet itself is also a contributing factor in the development of many chronic diseases including obesity, cardiovascular disease, hypertension, stroke, type 2 diabetes, metabolic syndrome, some cancers, and perhaps some neurological diseases.[8] It is of immense concern that prevalence of these diseases in Asian countries are also escalating that affects the quality of life of people lives in these regions and current studies revealed the metabolic risk factors including obesity, and overweight population mostly with central obesity.[9] To overcome these health crises, strategies employed were largely targeted to reduce poverty to make possible the availability of food to the population, to increase food production, and food fortification to optimize food utilization. The current analysis expands on our earlier investigation into the relationship between food security and nutrition competence and the role of GDP in predicting nutritional issues across Asian countries.[10]

Nutrition professionals play a pivotal role not only in addressing the epidemiological aspects of nutrition-related diseases but also in enhancing access to social, health, and basic services. Consequently, the presence of professionals with an academic background in nutrition within the public health field offers a promising resource for the formulation of action plans aimed at eradicating these nutritional concerns. Furthermore, their involvement in emergency preparedness and response efforts, capacity building, and training initiatives underscores the breadth of their impact. In times of crisis, nutrition professionals can ensure access to nutritious food and essential services, mitigating the effects on nutrition-related health outcomes. Overall, their expertise and engagement are essential for developing targeted and effective action plans that encompass a wide range of social, health, and basic service considerations, ultimately working towards the eradication of nutritional concerns. Certainly, the inclusion of nutritionists in multidisciplinary teams is imperative, given their academic expertise and understanding of diseases linked to diet. Their ability to suggest preventive measures and treatment options adds significant value to such teams.[11]

This study aimed (i) to estimate the nutrition profession competence in Asia, (ii) to explore the association of nutrition competence with food security and nutrition situation in Asia and (iii) to elucidate the potential of nutrition competence in determining the benefit from higher income of countries.

Main Points

- Malnutrition remains a public health problem worldwide despite of several nutritional interventional programs.
- Strategies used to reduce the burden of malnutrition usually focusing on alleviating poverty, food fortification, and supplements provision.
- However, despite all these efforts, the area of nutrition education and research is still not in the limelight.
- This research estimated the nutrition profession competence in Asia and also explored its association with food security and the nutrition situation.
- The findings supports that Nutrition Competence has the potential to reduce the impact of GDP variations on food security and malnutrition globally.

Methodology

Study Variables and Data Resources: This research is based on the use of secondary data in which information about the countries was retrieved from documents and statistics publicly available on the websites of international organizations. In this study, groups of variables related

to GDP and food insecurity as a predictor of nutritional issues in Asian countries as well as to develop nutritional competence were carefully selected. The prime source of data for information about GDP and Nutritional issues (including Anemia in under 5-year child, Hypertension, overweight in Adults and children, severe Wasting Under 5, Stunting Under-5, Undernourished Population and wasting Under-5) in Asian countries is taken from the website of "The World Bank" and information about the indicators to assess the status of food insecurity in these countries was extracted from the website of "Economist Impact".[12,13]

Measurement of Nutrition Profession Index: The estimation of Countries' Nutrition Profession status was done by assessing commitment to and competence in the field of nutrition. "Participation in nutrition activity" and "availability of higher education opportunities in nutrition" indicated commitment while research output and quality of research output indicated competence. Counties were ranked on these parameters in tertiles and sum of scores on these variables was used as Nutrition Profession Index. Higher scores were expected to indicate higher action potential. Validity of the index was judged by using the publication of national food based dietary guidelines as an outcome variable. NPI of countries that have published or not published NFBDG was compared and was found to be significantly higher P=0.029 for countries that have published NFBDG (8.2) as compared to those that have not published NFBDG (6.8).

(i) Nutrition Higher Education Score in which proportion of Higher Education Institutes in a country that are offering nutrition degree programs (Number of institutions offering nutrition/total number of HEIs listed in World higher Education Database) https://www.whed.net/home.php. (ii) Nutrition research Excellence Score: H-Index of all the Scholars from any country that are listed in AD scientific Index as Scientists in the field of Nutrition and Dietetics https://www.adscientificindex.com. (iii) Nutrition research Activity Score: Research output was estimated by comparing the number of scientific publications in the past 5 years in the area of human Nutrition in Google Scholar. The ratio of population to number of publications and Nutrition Research Activity Score (NRAS) was generated by converting this information to normal scores. (iv) Nutrition Professional Activity Score: Information about membership of country's nutrition organizations in international bodies i.e. the International Union of Nutritional Sciences (IUNS), the International Confederation of Dietetic Associations (ICDA) and International Affiliate of the Academy of Nutrition and Dietetics (IAAND) was retrieved from relevant websites and scores were assigned according the number of bodies in which country's nutrition bodies participated.[14,15,16]

Data Analysis: Data was analyzed using SPSS version 20. Scale level data was transformed as ranks to represent the relative position of various countries in relation to the study variables. Countries were categories in groups to study associations with indictors having data as categories. Associations between variables was assessed via Pearson correlation. Multiple Linear Regression analysis was done to estimate the relative role of various indicators in determining the outcome.

Results

1. Nutrition competence in Asia

Status of the Nutrition competence is Asia among six continents were presented as:

(i) State of Nutrition Focus in HEIs in Asia

Table 1 and Table 2 provides basic descriptive statistics of the proportion of HEIs with Nutrition programs in various continents. Results shows that Asia ranked 5th among 6 continents (Table 1) with HEIs with Nutrition programs and among 42 countries in Asia 12 countries are those which does not has the Nutrition programs in their universities (Table 2).

Table 1. Mean proportion of HEIs with nutrition programs in various continents

Continent Name	Africa	Asia	Europe	North America	Oceania	South America
Mean	7.79	7.11	5.62	10.64	7.78	20.90
SD	10.14	8.61	6.32	9.84	10.35	14.11

Table 2. Proportion of countries having various percentage of HEI with nutrition programs

Continent name	None		1 to 10%		>10%		Total	
	n	Row %	n	Row %	n	Row %	n	Row %
Africa	17	34.7%	19	38.8%	13	26.5%	49	100%
Asia	12	28.6%	19	45.2%	11	26.2%	42	100%
Europe	15	35.7%	20	47.6%	7	16.7%	42	100%
North America	6	30.0%	3	15.0%	11	55.0%	20	100%
Oceania	4	57.1%	0	0.0%	3	42.9%	7	100%
South America	2	16.7%	1	8.3%	9	75.0%	12	100%

Table 3. Dietetic research output

Continent name	Dietetic OP level					
	Low DO overall		Medium DO overall		High DO overall	
	Count	Row N%	Count	Row N%	Count	Row N%
Africa	22	40.7%	17	31.5%	15	27.8%
Asia	17	33.3%	16	31.4%	18	35.3%
Europe	11	22.9%	15	31.3%	22	45.8%
North America	13	38.2%	12	35.3%	9	26.5%
Oceania	7	36.8%	9	47.4%	3	15.8%
South America	2	16.7%	4	33.3%	6	50.0%

(ii) Nutrition research output and Excellence in Asia

Dietetic research output

Table 3 represents the distribution of dietetics research output (score based on the ratio of continent's population to number of publications in Nutrition in the past 5 years) across different continents. The table shows the number of dietetic research outputs at three different levels: low, medium, and high. According to the results Africa has highest research output (54) among other continents. Asia has second highest rate of dietetic research output (51) among others in which 17 were at the low level (33.3% of the total), 16 were at the medium level (31.4% of the total), and 18 were at the high level (35.3% of the total). Whereas, least was observed in South America.

Nutrition research excellence

Table 4 shows that countries in continent Oceania actively contribute to promoting Nutrition research than others. Asia ranked 3rd in Nutrition Research excellence with moderate number of researchers in this field (13.44), number of research institute (15.55) and mean H-index of researchers (21.53).

(iii) Nutrition Professional Activity in Asia:

Nutrition profession activity score was measured from number of memberships of country's nutrition organizations in international bodies (IUNS, ICDA and IAAND) (Figure 1) and results revealed that among 51 countries in Asia 25 countries has memberships with Nutrition related international organizations (Table 5).

2. Nutrition competence index:

Overall, all four indicators to assess Nutrition competence in Asia shows a positive correlation (Table 6).

3. Association of nutrition competence with food security and nutrition situation in Asia

Table 7 shows a positive, statistically significant correlations ($p<0.01$and $p<0.05$) were observed between

Table 4. Nutrition research excellence

Reserch parameters	Continents					
	Africa	Asia	Europe	North America	Oceania	South America
	Mean	Mean	Mean	Mean	Mean	Mean
Number of Researchers	6.04	13.44	9.82	31.27	37.33	5.38
Number of Institutions	7.32	15.55	25.15	8.16	23.11	7.68
Mean H INDEX of Researchers*	10.21	21.53	18.32	62.27	65.67	6.50

Table 5. Membership of countries from Asia in international organizations

		Continent						Total
		Africa	Asia	Europe	North America	Oceania	South America	
None	Count	32	26	24	24	17	6	129
	%	59.3%	51.0%	50.0%	70.6%	89.5%	50.0%	59.2%
IUNS	Count	20	13	6	4	0	4	47
	%	37.0%	25.5%	12.5%	11.8%	0.0%	33.3%	21.6%
ICDA	Count	0	3	3	2	0	0	8
	%	0.0%	5.9%	6.3%	5.9%	0.0%	0.0%	3.7%
ICDA-IUNS	Count	2	9	15	4	2	2	34
	%	3.7%	17.6%	31.3%	11.8%	10.5%	16.7%	15.6%
Total	Count	54	51	48	34	19	12	218
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 6. Association between nutrition competence indicators

		Nutrition competence index	Nutrition professional activity score	Nutrition higher education score	Nutrition research excellence score
Nutrition professional activity score	Pearson Corr.	.626**			
	Sig. (2-tailed)	.000			
	N	51	51		
Nutrition higher education score	Pearson Corr.	.599**	.169		
	Sig. (2-tailed)	.000	.283		
	N	42	42	42	
Nutrition research excellence score	Pearson Corr.	.384*	.292	-.077	
	Sig. (2-tailed)	.021	.084	.685	
	N	36	36	30	36
Nutrition research activity score	Pearson Corr.	.486**	.042	.286	.407*
	Sig. (2-tailed)	.000	.777	.067	.017
	N	49	49	42	34

Table 7. Association between countries' nutrition competence and food security indicators in Asia

		Nutrition competence index	Nutrition professional activity score	Nutrition higher education score	Nutrition research excellence score	Nutrition research activity score
Food security score	Pearson Cor.	.568**	.341	.470*	.591**	.214
	N	26	23	19	26	26
Food affordability score	Pearson Cor.	.505**	.191	.487*	.565**	.151
	N	26	23	19	26	26
Food availability score	Pearson Cor.	.543**	.413	.409	.399*	.391*
	N	26	23	19	26	26
Food quality score	Pearson Cor.	.411*	.215	.307	.564**	.053
	N	26	23	19	26	26
Food resilience score	Pearson Cor.	.085	.255	-.041	.101	-.097
	N	26	23	19	26	26

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 8. Association between countries' nutrition competence & nutrition relevant indicators in Asia

	Nutrition competence index	Nutrition professional activity score	Nutrition higher education score	Nutrition research excellence score	Nutrition research activity score
	(Pearson Correlation)				
Anemia Under 5 Child	-.305*	-.251	-.135	-.310	-.451**
Hypertension	-.170	-.237	-.412**	-.264	-.043
Overweight Adults	.217	-.084	.032	.221	.327*
Overweight Child	.181	-.022	.024	.108	.290*
Severe Wasting Under 5	.134	.198	-.077	.321	-.039
Stunting Under-5	-.146	.088	-.358*	.235	-.136
Undernourished Population	.007	-.044	-.218	.240	.254
Wasting Under-5	-.050	.139	-.098	.089	-.341*

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

the Nutrition Competence Index and food security score (r=0.568), Food Affordability Score (r =0.505), Food Availability Score (r = 0.543) and Food Quality Score (r=0.411). Table 7 also indicted the significant positive association (p<0.01) between Nutrition research Excellence Score with Food Security Score (r=0.591), Food Affordability Score (r=0.565) and Food Quality Score (r=0.564) even after controlling for GDP.

Association between Countries' Nutrition Competence & Nutrition Relevant Indicators in Asia are presented in Table 8. After controlling for GDP, It is clear that, hypertension had significant negative correlation with Nutrition Higher Education Score (r=-0.410, P=0.0129) and marginally significant correlation with Nutrition Professional Activity Score (r=-0.321, P=0.055). Undernourishment had significant positive correlation with Nutrition research activity (r=0.371, P=0.026).

Table 9. (a). Nutrition competence variables as predictor of nutritional issues (Anemia)

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	41.402	4.836		8.560	.000
	GDP.PC	.000	.000	-.405	-1.956	.063
	Nutrition Higher Education Score	-.003	.223	-.002	-.012	.991
	Nutrition research Excellence Score	.177	.210	.141	.842	.409
	Nutrition research activity score	-.117	.053	-.462	-2.226	.037
	Nutrition Professional Activity Score	-2.356	2.614	-.136	-.901	.377
(b). Nutrition competence variables as predictor of nutritional issues (Stunting)						
1	(Constant)	29.969	4.967		6.034	.000
	GDP.PC	.000	.000	-.114	-.605	.552
	Nutrition Higher Education Score	-.388	.226	-.303	-1.713	.103
	Nutrition research Excellence Score	-.075	.197	-.060	-.378	.709
	Nutrition research activity score	-.117	.055	-.449	-2.132	.046
	Nutrition Professional Activity Score	2.184	2.749	.133	.795	.437

Wasting Under-5 had significant positive correlation with Nutrition Professional Activity Score (r=0.333, P=0.046).

The relationship between GDP, Nutrition Competence, and the prevalence of anemia among children under the age of 5 is shown in Figure 2. The data suggests that higher GDP is associated with lower prevalence of anemia, while higher nutrition competence is also associated with lower prevalence of anemia. Additionally, the data shows that there are significant differences in the prevalence of anemia between different GDP and nutrition competence groups. Table 9 (a) and Table 9 (b) shows the Nutrition Competence Variables as predictor of anemia and stunting under five years of age. Nutrition research activity scores predicted Rates of Anemia under 5-year-old children, R2 = .52, F(5, 22) = 4.932, p = .004 (Table 9 a). Nutrition research activity scores predicted Rates of STUNTING under 5-year-old children, R2 = .58, F(5, 19) = 5.321, p = .003 (Table 9 b).

Discussion

Many factors influences the health status of individuals in a population. These factors ranges from country level aspects e.g. GDP.PC, food security conditions, investment in the health care system to household level e.g. dietary practices, hygienic conditions etc. The effect of these elements on health issues has already been extensively studied. The positive impact of economic growth on increased life expectancy and lower infant mortality has already been established.[17]

But besides these, there is also an important element that is still neglected i.e. Nutrition competency. The most common nutrition competencies includes skills in nutrition assessment, the ability to prescribe dietary interventions in the prevention and treatment of disease, knowledge of the role of nutrition in health promotion and disease prevention and knowledge of the social and cultural importance of food, including food consumption trends and current nutrition recommendations.[18] In this study nutrition competencies among various continents were measured on the basis of number of HEI with Nutrition programs, Nutrition research excellence and Nutrition Professional Activity. Our results showed that South America has highest number of HEI among other continents. This continent ranked 4th in the list of by GDP per capita (PPP) provided by International Monetary Fund in 2023. The continent Oceania (ranked 2nd in 2023 list of GDP.PC provided by IMF) has highest score in Nutrition Research Excellence with highest number of researchers, Institutions and mean H INDEX of researchers. As far as continent Asia is concerned, it ranked 5th in having Higher

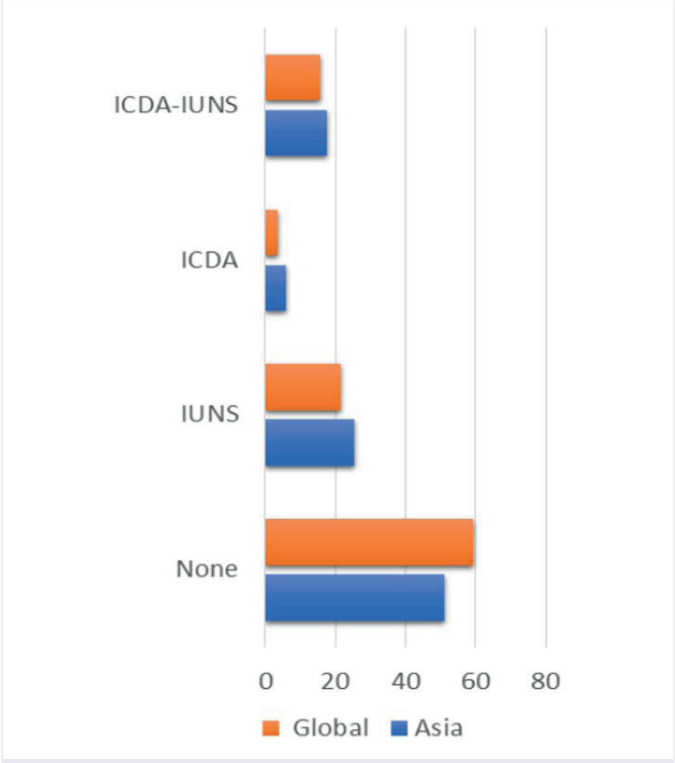

Figure 1. Membership of countries from Asia in international organizations

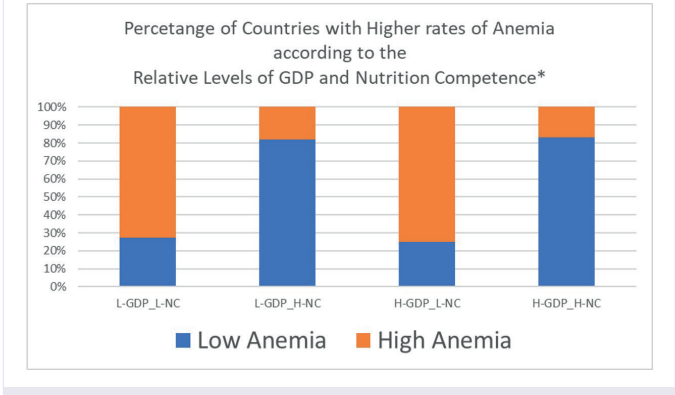

Figure 2. Relationship between GDP, nutrition Competence, and the prevalence of anemia among children under the age of 5

Education Institutes with Nutrition programs among other continents and has second highest rate of dietetic research output with a significant level of memberships in Nutrition related International organizations.

It is obvious from the current study that even countries with low GDP and high Nutrition competence has low rate of anemia in under 5 years old children (Figure 2) as compared to the countries with high GDP but with low nutrition competence. Similarly, our results also suggested that countries with high GDP but low nutrition competence has high ratio of stunting among children under 5 years of age (26.26) as compared to those countries with high GDP but low nutrition competence (10.32). Previous studies clearly demonstrated the effect of nutrition knowledge on prevalence of anemia in pre-school children and stunting in the same age group.[19,20] Our finding indicates that GDP per capita (GDP.PC) has a negative standardized coefficient of -.405, indicating that as GDP per capita increases, the rates of anemia in children decrease. Moreover, the nutrition research activity score has a negative standardized coefficient of -.449, indicating that as the nutrition research activity score increases, the rates of stunting in children decrease. Overall, the results suggest that the nutrition research activity score is a significant predictor for both anemia and stunting rates in under 5-year-old children, while the other variables do not show significant relationships. Our findings provide strong evidence of the positive impact of nutrition research activity on nutritional issues.

Conclusion

Globally and more so in Asia, the Nutrition Competence has potential to decrease the impact of variations in GDP on food security and Malnutrition however there are continent wise variations in strength and utilization of this potential. But presence of NC alone may not give the optimum benefits if there is no assurance of utilization of competence. Challenges in estimation of nutrition competence and flexibilities in human resource management are probably the biggest hindrance in capacity building and capacity utilization.

Strength and Weaknesses

The comprehensive data sources and a multidimensional approach to measuring nutrition competence provide strength in data collection. The use of standardized coefficients and numerical values, such as the negative coefficients for GDP per capita and nutrition research activity score, adds precision to the findings. This quantitative approach enhances the objectivity and reliability of the study. However, limitations can be in the potential data limitations only secondary sources are used, considering the exclusivity of data sources, "The World Bank" and "Economist Impact" might introduce a bias, minimizing subjectivity in scoring, as scoring criteria is missing, which can create the bias, study period is only five years, which can be considered as a limitation.

Ethical approval

The study did not require ethical approval as it was based on secondary data analysis.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: RH, RS; data collection: RH; analysis and interpretation of results: MJ; draft manuscript preparation: MJ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Association of c-reactive protein albumin ratio with disease severity and nutritional risk in patients with acute ischemic stroke

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ABSTRACT

Background: CAR is a novel biomarker that predicts disease prognosis in inflammation-related diseases such as stroke.

Aim: We aimed to evaluate the relationship between CAR and disease severity and nutritional status in patients with acute ischemic stroke (AIS).

Method: This research is a cross-sectional, descriptive study. The sample consists of 99 AIS patients. A face-to-face interview questionnaire was used to determine the sociodemographic characteristics. The nutritional status was assessed by NRS-2002, SNAQ, MUST, and SGA, and disease status was determined by NIHSS and Modified Rankin Scale. Anthropometric measurements were taken. Biochemical parameters were obtained retrospectively from the patient records.

Results: 21.2% (n = 21) of the patients had an NRS-2002 score ≥ 3. When the combined effect of NIHSS and MUST on CAR was evaluated using Univariate ANOVA, the main effect of both MUST and NIHSS separately was significant. However, the combined effect of NIHSS and MUST was not found ($p > 0.05$). CAR of those at low risk of malnutrition (6.2±13.7) was significantly lower than that of those at moderate risk of malnutrition (13.7±17.2) according to MUST ($p < 0.05$). NRS-2002 significantly predicted a higher CAR (B = 10.89, p = 0.002). CAR significantly predicted higher NIHSS (B = 0.02, p = 0.003). The total effect analysis showed that malnutrition was positively associated with disease severity (B = 0.72, p = 0.002).

Discussion: This study revealed that nutritional risk (NRS-2002) was significantly associated with disease severity (NIHSS), both directly and indirectly. CAR mediated this relationship. Using CAR may facilitate the detection of nutritional risk.

Keywords: nutrition, NIHSS, MUST, NRS-2002, CAR

Introduction

Stroke is the second most common cause of death and the third leading cause of disability-adjusted life years worldwide. Approximately 12 million stroke cases and 6.5 million stroke-related deaths occur annually.[1] Acute ischemic stroke (AIS) is more common than hemorrhagic stroke (AHS) and is also the primary cause of temporary or chronic disability. It has important social and economic consequences.[2]It is known that inflammation occurs in the pathophysiology of AIS.[3] Necrotic cells formed in the brain as a result of vascular occlusion trigger inflammation.[4] New biomarkers that will predict the patient's prognosis, better understand the pathophysiology, and offer new

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treatment options may be beneficial.[3] In recent years, the C-reactive protein (CRP) to albumin (ALB) ratio (CAR) has begun to be defined as a new inflammatory indicator. C-reactive protein is an acute-phase reactant produced by the liver, and its levels increase in response to inflammation. It is widely used as a clinical indicator of inflammatory status. ALB, also produced by the liver, is a useful marker reflecting both inflammatory and nutritional states.[5]CAR has previously been shown to be associated with inflammatory conditions and poor prognosis, including in diabetic nephropathy, cancer, and cardiovascular disease.[6,7,8]According to data from the NHANES cohort, high CAR is associated with an increased risk of long-term mortality for individuals who have had a stroke.[9] In studies conducted on elderly patients with AIS, higher CAR was also associated with in-hospital mortality, hemorrhagic transformation, and worsening functional outcomes.[10,11] This suggests that CAR can be used as a poor prognosis predictor.

Malnutrition is common in stroke patients, who are mostly elderly individuals. Malnutrition in stroke patients is recognized to be negatively associated with a variety of clinical outcomes, particularly disability and death, in both the short and long term.[2,12]Despite its importance for prevention and treatment, assessment of nutritional status is not sufficiently considered in the multidisciplinary approach to diagnosing and treating patients affected by acute or chronic diseases.[2] In a study of 325 hospitals in 25 European countries, it was reported that routine nutritional status screening was performed in only 52% of hospitals.[13] Malnutrition is a disordered nutritional state caused by a combination of inflammation and negative nutrient balance, leading to alterations in body composition and function. The definitive diagnosis of malnutrition should be based on the assessment of these factors.[14] It is essential to identify a rapid, simple, cost-effective, and reliable approach for nutritional assessment that is validated in the clinical setting. Many tools/procedures are used for nutritional screening worldwide. Basic laboratory tests, such as albumin and CRP levels, have been incorporated into other tools as they are associated with inflammatory status and clinical outcomes.[2]Subjective assessment of malnutrition is challenging due to limitations inherent in screening and assessment tools, such as inter-observer variability, difficult reproducibility, requiring expert experience, and some tools being time-consuming and expensive.[15]Therefore, there is no gold standard for nutrition screening or a complete nutrition assessment.[16]

The fact that high CAR scores predict worsening prognosis in many inflammatory conditions and the association of both CRP and ALB with malnutrition suggest that they can be used as indicators of malnutrition in patients with AIS.

Albumin and CRP values are routinely evaluated, inexpensive, and easily accessible, which may provide convenience for clinicians. This study aimed to evaluate the association between CAR, nutritional risk (NRS-2002), and stroke severity (NIHSS) in patients with acute ischemic stroke.

Main Points

- CAR is significantly associated with both malnutrition risk and disease severity in patients with acute ischemic stroke (AIS).
- CAR partially mediates the effect of malnutrition on disease severity.
- Use of CAR may facilitate early identification of malnutrition risk and disease prognosis in patients with AIS.

Methods

This research is a cross-sectional, descriptive study. The research sample consisted of 99 AIS patients hospitalized in the Neurology clinic of Kastamonu Training and Research Hospital between January and February 2024. Kastamonu University Clinical Research Ethics Committee approval was obtained for the study. The sample size in the study was calculated using G*Power 3.1 software. The analysis was performed using the "R^2 increase" option in the linear multiple regression model. Statistical significance was set at $\alpha = 0.05$, test power was 80% ($1-\beta = 0.80$), and the effect size was accepted as moderate ($f^2=0.10$), considering the findings on the relationship between CAR and stroke in the literature.[17,18] According to these parameters, the minimum sample size was calculated as 81. Considering the probability of missing and incomplete data (15%), the target sample size was determined to be at least 93. Patients who were confused had advanced dementia, could not cooperate, were aphasic after stroke, had hemorrhagic stroke, or had PEG were excluded. The sample was selected using purposive and convenience sampling. Anthropometric measurements and biochemical data were obtained, and scales were applied within the first 3 days after hospitalization.

A face-to-face interview questionnaire was used to determine the sociodemographic characteristics of the patients, such as age, occupation, marital status, and cohabitation status. The nutritional status of the patients was assessed by Nutritional Risk Screening-2002 (NRS-2002), Simplified Nutritional Assessment Questionnaire (SNAQ), Malnutrition Universal Screening Tool (MUST), Subjective Global Assessment (SGA), and disease status was determined by National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale. The researchers took anthropometric measurements (height, weight, and mid-upper arm circumference). Biochemical parameters were obtained retrospectively from the patient records. A flowchart of the study is given in Figure 1.

Anthropometric measurements

Height: When the individual is in the standard anatomical position, height is the measurement of the vertical distance from the ground to the vertex, the highest head point.[19]

Body weight: Weighing was preferably done in thin clothes and on an empty stomach.[19]

Body mass index (BMI): Body mass index values were calculated by dividing body weight by the square of height (Body weight (kg) / Height (m^2)), and the results obtained were evaluated according to the World Health Organization (WHO) classification.[20]

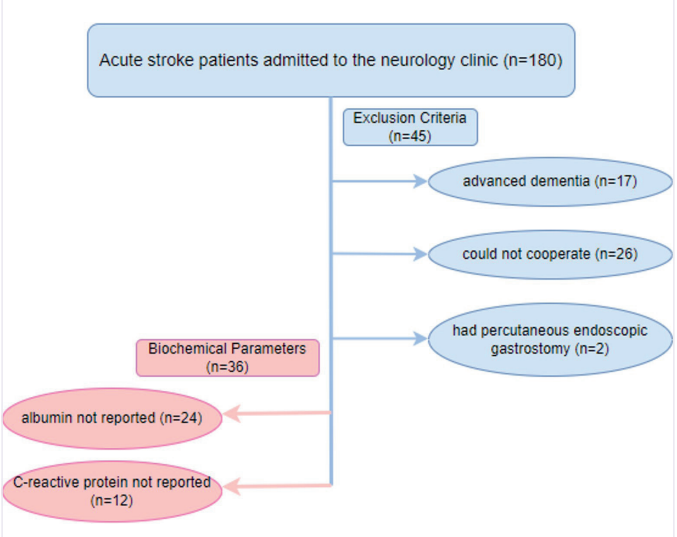

Figure 1. Flowchart of the study

Mid-upper arm circumference (MUAC): The left arm of the patient was bent 90 degrees, and the midpoint between the acromial process at the shoulder and the olecranon process at the elbow was marked. The arm was released, and the arm circumference was measured with a tape measure.[19]

Nutrition status

We included four different nutritional screening tools (SNAQ, NRS-2002, SGA, and MUST) in our study to provide a comprehensive framework and allow for comparison of other approaches. However, we focused our analyses primarily on the NRS-2002 and MUST because these two methods are the most widely used tools in clinical practice and provided the most appropriate results for our study sample.

Nutritional risk screening test-2002 (NRS-2002)

The nutritional risk screening test-2002 was developed by Kondrup et al. in 2002 to screen the risk of malnutrition in patients admitted to the hospital. The scoring system consists of two parameters: "nutritional status" and "disease severity". A total NRS-2002 score ≥3 points is considered at high nutritional risk, while those with a score below 3 points are considered at low nutritional risk.[21]

Malnutrition universal screening tool (MUST)

It is a five-step screening tool recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the British Association for Parenteral and Enteral Nutrition (BAPEN). The total MUST score is interpreted as follows: a score of 0 indicates low risk of malnutrition; a score of 1 indicates medium risk; and a score of 2 or more indicates high risk.[22]

Simplified nutritional assessment questionnaire (SNAQ)

This screening method, developed by Kruizenga et al. (2005), includes parameters questioning the presence of recent weight loss, lack of appetite, and the status of receiving nutritional support. The total SNAQ score ranges from 4 to 20 points, with scores of 14 or below indicating a malnourished, while scores above 14 indicate a well-nourished[23]

Subjective global assessment (SGA)

Subjective global assessment is a screening tool described by Detsky et al. (1984). Patients are evaluated subjectively based on data obtained from clinical assessment and physical examination. Gastrointestinal symptoms are considered only if they have been present for ≥ 2 weeks. According to the Subjective Global Assessment (SGA), patients are classified as nourished (A), mild to moderately malnourished (B), or severely malnourished (C) [24]

Disease Severity

National institutes of health stroke scale (NIHSS):

The NIHSS is a scale for determining stroke severity. It has 11 categories and a score ranging from 0 to 42. The NIHSS Stroke Scale measures various aspects of brain function, including consciousness, vision, sensation, movement, speech, and language. A certain number of points is given for each of these physical and cognitive functions during a focused neurological examination.[25]

Modified rankin scale

It is used to measure the degree of disability and dependency in patients due to stroke or another neurological problem. It is a scale that evaluates between 0 and 6 points.[26]

Biochemical Parameters

Biochemical parameters (Creatinine, ALB, CRP, Cholesterol, Triglycerides, Low Density Lipoprotein [LDL], High Density Lipoprotein [HDL]) were obtained retrospectively from the patient records.

CRP albumin ratio (CAR) was calculated by dividing CRP by ALB.

Statistical analysis

IBM SPSS 25 program was used to analyze the data. The values of descriptive variables were expressed as number (n), percentage (%), mean, standard deviation (SD), median, and minimum and maximum values. The normality of data was tested using the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical variables. Mann-Whitney U test was used for non-normally distributed data. A Univariate ANOVA test was used to evaluate the effect of disease severity and nutritional risk on CAR. The significance level was set at $p < 0.05$. The mediating role of CAR in the relationship between disease severity (NIHSS) and nutritional risk (NRS-2002) was analyzed using Hayes' PROCESS macro (version 4.2).

Results

General and clinical characteristics of the patients are given in Table 1. The number of patients included in the study was 99, and the mean age was 72.0±14.2 years. 21.2% (n = 21) of the patients had NRS-2002 score ≥3 and there was no difference between genders ($p > 0.05$). According to the SGA nutritional assessment tool, 94.9% of the patients had no malnutrition, whereas 3% had severe malnutrition. Nutritional screening results indicated that 33.3% were malnourished based on SNAQ (≥5% weight loss), 20.2% were at medium risk according to MUST, and no patient was categorized as high risk ($p > 0.05$). When the NIHSS scores of the patients were evaluated, 30.32% had no stroke symptoms, 28.3% had minor stroke, 33.3% had moderate stroke and 8.1% had severe stroke and there was no difference between genders ($p > 0.05$). Functional status evaluated by the modified Rankin Scale indicated that most patients had slight (25.3%) or moderate (17.2%) disability, while 22.2% had moderately severe disability and 15.2% had severe disability ($p > 0.005$). Anthropometric measurements showed a mean BMI of 28.5±5.6 kg/m² and MUAC of 28.8±3.6 cm, with no significant difference between genders. When the BMI of the patients was classified, 20.2% were underweight, 37.4% were normal weight and 42.4% were overweight.

The evaluation of biochemical parameters of the patients according to nutritional risk status (NRS 2002) is given in Table 2. Serum albumin median values of patients with an NRS-2002 score ≥ 3 (3.5 [1.8 - 4.0]) were significantly lower than those of patients with NRS-2002 scores <3 (3.7 [2.8 - 4.7]) ($p < 0.05$). Median CRP levels were 22.0 mg/L (range: 0.8–307.2) in patients with NRS-2002 scores ≥ 3, compared with 5.8 mg/L (0.2–189.5) in those with scores < 3 ($p = 0.008$). Similarly, the median CRP/albumin ratio (CAR) was 7.1 (0.2–83.0) in an NRS-2002 scores ≥ 3, 1.6 (0.0–67.7) in scores < 3 ($p = 0.004$). Total cholesterol, triglyceride, and HDL values of those with NRS-2002 scores ≥ 3 were lower than those with NRS-2002 scores < 3 ($p = 0.049$, $p = 0.045$, $p = 0.016$, respectively).

Table 1. General and clinical characteristics of the patients

	Female(n=62,62.6%)	Male(n=37,37.4%)	Total (n=99)	p
Age (Mean±SD)	73.5±14.8	69.5±13.1	72.0±14.2	0.068#
Education	n (%)	n (%)	n (%)	
Illiterate	31 (50.0)	1 (2.7)	32 (32.3)	**<0.001**
Literate	13 (21.0)	3 (8.1)	16 (16.2)	
Primary school	15 (24.2)	25 (67.6)	40 (40.4)	
Secondary school	-	2 (5.4)	2 (3.7)	
High school	1 (1.7)	5 (13.5)	6 (5.2)	
Undergraduate/graduate	2 (3.3)	1 (2.7)	3 (3.0)	
Marital status				
Married	26 (41.9)	32 (86.5)	58 (58.6)	**<0.001**
Single	2 (3.3)	-	2 (2.0)	
Divorced	2 (3.2)	-	2 (2.0)	
Lost spouse	32 (51.6)	5 (13.5)	37 (37.4)	
Cohabitation status				
Alone at home	9 (14.5)	3 (8.1)	12 (12.1)	**0.000**
At home with spouse	11 (17.7)	16 (43.3)	27 (27.3)	
With spouse and children	15 (24.3)	15 (40.5)	30 (30.3)	
With children/relatives	27 (43.5)	3 (8.1)	30 (30.3)	
Income				
Below minimum wage	49 (79.0)	19 (51.4)	68 (68.7)	**0.004**
Above minimum wage	13 (21.0)	18 (48.6)	31 (31.3)	
Presence of other diseases				
No	6 (9.7)	8 (21.6)	14 (14.1)	0.099
Yes	56 (90.3)	29 (78.4)	85 (85.9)	
Cardiovascular disease	47 (75.8)	22 (59.5)	69 (69.7)	
Diabetes	20 (32.3)	13 (35.1)	33 (33.3)	
Thyroid diseases	2 (3.2)	2 (5.4)	4 (4.0)	
Respiratory diseases	5 (8.1)	4 (10.8)	9 (9.1)	
Neurological diseases	12 (19.4)	3 (8.1)	15 (15.2)	
Autoimmune diseases	1 (1.6)	-	1 (1.0)	
Sensory loss	3 (4.8)	1 (2.7)	4 (4.0)	

Chi-Square test # Mann Whitney U test BMI: Body Mass Index* While categorizing BMI, the World Health Organization BMI classification according to age was used. MUAC: Mid-upper arm circumference NRS 2002: Nutritional Risk Screening-2002 SNAQ: Simplified Nutritional Assessment Questionnaire MUST: Malnutrition Universal Screening Tool SGA: Subjective Global Assessment NIHSS: National Institutes of Health Stroke Scale.

Table 1. Continued

	Female(n=62,62.6%)	Male(n=37,37.4%)	Total (n=99)	p
Nutritional screening tests				
NRS 2002				
NRS-2002 score < 3	45 (72.7)	33 (89.2)	78 (78.8)	0.051
NRS-2002 score ≥ 3	17 (27.4)	4 (10.8)	21 (21.2)	
SNAQ				
Well nourished (<5% weight loss)	37 (59.7)	29 (78.4)	66 (66.7)	0.056
Malnourished (≥5% weight loss)	25 (40.3)	8 (21.6)	33 (33.3)	
MUST				
Low risk	49 (79.0)	30 (81.1)	79 (79.8)	0.806
Medium risk	13 (21.0)	7 (18.9)	20 (20.2)	
High risk	-	-	-	
SGA				
Nourished (A)	60 (96.8)	34 (91.9)	94 (94.9)	0.283
Mild to moderately malnourished (B)	2 (3.2)	-	2 (2.0)	
Severely malnourished (C)	-	3 (8.1)	3 (3.0)	
NIHSS				
No stroke symptoms	15 (24.2)	15 (40.5)	30 (30.3)	0.380
Minor stroke	19 (30.6)	9 (24.3)	28 (28.3)	
Moderate stroke	23 (37.1)	10 (27.0)	33 (33.3)	
Severe stroke	5 (8.1	3 (8.1)	8 (8.1)	
Modified Rankin Scale				
No symptoms	-	2 (5.4)	2 (2.0)	0.524
No significant disability	10 (16.1)	8 (21.6)	18 (18.2)	
Slight disability	16 (25.8)	9 (24.3)	25 (25.3)	
Moderate disability	11 (17.7)	6 (16.2)	17 (17.2)	
Moderately severe disability	15 (24.2)	7 (18.9)	22 (22.2)	
Severe disability	10 (16.1)	5 (13.5)	15 (15.2)	
Anthropometric measurements	Mean±SD	Mean±SD	Mean±SD	
BMI	28.1±5.5	29.2±5.8	28.5±5.6	0.383[#]
MUAC	28.7±3.9	29.0±3.1	28.8±3.6	0.663[#]
BMI Classification*	n(%)	n(%)	n(%)	
Underweight	14 (22.6)	6(16.2)	20(20.2)	0.729
Normal	22(35.5	15(40.5)	37(37.4)	
Overweight	26(41.9)	16(43.2)	42(42.4)	

Chi-Square test [#] Mann Whitney U test BMI: Body Mass Index* While categorizing BMI, the World Health Organization BMI classification according to age was used. MUAC: Mid-upper arm circumference NRS 2002: Nutritional Risk Screening-2002 SNAQ: Simplified Nutritional Assessment Questionnaire MUST: Malnutrition Universal Screening Tool SGA: Subjective Global Assessment NIHSS: National Institutes of Health Stroke Scale.

Table 2. Evaluation of biochemical parameters of patients according to nutritional risk status (NRS-2002)

Biochemical parameters	NRS-2002 score ≥ 3	NRS-2002 score <3	Total	p*
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Creatinine mg/dL	0.8 (0.2- 1.6)	0.8 (0.3- 6.3)	0.8 (0.2- 6.3)	0.201
ALB g/dL	3.5 (1.8 – 4.0)	3.7 (2.8- 4.7)	3.7 (1.8- 4.7)	**0.001**
CRP mg/dL	22.0 (0.8- 307.2)	5.8 (0.2- 189.5)	7.3 (0.2- 307.2)	**0.008**
CAR	7.1 (0.2-83.0)	1.6 (0.0-67.7)	1.9 (0.0-83.0)	**0.004**
Total Cholesterol mg/dL	122.0 (0.0 – 300.0)	174.0 (0.0 – 338.0)	167.0 (0.0 – 338.0)	**0.049**
Triglycerides mg/dL	66.0 (0.0 – 405.0)	116.0 (0.0 – 410.0)	106.0 (0.0 – 410.0)	**0.045**
LDL mg/dL	86.0 (0.0 – 240.0)	121.5 (0.0 – 259.0)	117.0 (0.0 – 259.0)	0.052
HDL mg/dL	43.0 (0.0 – 80.0)	47.5 (0.0 – 82.0)	45.0 (0.0 – 82.0)	**0.016**

*Mann Whitney U test, CRP: C- reaktive protein ALB: Albumin CAR: CRP/ALB ratio LDL: Low-density lipoprotein, HDL: High-density lipoprotein, NRS 2002: Nutritional Risk Screening-2002

Table 3. Evaluation of CAR according to NIHSS and NRS-2002 score

	CAR					
	Sum of Squares	Sd	K.O.	F	p	Partial Eta Squares
NRS-2002	108.925	1	108.925	0.612	0.436	0.007
NIHSS	2687.501	3	895.834	5.034	**0.003**	0.141
NIHSS*NRS-2002	222.608	2	111.304	0.625	0.537	0.013

R^2= 0.225, Univariate ANOVA test. NIHSS: National Institutes of Health Stroke Scale, NRS: Nutritional Risk Screening-2002

The evaluation of CAR according to NIHSS and NRS-2002 score is given in Table 3. Descriptive statistics of Tables 3 and 4 are given in Table 5. The main effect of NRS-2002 score was not significant on CAR ($p > 0.005$). The main effect of NIHSS was significant on CAR ($p < 0.05$). Patients with no stroke symptoms, minor stroke, and moderate stroke had significantly lower CAR (2.9±4.3, 6.3±11.5, 8.0±15.0, respectively) than patients with severe stroke (29.2±27.6, $p < 0.001$). The combined effect of NIHSS and NRS-2002 scores on CAR was not significant ($p > 0.05$).

The evaluation of CAR according to NIHSS and MUST score is given in Table 4. The main effect of MUST score is significant on CAR ($p < 0.001$). The CAR of patients at low risk of malnutrition (6.2±13.7) was significantly lower than that of those at moderate risk of malnutrition (13.7±17.2) ($p < 0.05$). The main effect of NIHSS was significant on CAR ($p < 0.05$). The CAR of those with no stroke symptoms (2.6±2.8) was the lowest, while that of severe strokes (30.3±4.7) was significantly the highest. The combined effect of NIHSS and MUST scores on CAR was not significant ($p > 0.05$).

Mediation of the association between nutritional risk (NRS-2002) and disease severity (NIHSS) by the CAR is presented in Table 6. NRS-2002 significantly predicted a higher CAR (B = 10.89, p = 0.002). CAR significantly predicted higher NIHSS (B = 0.02, p = 0.003). The total effect analysis showed that nutritional risk was positively associated with disease severity (B = 0.72, p = 0.002). The direct effect indicated that even after controlling for CAR, nutritional risk remained a significant predictor of NIHSS (B = 0.51, p = 0.027). The indirect effect analysis demonstrated that the bootstrap 95% confidence interval [0.03, 0.45] did not include zero, thus confirming a significant partial mediation effect of CAR.

Discussion

Malnutrition before and after AIS is responsible for longer hospital stays, worse functional outcomes, and increased mortality rates after stroke. Early detection of malnutrition using anthropometric measurements or laboratory parameters after AIS is important to prevent a poor prognosis. In the literature, malnutrition has

Table 4. Evaluation of CAR according to NIHSS and MUST score

	CAR					
	Sum of Squares	**Sd**	**K.O.**	**F**	**p**	**Partial Eta Squares**
MUST	5064.131	3	1688.044	10.391	**<0.001**	0.255
NIHSS	824.134	1	824.134	5.073	**0.027**	0.053
NIHSS*NRS-2002	1319.368	3	439.789	2.707	0.050	0.082

R^2= 0.301, Univariate ANOVA test. NIHSS: National Institutes of Health Stroke Scale, MUST: Malnutrition Universal Screening Tool.

Table 5. Descriptive statistics of Tables 3 and 4

NIHSS	**CAR**		**Total**	**CAR**			**Total**
	NRS-2002			**MUST**			
	NRS-2002 score≥3 (n=21)	**NRS-2002 score<3 (n=78)**	**Mean±SD**	**Low risk (n=79)**	**Medium risk (n=20)**	**High risk (n=0)**	**Mean±SD**
	Mean±SD	**Mean±SD**		**Mean±SD**	**Mean±SD**	**Mean±SD**	
No stroke symptoms (n=30)	2.7 ± 3.5	2.9 ± 4.4	2.9 ± 4.3[a]	3.1 ± 4.8	2.0 ± 1.5	-	2.6 ± 2.8[a]
Minor stroke (n=28)	6.3 ± 8.9	6.3 ± 12.2	6.3 ± 11.5[a]	6.0 ± 12.5	7.3 ± 7.7	-	6.7 ± 2.9[ab]
Moderate stroke (n=33)	16.4 ± 22.9	6.9 ± 13.8	8.0 ± 15.0[a]	5.3 ± 12.5	27.6 ± 19	-	16.5 ± 3.4[bc]
Severe stroke (n=8)	29.2 ± 27.6	-	29.2 ± 27.6[b]	25.7 ± 32.7	34.9 ± 21.4	-	30.3 ± 4.7[c]
Total (n=99)	16.3 ± 22.2	5.4 ± 11.0	7.7 ± 14.7	6.2 ± 13.7[a]	13.7 ± 17.2[b]	-	7.7 ± 14.7

Univariate ANOVA test, Bonferroni test, a-b: No difference exists between scores with the same letter, CAR: C- reactive protein/Albumin ratio, NIHSS: National Institutes of Health Stroke Scale, NRS: Nutritional Risk Screening-2002, MUST: Malnutrition Universal Screening Tool.

Table 6. Mediation of the association between nutritional risk (NRS-2002) and disease severity (NIHSS) by the CAR

Path	**B**	**SE**	**t**	**p**	**LLCI**	**ULCI**	**β**
Path a NRS-2002 → CAR	10.89	3.46	3.15	**0.002**	4.03	17.75	0.742
Path b NRS-2002 → NIHSS	0.51	0.23	2.24	**0.027**	0.06	0.97	0.532
CAR → NIHSS	0.02	0.01	3.00	**0.003**	0.01	0.03	0.293
Total Effect (c path)	0.72	0.23	3.19	**0.002**	0.27	1.17	0.749
Direct Effect (c' path)	0.51	0.23	2.24	**0.027**	0.06	0.97	0.532
Indirect Effect (a×b)	0.21	0.11	–	–	0.03	0.45	0.217

Hayes' PROCESS macro (version 4.2), B = unstandardized coefficient; SE = standard error; LLCI/ULCI = 95% bootstrap confidence interval lower/upper limits (5,000 samples). CAR: C- reactive protein/Albumin ratio, NIHSS: National Institutes of Health Stroke Scale, NRS: Nutritional Risk Screening-2002

been shown to increase as disease severity increases in patients with AISand that markers such as CRP and albumin are associated with disease severity.[27,28] In recent years, CAR, a new biomarker used alongside CRP and albumin—indicators of systemic inflammation and nutritional status—is an independent prognostic marker in many diseases. In a study conducted in 2024 employing a method similar to ours, it was suggested that the CAR could be used as an indicator for assessing nutritional status in hemodialysis patients.[29] This study aimed to evaluate the relationship of CAR with disease severity and malnutrition.

In the present study, 21.2% of patients were identified as being at nutritional risk according to NRS-2002. SNAQ identified 33.3% of patients as malnourished, while MUST indicated that 20.2% of patients were at medium risk, with no patients classified as high risk. There was no significant

difference between genders. This prevalence is partially consistent with previous studies in stroke populations, which have reported varying rates of nutritional risk: 35–50% according to NRS-2002, 22–37% according to MUST, and 18.4% of patients classified as malnourished according to SNAQ.[2,30] These findings indicate that a significant proportion of stroke patients are at risk of malnutrition, highlighting the critical importance of routine nutritional screening for early identification of at-risk individuals and timely implementation of interventions that can improve clinical outcomes.

In this study, patients at risk for malnutrition had lower median serum albumin levels (3.5 vs. 3.7 g/dL), indicating impaired protein status, consistent with previous reports linking hypoalbuminemia to malnutrition in stroke populations.[31,32] Additionally, inflammatory markers were significantly higher in the high malnutrition risk group, with median CRP levels of 22.0 mg/L (0.8-307.2) compared with 5.8 mg/L (0.2-189.5) in the low malnutrition risk group ($p = 0.008$). This finding aligns with literature suggesting that malnourished patients frequently exhibit systemic inflammation, which may exacerbate nutritional deficiencies and worsen clinical outcomes.[33] The observed differences in albumin and CRP highlight the utility of combining nutritional screening tools with biochemical markers for a more comprehensive assessment of nutritional status. Early identification of patients with laboratory findings of malnutrition and elevated inflammatory markers may allow for targeted nutritional interventions, improving recovery and reducing post-stroke complications.

In this study, based on NRS-2002, the CAR of patients with nutritional risk is higher than that of those without nutritional risk. When NRS-2002 and NIHSS were evaluated separately with the Univariate ANOVA test, it was found that NIHSS had a significant effect on CAR ($p < 0.05$), while NRS-2002 had no effect. NIHSS and NRS-2002 scores together do not have a significant impact on CAR. When MUST and NIHSS were evaluated separately, it was determined that both had a significant effect on CAR ($p < 0.05$). However, when NIHSS and MUST scores are evaluated together, there is no significant effect on CAR. CRP and albumin are acute phase proteins. As an acute phase reactant, CRP increases and albumin decreases in inflammation. Many studies have investigated the relationship between CRP and disease severity, functional outcome, in-hospital mortality, long-term mortality, and infarct volume in ischemic stroke patients.[4,17] In a study where disease severity was measured using the Modified Rankin Score, it was found that disease severity increased with increased CAR values in young stroke patients.[34] In a 116-month follow-up study examining the relationship between CAR values and disease prognosis, it was shown that there was a positive correlation between high CAR values and the risk of death from all causes in stroke patients.[9] In a 6-year follow-up study conducted by Li et al., it was stated that CAR could be a proper measurement when predicting in-hospital mortality in elderly patients with ischemic stroke.[10] In another study, high CAR was found to be associated with increased risk of hemorrhagic transformation and poor functional outcomes in individuals with ischemic stroke.[11]These data support that disease severity and prognosis are associated with increased CAR values, as we found in our study.

In Univariate ANOVA analysis, CAR values were more strongly correlated with disease severity (NIHSS), while no significant direct difference was observed with nutritional risk (NRS-2002). However, Hayes' mediator analysis revealed an unseen indirect effect of this relationship. Nutritional risk (NRS-2002) increased CAR, while CAR increased disease severity (NIHSS). Furthermore, nutritional risk increased disease severity, and this effect was mediated through CAR. Previous studies have shown that nutritional risk is associated with the risk of stroke complications and that CAR is significantly associated with both functional outcomes and mortality.[17,35] While these studies have investigated the relationships between disease severity, nutritional risk, and CAR separately, their interaction was not evaluated. In our study, we revealed the interaction of these variables and the mediating role of CAR. Inflammation is known to play a central role in the pathophysiology of stroke. Especially in the acute phase, systemic inflammation can accelerate both tissue damage and clinical deterioration; Parameters such as CAR emerge as sensitive indicators of this process. Therefore, the mediator role of CAR is consistent with the literature and is a unique aspect of our study. These data reveal a mechanism by which malnutrition not only directly increases stroke severity but also partially mediates this effect by interacting with inflammation. This highlights the importance of CAR in clinical practice for both early assessment of nutritional status and monitoring inflammation for stroke prognosis.

This study has several strengths. To our knowledge, it is the first to evaluate the combined effect of CAR on both malnutrition and disease severity in patients with AIS. The mediation analysis in this study explains the

biological mechanism underlying this relationship in more detail. This study also has some limitations. Due to its cross-sectional design, causal relationships cannot be firmly established. The absence of a control group and the lack of assessment of prognostic parameters such as length of hospital stay, functional outcomes, or mortality constitute additional limitations of the study.

Conclusion

CRP and albumin are biomarkers routinely used in the clinic to assess malnutrition and inflammation. They are practical, economical, and frequently evaluated, especially in diseases such as AIS, which has inflammation in its pathophysiology and is often associated with malnutrition. According to the results of this study, CAR was found to be closely related to both disease severity and malnutrition. It was determined that CAR increases in malnutrition. Therefore, CAR may facilitate the detection of malnutrition, a condition that is challenging to diagnose and requires expertise. However, more comprehensive studies are needed to expand its routine use.

Ethical approval

This study has been approved by the Kastamonu University Clinical Research Ethics Committee (approval date 20.12.2023, number 2023-KAEK-178). Verbal informed consent was obtained from each patient who volunteered to participate in the study.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: TT, FHZ, RY, ENA; data collection: RY, ENA; analysis and interpretation of results: TT, FHZ; draft manuscript preparation: TT, FHZ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Detection of skeletal muscle loss using ultrasound and its association with the plasma C-terminal agrin fragment biomarker in acute ischemic stroke patients in the neurological intensive care unit

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ABSTRACT

Objective: Skeletal muscle loss is a common problem in patients admitted to the intensive care unit (ICU) following acute ischemic stroke and adversely affects prognosis. This study aimed to monitor the changes in rectus femoris muscle (RFM) thickness over time using ultrasound and to evaluate whether plasma C-terminal agrin fragment (CAF) levels reflect muscle loss.

Methods: A total of 44 patients (23 women, 21 men) diagnosed with acute ischemic stroke and requiring ICU care were included in the study. Demographic data and body mass index (BMI) were recorded. RFM thickness was measured on days 1, 7, and 21 using a 7.5 MHz ultrasound probe. Plasma CAF levels were measured from venous blood samples on days 7 and 21. RFM thickness and CAF levels were analyzed statistically.

Results: Mean RFM thickness (right and left) (in mm) was 11.98 (range: 6.00 to 20.45) on day 1, 10.84 (range: 4.70 to 17.95) on day 7, and 9.74 (range: 3.95 to 17.55) on day 21 ($p < 0.001$). Plasma CAF levels also showed a significant change between day 7 and day 21 ($p < 0.001$). However, the difference in RFM thickness between days 7 and 21 showed a weak, non-significant negative correlation with the corresponding difference in CAF levels ($r = –0.023$, $p > 0.05$).

Conclusions: Patients with acute ischemic stroke in the ICU experience significant and progressive muscle loss. While plasma CAF has been proposed as a biomarker of muscle mass and function, its utility in tracking muscle loss remains uncertain.

Keywords: C-terminal agrin fragment, ischemic stroke, rectus femoris muscle thickness, ultrasound

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Introduction

Stroke, defined as neurological impairment resulting from vascular injury to the central nervous system,[1] is a leading cause of death and long-term disability among adults worldwide.[2] Acute ischemic stroke, in particular, is a critical condition that requires timely and appropriate intervention, as it significantly affects patients' functional capacity.[3]

Prolonged immobilization following acute ischemic stroke leads to substantial skeletal muscle loss, hindering recovery.[1] Muscle atrophy that occurs after stroke onset is referred to as 'stroke-related sarcopenia' and is associated with adverse clinical outcomes, including increased mortality and impaired physical function.[4] This condition is more pronounced in intensive care patients and contributes to greater muscle weakness and higher mortality rates.[5] Stroke-related sarcopenia is reported in up to 42% of stroke patients, affecting both the involved and uninvolved limbs.[6,7]

Monitoring muscle loss is essential for improving post-stroke outcomes.[8] Several tools are used to assess skeletal muscle mass after stroke, including computed tomography (CT), ultrasound, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), biomarkers, and anthropometric measurements.[9] Among these, ultrasound is particularly useful for patients with limited mobility or those without easy access to CT or MRI.[10]

Beyond physical measurements, muscle loss is also being investigated using biochemical markers for a more comprehensive assessment.[11] In 2012, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed the C-terminal agrin fragment (CAF), a biomarker of neuromuscular junction (NMJ) stability, as a potential tool for evaluating sarcopenia.[12] Subsequent studies have confirmed that CAF can be detected in circulation and may reflect skeletal muscle degradation.[13] Agrin is a protein critical to NMJ integrity, and its excessive cleavage by neurotrypsin produces CAF, which may contribute to NMJ dysfunction.[13] Research has shown that NMJ breakdown and muscle denervation play a key role in the pathogenesis of sarcopenia.[11,14-16]

Accurately assessing skeletal muscle loss, both physically and biochemically, is crucial for developing effective rehabilitation strategies and incorporating early interventions into stroke care.[17]

The primary aim of this study was to evaluate time-dependent changes in rectus femoris muscle thickness using ultrasound in patients with acute ischemic stroke admitted to the intensive care unit, and to assess the extent to which these changes were associated with muscle loss. The secondary aim was to examine plasma CAF levels and assess their potential as a biomarker for tracking and evaluating skeletal muscle loss.

Main Points

- Patients with acute ischemic stroke who are monitored in the intensive care unit experience significant muscle loss that worsens over time.
- Ultrasound remains a reliable, non-invasive method for the early detection and monitoring of muscle atrophy.
- While plasma CAF has been proposed as a biomarker of muscle mass and function, its utility in tracking muscle loss remains uncertain.

Material and Method

Study population and data collection

This observational prospective descriptive study was conducted between April 2023 and May 2024 on 44 patients diagnosed with acute ischemic stroke based on clinical and neuroimaging findings and monitored in the Neurology Intensive Care Unit of Dicle University Medical Faculty Hospital, Diyarbakır, Türkiye. Informed written consent was obtained from all participants or, in the case of patients with moderate to severe neurological deficits, from their first-degree relatives or legal representatives. All procedures were approved by the Dicle University Non-Invasive Clinical Research Ethics Committee (Approval No: 207, Date: June 09, 2022).

Inclusion criteria included: age ≥18 years, NIHSS (National Institutes of Health Stroke Scale) score ≥5, diagnosis of moderate or moderately severe acute ischemic stroke, and a modified Rankin Scale (mRS) score ≤2.

Exclusion criteria included: age <18 years; NIHSS <5; mRS ≥3; BMI ≥40 or ≤18; orthopedic, traumatic, or structural abnormalities and deformities of the lower extremities (e.g., fractures, dislocations, burn scars); oncologic diseases; severe renal or hepatic failure;

advanced heart failure; severe dementia or cognitive impairment due to neurodegenerative diseases; severe psychiatric disorders; progressive chronic inflammatory or rheumatologic diseases; skeletal disorders preventing supine positioning (e.g., kyphoscoliosis); and ICU stays of less than 21 days due to death, early discharge, or rehabilitation.

All patients included in the study presented with moderate to moderately severe neurological deficits (NIHSS ≥5). The most common neurological findings were hemiparesis or hemiplegia, frequently accompanied by varying degrees of facial weakness and speech disturbance. Sensory deficits were present in approximately half of the patients, and the severity of motor impairment ranged from mild paresis to complete hemiplegia.

For all included patients, demographic characteristics (age, sex), BMI, APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, and ICU length of stay were recorded. Height was measured on the first day of ICU admission in the supine position using a tape measure from the top of the head to the heel and recorded in centimeters. Body weight was measured in kilograms using a Rotkon scale integrated into a Dolsan hospital bed.

Approximately 75% of the patients (n = 32) required mechanical ventilation (median duration: 7 days, range: 3–14 days). The mean ICU length of stay was 21 days, and the mean total hospital stay was 28 days. During the ICU follow-up, routine physiotherapy interventions were implemented.

These interventions included early passive joint mobilization, proper positioning, and respiratory exercises, performed under the supervision of a physiotherapist or with nursing assistance at least twice daily. Active mobilization and neuromotor rehabilitation programs were initiated only in patients who were clinically stable, cooperative, and extubated.

Nutritional management

Patients with inadequate oral intake (n = 27) received enteral nutrition via a nasogastric tube, mainly during the first two weeks of their intensive care unit stay, due to the need for intubation or insufficient oral intake tolerance; patients with adequate intake (n = 17) continued oral feeding. Approximately two-thirds of the patients required mechanical ventilation, and some were able to tolerate oral intake after extubation. None of the patients required parenteral nutrition. Caloric and protein requirements were calculated according to intensive care nutrition guidelines, targeting approximately 25–30 kcal/kg/day and 1.2–1.5 g protein/kg/day.

During the ICU follow-up period, nutritional screening using the Nutrition Risk Screening-2002 (NRS-2002) scale identified mild-to-moderate malnutrition or malnutrition risk in approximately one-third of the patients (n = 13, 30%), whereas no severe malnutrition was observed.

Serum albumin, prealbumin, and C-reactive protein (CRP) levels were measured periodically during ICU follow-up.

Ultrasound assessment of stroke-related skeletal muscle loss

The rectus femoris muscle (RFM) is a standard site for assessing muscle mass via ultrasound. RFM thickness was measured on days 1, 7, and 21 of ICU admission using a Toshiba SSH-140A ultrasound device with a 7.5 MHz PLF-703NT transducer. Patients were positioned supine, with relaxed and extended knees, and toes pointing upward. The transducer was placed perpendicular to the long axis of the thigh with minimal pressure. Measurements were obtained bilaterally from both the paretic and non-paretic limbs at two-thirds of the distance between the anterior superior iliac spine and the proximal patella. Three consecutive measurements were obtained from each limb, and the mean RFM thickness was recorded in millimeters. All assessments were performed by the same intensive care and ultrasound specialist to minimize inter-operator variability. Results were reported as mean ± standard deviation.

Plasma CAF measurements

Plasma CAF levels were determined on days 7 and 21 using 5 mL blood samples drawn from the forearm vein. Samples were collected into EDTA-containing tubes, centrifuged at 4°C and 4000g for 10 minutes, and plasma was separated and stored in two Eppendorf tubes at −80°C. Analyses were performed using a BT Lab® ELISA kit according to the manufacturer's instructions. Frozen samples were thawed at room temperature prior to analysis, and repeated freeze-thaw cycles were avoided. CAF concentrations were quantitatively measured by ELISA in the clinical biochemistry laboratory.

Plasma CAF measurements were initiated on day 7 to avoid the effects of transient metabolic or stress-related fluctuations during the hypercatabolic acute phase and to ensure that the results more accurately reflected neuromuscular junction (NMJ) degradation. It was also considered that measurable changes in CAF levels were more likely to emerge within the first week. This approach is also consistent with a study investigating CAF dynamics in critical illness.[18]

Statistical analysis

Data analysis was performed using SPSS (Statistical Package for the Social Sciences). Descriptive statistics were expressed as mean, standard deviation, frequency, and percentage. For non-normally distributed variables, median and interquartile range (IQR) were used. Normality was assessed through visual methods (histograms and probability plots) and statistical tests (Kolmogorov-Smirnov and Shapiro-Wilk). For non-normally distributed variables, the Wilcoxon signed-rank test was used for paired comparisons, and the Friedman test was used for comparing three or more related groups. Correlations between non-normally distributed variables were assessed using Spearman's correlation coefficients. A Type I error threshold of 5% was used, and p-values <0.05 were considered statistically significant.

Results

Forty-four patients were included in the study, consisting of 23 women (52.27%) and 21 men (47.73%). The mean age was 69.52 years (range: 55 to 82 years). The average APACHE II score was 13.38, ranging from 8 to 22. The mean BMI was 27.20, with values between 21.28 and 37.46 (Table 1).

During the ICU follow-up, serum albumin levels on days 1, 7, and 21 were 3.4 ± 0.5, 3.2 ± 0.4, and 3.1 ± 0.4 g/dL, respectively. Prealbumin levels were 22.6 ± 4.8 mg/dL, 20.8 ± 4.5 mg/dL, and 19.3 ± 4.1 mg/dL on the same days. CRP levels were initially elevated (11.8 ± 3.6 mg/dL) and gradually decreased over time, reaching 8.2 ± 3.0 mg/dL on day 7 and 5.4 ± 2.1 mg/dL on day 21.

Table 1. Patient demographics

Variable		Mean	SD	Min	Max
Age (years)		69.52	6.38	55.00	82.00
BMI (kg/m^2)		27.20	4.62	21.28	37.46
APACHE II		13.386	3.954	8.000	22.000
Sex (n, %)	Female	23		52.27%	
	Male	21		47.73%	

Nutritional screening using the Nutrition Risk Screening-2002 (NRS-2002) scale identified mild-to-moderate malnutrition or malnutrition risk in approximately one-third of the patients (n = 13, 30%), whereas no severe malnutrition was observed.

The right RFM thickness was measured on days 1, 7and 21 as 11.98 mm (range: 4.00 to 20.30 mm), 10.85 mm (range: 4.90 to 18.00 mm), and 9.94 mm (range: 4.10 to 16.90 mm), respectively. A statistically significant difference was observed among the three measurements ($p<0.001$). Pairwise comparisons using Bonferroni correction also showed statistically significant differences between all three time points ($p<0.001$) (Table 2).

Left RFM thickness on days 1, 7, and 21 was measured as 11.98 mm (range: 5.80 to 20.60 mm), 10.82 mm (range: 4.00 to 17.90 mm), and 9.55 mm (range: 2.90 to 18.20 mm), respectively. A significant difference was found across the three time points ($p<0.001$). Pairwise comparisons using Bonferroni correction also revealed statistically significant reductions at each time point ($p<0.001$) (Table 3).

A comparison of the mean RFM (right and left) thickness measurements on days 1, 7, and 21 revealed a statistically significant difference across the three time points ($p<0.001$). Pairwise comparisons between the three measurements, adjusted using the Bonferroni correction, also showed statistically significant differences ($p<0.001$) (Table 4, Figure 1).

On the paretic side, the mean RFM thickness was 11.16 ± 3.48 mm on day 1, 10.13 ± 3.39 mm on day 7, and 8.96 ± 3.46 mm on day 21, whereas on the non-paretic side, the corresponding values were 12.74 ± 3.19 mm, 11.54 ± 3.22 mm, and 10.62 ± 3.24 mm, respectively. The differences between sides were statistically significant at all time points ($p <0.001$). Bilateral comparisons showed a progressive reduction in muscle thickness over time on both sides, with a more pronounced decline on the paretic side. These findings indicate a progressive and significant loss of muscle thickness, particularly on the affected side.

Table 2. Comparison of right rectus femoris muscle thickness by day

Day	Mean	SD	Min	Max	25th Pctl	Median	75th Pctl	p*
Day 1	11.98	3.48	4.00	20.30	9.78	12.25	14.23	<0.001
Day 7	10.85	3.41	4.90	18.00	8.85	10.50	13.88	
Day 21	9.94	3.55	4.10	16.90	6.70	9.70	13.20	

*Friedman test.

Table 3. Comparison of left rectus femoris muscle thickness by day

Day	Mean	SD	Min	Max	25th Pctl	Median	75th Pctl	p*
Day 1	11.98	3.45	5.80	20.60	9.50	11.40	14.83	<0.001
Day 7	10.82	3.36	4.00	17.90	8.73	10.05	12.80	
Day 21	9.55	3.35	2.90	18.20	7.23	9.30	11.70	

*Friedman test.

Table 4. Comparison of the mean RFM (right and left) thicknesses by day

Day	Mean	SD	Min	Max	25th Pctl	Median	75th Pctl	p*
Day 1	11.98	3.31	6.00	20.45	9.43	12.40	14.40	<0.001
Day 7	10.84	3.23	4.70	17.95	8.31	11.15	12.71	
Day 21	9.74	3.32	3.95	17.55	7.01	9.60	11.96	

*Friedman test.

Plasma CAF levels were measured on days 7 and 21. A statistically significant reduction was found between the two time points (p<0.001) (Table 5, Figure 2).

Association between RFM thickness and plasma CAF levels

When the difference in mean right and left RFM thickness between day 1 and day 7 measurements was compared with the change in CAF levels between day 7 and day 21 measurements, a moderate positive but statistically non-significant correlation was found (r = 0.294, p> 0.05).

When the difference in mean RFM thickness (right+left) between day 1 and day 21 measurements was compared with the difference in CAF levels between day 7 and day 21 measurements, a weak positive and statistically non-significant correlation was observed (r = 0.262, p> 0.05).

When the difference in mean RFM thickness (right+left) between day 7 and day 21 measurements was compared with the difference in CAF levels between the same time points, a weak negative and statistically non-significant correlation was observed (r=-0.023, p> 0.05) (Table 6).

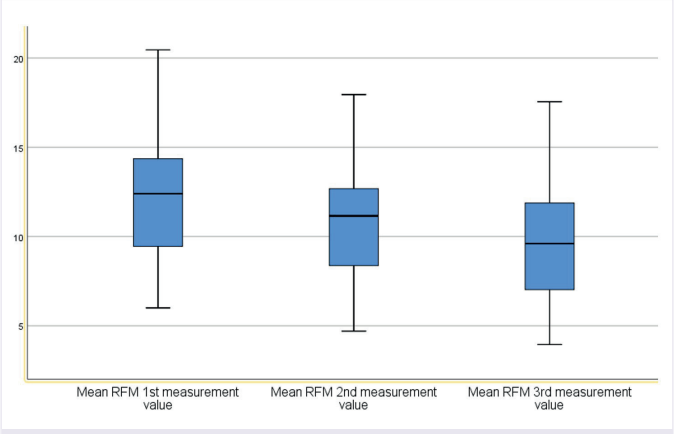

Figure 1. Mean RFM thickness (right and left) over time

Table 5. Change in plasma C-terminal agrin fragment levels by day

Time Point	Mean	SD	Min	Max	25th Pctl	Median	75th Pctl	p*
Day 7	0.10689	0.01268	0.09700	0.14900	0.10000	0.10100	0.11000	<0.001
Day 21	0.10295	0.00851	0.09100	0.13100	0.09700	0.10000	0.10525	

*Wilcoxon test.

Table 6. Correlation between differences in mean RFM thickness (right and left) and plasma CAF levels.

Change in Mean RFM Thickness (Right and Left)	Change in CAF Levels		
Day 1 to Day 7	Day 7 to Day 21	r	0.294
		p	0.053
Day 1 to Day 21	Day 7 to Day 21	r	0.262
		p	0.086
Day 7 to Day 21	Day 7 to Day 21	r	-0.023
		p	0.882

*Spearman test.

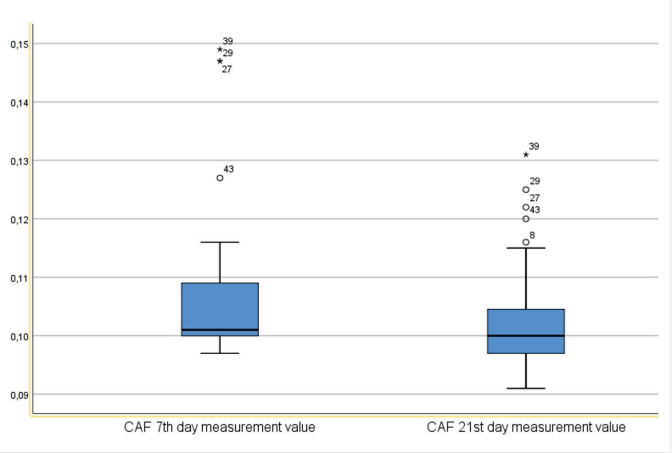

Figure 2. Plasma C-terminal agrin fragment levels over time

Discussion

In this single-center study, we assessed rectus femoris muscle loss using ultrasound and measured plasma CAF levels in patients with acute ischemic stroke admitted to a neurology ICU. Our findings indicate a significant and progressive reduction in the thickness of both right and left rectus femoris muscles during the ICU stay. However, no clear correlation was observed between changes in average RFM thickness and plasma CAF levels across different measurement combinations. Consistent with the literature, our results align with previous findings on post-stroke muscle loss.

Muscle atrophy typically results from immobilization, neurological damage, and inflammatory processes. These effects are often accelerated in critically ill patients. Considering the limited mobility of stroke patients, ultrasound emerges as a reliable, bedside, and non-invasive tool for tracking muscle loss, especially in cases where access to CT or MRI is limited.[10,19]

Our findings demonstrated a progressive reduction in rectus femoris muscle (RFM) thickness on both sides during the ICU stay, with a more pronounced decline on the paretic side. This observation is consistent with previous ultrasound-based studies reporting greater muscle wasting in paretic limbs after stroke. In particular, Park et al. (2022) reported significantly reduced quadriceps muscle thickness on the paretic side in acute hemiplegic stroke patients.[20]

Pardo et al. investigated the reliability of ultrasound measurements of quadriceps muscle thickness and its progression over the first three weeks post ICU admission in 29 critically ill patients. They measured quadriceps muscle thickness on days 1, 3, 5, 7, and 21 using a 12 MHz linear probe, and found that quadriceps femoris muscle thickness decreased by more than 16% in the first week and by 24% by day 21.[21]

Parry et al.[22] analyzed sequential ultrasound images of the quadriceps in 22 adult patients who were intubated for more than 48 hours. Measurements were taken during

the first 10 days, upon awakening, and at discharge. The study reported a 30% reduction in vastus intermedius and rectus femoris thickness and cross-sectional area within the first 10 days of ICU admission.

Gruther et al.[8] also measured quadriceps femoris thickness using ultrasound in ICU patients. They included 17 pilot patients with baseline and 28-day measurements and an additional 101 randomly selected ICU patients. The study showed that muscle thickness was significantly associated with length of stay, with greater muscle loss occurring in the first 2–3 weeks. The findings support ultrasound as a valid and practical tool for daily muscle assessment.

Tillquist et al. demonstrated that bedside ultrasound performed by various healthcare professionals without prior ultrasound experience was a practical and reliable method for assessing quadriceps muscle layer thickness (QMLT) in healthy volunteers.[3]

In a study by English et al., the test-retest reliability of ultrasound-based muscle thickness measurements was evaluated in patients with acute stroke. Measurements taken at four anatomical sites—anterior upper arm, posterior upper arm, abdomen, and anterior thigh—were found to be within acceptable reliability ranges, supporting the use of ultrasound in these regions.[23]

In our study, we observed a 9.73% decrease in RFM thickness within the first week of ICU admission, reaching 20.27% by day 21. A statistically significant association was found between length of ICU stay and muscle mass ($p < 0.01$). These results support the notion that muscle loss accelerates during the early stages of ICU admission and highlight the importance of monitoring muscle thickness. Additionally, ultrasound proved to be a reliable tool for detecting and tracking muscle loss and offers valuable insights into its progression during critical illness.

Scherbakov et al. investigated the potential of CAF in assessing muscle mass and physical performance after acute stroke.[24] They compared 123 patients with ischemic or hemorrhagic stroke undergoing rehabilitation with 26 age- and BMI-matched healthy controls. CAF levels were significantly higher in stroke patients and partially decreased during rehabilitation. CAF was associated with physical performance parameters, grip strength, and muscle cell integrity. Notably, improvement in grip strength of the paretic arm was independently associated with a reduction in CAF levels, but only in patients who showed an increase in muscle mass. These findings suggest that CAF may reflect dynamic changes in muscle condition during the subacute phase after stroke and highlight its potential role in guiding rehabilitation, warranting further investigation.

Monti et al. reviewed all published studies from 2013 (when CAF was first measured in human serum) to 2022 that included CAF measurements.[25] Their comprehensive analysis examined CAF's role in aging and muscle-wasting conditions. CAF levels were found to be elevated in older adults and patients with sarcopenia, as well as in non-sarcopenic conditions such as diabetes, COPD, chronic heart failure, cancer, and stroke. The review emphasized that renal function may affect CAF levels and should not be overlooked. Importantly, the authors noted that increased CAF levels due to immobilization could be mitigated through exercise. CAF may be a reliable biomarker for assessing muscle mass and function, though its clinical utility still requires validation through broader studies.

In our study, no inverse correlation was identified between plasma CAF levels and muscle thickness. While a moderate correlation was observed between changes in right RFM measurements and CAF levels, this relationship was not evident for the left side. Overall, no clear association was found between mean RFM thickness (right+left) measurements and plasma CAF levels.

Limitations

Several factors may have influenced our findings. These include the timing of CAF measurements, the single-center design, the characteristics of the patient population, the ELISA kit used, the sample size, and the exclusion of patients with advanced systemic diseases such as severe heart or renal failure. These variables may have affected the relationship between CAF levels and muscle loss.

In addition, the lack of serial NIHSS assessments prevented the evaluation of longitudinal correlations between changes in neurological status, RFM thickness, and CAF levels.

Conclusions

In ICU patients with acute ischemic stroke, significant changes in RFM thickness across all time points indicate that muscle loss is both progressive and continuous.

These findings support the presence of substantial muscle wasting that worsens over time. Ultrasound remains a reliable, non-invasive method for the early detection and monitoring of muscle atrophy.

Although plasma CAF has been proposed as a potential biomarker for muscle mass and function, its utility in tracking muscle loss remains uncertain. Future multicenter studies with larger and more diverse patient populations, incorporating additional biochemical markers, are needed to clarify the relationship between CAF levels and muscle loss.

Ethical approval

This study has been approved by the Non-Interventional Clinical Research Ethics Committee of Dicle University (approval date 09.06.2022, number 207). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: MUÇ, EA; data collection: NBF; analysis and interpretation of results: NBF, HG, MUA, AE; draft manuscript preparation: NBF, AE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Readability assessment of Turkish orthorexia nervosa scales with confirmed reliability and validity

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ABSTRACT

Objective: This study aimed to assessment the readability levels of Turkish adapted orthorexia nervosa self-report scales with confirmed reliability and validity. While psychometric properties of these scales have been previously examined, their linguistic accessibility and readability which affect user comprehension and data quality have been largely overlooked.

Methods: A descriptive document analysis was conducted by collecting Turkish versions of nine orthorexia nervosa scales validated for adult individuals. These scales were identified through a comprehensive literature search performed in widely used academic databases. The readability of scale items was assessed using two formulas appropriate for Turkish texts: the Ateşman Readability Formula and the Çetinkaya-Uzun Readability Formula. Textual features such as total word count, sentence count, average word length, and average sentence length were calculated. Readability scores were then classified according to established educational level benchmarks for each formula.

Results: The nine scales evaluated in this study were the Barcelona Orthorexia Scale (BOS), Düsseldorf Orthorexia Scale (DOS), Eating Habits Questionnaire (EHQ), Orthorexia Nervosa Inventory (ONI), Orthorexia Nervosa Scale (ONS), ORTO-11, ORTO-R, Test of Orthorexia Nervosa (TON-17), and Teruel Orthorexia Scale (TOS). According to the Ateşman formula, all scales except ORTO-R were categorized as "somewhat difficulty", corresponding approximately to comprehension at the high school level (11th-12th grade). ORTO-R required a university level reading ability and was classified as "difficult". Using the Çetinkaya-Uzun formula, all scales were classified within the "educational reading" category, indicating an 8th-9th grade comprehension level.

Conclusion: Overall, the Turkish-adapted orthorexia nervosa scales demonstrated moderate readability suitable for individuals with high school education. However, their applicability may be limited among populations with lower education and health literacy levels. Future adaptation studies should include readability analyses and pilot testing across diverse educational backgrounds to ensure inclusivity and accurate assessment.

Keywords: orthorexia nervosa, readability, reliability, validity

Introduction

Orthorexia nervosa (ON), which has been extensively researched in recent years, is derived from the Greek words "ortho" (correct) and "orexia" (appetite) and was first defined by Steven Bratman in 1997 as an obsessive and compulsive preoccupation with healthy eating.[1] Initially described as a disorder unrelated to weight and body shape concerns, focusing solely on food quality and purity, ON has since been recognized by researchers as a complex condition that may also include weight and body shape concerns.[2,3] Individuals with ON tend to prioritize the quality of food over its quantity, fixating intensely on aspects such as food purity, quality, preparation,

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and packaging.[4] This pathological preoccupation can dominate their daily lives and scauses difficulties in social relationships, family life, and work performance.[3] Whether ON should be classified as a distinct eating disorder or considered within the broader spectrum of mental health disorders remains a topic of ongoing debate. Although general diagnostic criteria have been proposed, ON is not currently included in official psychiatric classification systems such as International Classification of Diseases (ICD-11) or Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[5] This lack of consensus hinders the standardization of its definition and diagnosis. Nevertheless, especially in today's world where healthy eating trends are on the rise, preclinical disordered eating behaviors, including ON and other unhealthy preoccupations with body image, have increased at an alarming rate. Various studies have shown that the prevalence of ON varies widely across different populations, ranging from 6.9% to 90.6%.[6-8] Additionally, the identification of ON symptoms in approximately one-third of participants in a recent large scale meta-analysis highlights the serious public health concern posed by this condition.[9] In light of these concerns, the development of valid and reliable assessment instruments to detect ON early and guide interventions has become increasingly critical. Although no original ON scale has yet been developed in Türkiye, nine different ON scales have been adapted into Turkish. However, despite the emphasis on psychometric validation, the readability of these scales -the extent to which they are understandable to users- is often overlooked.[10]

Readability refers to how easily and accurately a text can be comprehended by its intended audience.[11] It is a parameter that is objectively measured using mathematical formulas based on quantitative characteristics such as the syntactic complexity, sentence length, and word length of texts.[12] In English texts, formulas such as the Flesch Reading Ease Formula, Flesch-Kinkaid Reading Grade Level, Gunning Frequency of Gobbledygook, and SMOG Index are commonly used.[13,14] In Turkish texts, the formulas developed by Ateşman,[15] Çetinkaya-Uzun,[16] and Bezirci-Yılmaz[17] are used. This study aims to evaluate the readability levels of Turkish adapted ON scales with confirmed reliability and validity, using the Ateşman and Çetinkaya-Uzun readability formulas. By doing so, it seeks to assess how comprehensible ON-related self-report scales are to users and to highlight the importance of integrating readability analyses into validation processes in order to enhance the quality and accessibility of such tools in both research and clinical contexts.

Main Points

- This study evaluated the readability of nine Turkish adapted ON scales using objective formulas.
- Most scales showed moderate readability, suitable for individuals with a high school education level.
- Future scale adaptation studies should integrate readability analyses and pilot testing to ensure broader applicability and comprehension across diverse populations.

Material and Method

Study design and data collection

This research is a descriptive document analysis study. A comprehensive literature search was conducted in July 2025 across the PubMed, Scopus, Web of Science, and Google Scholar databases. The search strategy included keywords such as "Orthorexia nervosa", "Orthorexia", "Orthorexic behavior", "Healthy eating obsession", "Screening tool", "Assessment tool", "Diagnostic tool", "Self-report scale", "Psychometric properties", "Measurement instrument", "Questionnaire", "Validation", "Reliability", and "Validity". Through this process, nine ON scales adapted into Turkish were identified. All of these scales are self-report measurement scales that have undergone validity and reliability studies in adult populations. Necessary permissions for use were obtained from the original researchers who adapted these scales. The identified scales and the researchers who adapted them into Turkish are listed in Table 1.

Ethical approval

As this study involved document analysis of published materials and did not include human subjects or interventions, ethical committee approval was not required. Similar studies in the literature have also been conducted without the need for ethical approval.[10,25]

Readability analysis

In this study, the readability levels of the scale items were assessed using the Ateşman[15] and Çetinkaya-Uzun[16] readability formulas. These two indices were used because they are the most widely applied and

Table 1. Turkish adapted orthorexia nervosa scales

Scales	Authors adapted into Turkish	Year	Number of Items
Barcelona Orthorexia Scale (BOS)	Bilekli-Bilger and Dağ[18]	2023	50
Düsseldorf Orthorexia Scale (DOS)	Yılmaz, Demirkol, Tamam, Özdemir-Yılmaz, Yeşiloğlu[19]	2024	10
Eating Habits Questionnaire (EHQ)	Bilekli-Bilger and Dağ[18]	2023	18
Orthorexia Nervosa Inventory (ONI)	Kaya, Uzdil, Çakıroğlu[20]	2022	24
Orthorexia Nervosa Scale (ONS)	Bilekli-Bilger and Dağ[18]	2023	15
ORTO-11	Arusoğlu, Kabakçı, Köksal, Kutluay-Merdol[21]	2008	11
ORTO-R	Kaya, Asil, Çakıroğlu, Sertdemir, Can, Muradoğlu[22]	2024	6
Test of Orthorexia Nervosa (TON-17)	Yassıbaş and Aydıldız[23]	2023	17
Teruel Orthorexia Scale (TOS)	Asarkaya and Arcan[24]	2023	16

cited Turkish readability formulas, with simple and comparable structures that facilitate the consistency and interpretability of results.[15,26,27] The Ateşman Readability Formula was developed based on the Flesch Reading Ease Formula, taking into account the unique structure of the Turkish language.[15,28] This formula calculates the readability level of a text based on the variables of average word length (number of syllables) and average sentence length (number of words).

Ateşman Readability Formula = 198.825 – (40.175 × average word length) – (2.610 × average sentence length)

The resulting score ranges from 0 to 100; with higher scores indicating easier readability.[15] The corresponding educational levels associated with score ranges are presented in Table 2. The readability scores were calculated based on the formulas described above.

The study also used the Çetinkaya-Uzun Readability Formula, which was developed specifically for Turkish texts.[16,26] It is similarly based on average word and sentence lengths but uses a different mathematical structure.

Çetinkaya-Uzun Readability Formula = 118.823 – (25.987 × average word length) – (0.971 × average sentence length)

Unlike the Ateşman formula, lower scores on the Çetinkaya-Uzun Formula indicate higher readability demands,[16] with corresponding educational level classifications detailed in Table 2.

During the analysis process, the total number of syllables, words, and sentences in each scale text was calculated and transferred to Microsoft Excel. Then, scores were calculated according to the Çetinkaya-Uzun Readability Formula and compared with the evaluation scales.

The statistical analyses are descriptive in nature. Since the study aims to summarize and compare inter scale readability scores rather than test specific hypotheses, inferential statistical tests or multiple comparison adjustments have not been applied.

Results

Descriptive statistics regarding the linguistic characteristics of the Turkish versions of the ON scales are presented in Table 3. Among the scales, the BOS contains the greatest number of words and sentences, as well as the highest total character count (4125) and total word count (491). In contrast, the ORTO-R scale, comprising only 6 items, features the shortest text length. Similarly, the DOS exhibits a concise language structure with a relatively short text. Regarding average word length, all scales maintain the typical Turkish three-syllable word structure. The highest average word length was observed in the ONS (3.09 syllables), while the lowest was in the ONI (2.85 syllables). For average sentence length, the ONI again had the highest value (12.4 words per sentence), whereas the EHQ had the shortest average sentence length (7.3 words).

Table 2. Readability and education levels according to Ateşman and Çetinkaya-Uzun readability formulas

Score	Readability Level	Education Level
Ateşman Readability Formula Score[15]		
90–100	Very easy	4th grade
80–89	Easy	5th–6th grade
70–79	Fairly easy	7th–8th grade
60–69	Moderate difficulty	9th–10th grade
50–59	Somewhat difficulty	11th–12th grade
30–49	Difficult	University level
1–29	Very difficult	Postgraduate level
Çetinkaya-Uzun Readability Formula Score[16]		
0–34	Assisted reading level	10th–12th grade
35–50	Educational reading	8th–9th grade
51 and above	Independent reading	5th–7th grade

Figure 1 shows the scores obtained from the Ateşman and Çetinkaya-Uzun readability formulas for the ON scales, which have been adapted in Turkish, while Table 4 shows the readability and education levels corresponding to these scores.

According to Ateşman readability scores, all scales except ORTO-R were determined to be in the "somewhat difficulty" category, indicating that they are generally comprehensible to individuals at the 11th to 12th grade (high school senior) education level (Table 4). The highest readability score belongs to the TON-17 scale (59.0), while the lowest score was found in the ORTO-R scale (47.9) (Figure 1). The ORTO-R scale was classified as "difficult" according to the Ateşman Readability Formula, implying that it requires a university level reading ability (Table 4). According to the Çetinkaya-Uzun Readability Formula, all scales are categorized as requiring "educational reading" ability, corresponding to an 8th to 9th grade educational level. Within this classification, the ONI had the highest readability score (42.09), while the ONS had the lowest (35.92) (Table 4).

Table 3. Descriptive linguistic statistics of the scales

Scales	Total Word Count	Total Character Count	Sentence Count	Difficult Word Count	Average Word Length	Average Sentence Length
BOS	491	4125	50	489	3.01	9.8
DOS	88	751	10	88	3.05	8.8
EHQ	131	1098	18	130	3.01	7.3
ONI	299	2382	24	296	2.85	12.4
ONS	134	1149	15	134	3.09	8.9
ORTO-11	100	822	11	99	2.93	9.1
ORTO-R	69	581	6	68	3.01	11.5
TON-17	155	1254	17	154	2.89	9.1
TOS	154	1280	16	154	2.97	9.6

BOS: Barcelona Orthorexia Scale, DOS: Düsseldorf Orthorexia Scale, EHQ: Eating Habits Questionnaire, ONI: Orthorexia Nervosa Inventory, ONS: Orthorexia Nervosa Scale, TON-17: Test of Orthorexia Nervosa, TOS: Teruel Orthorexia Scale

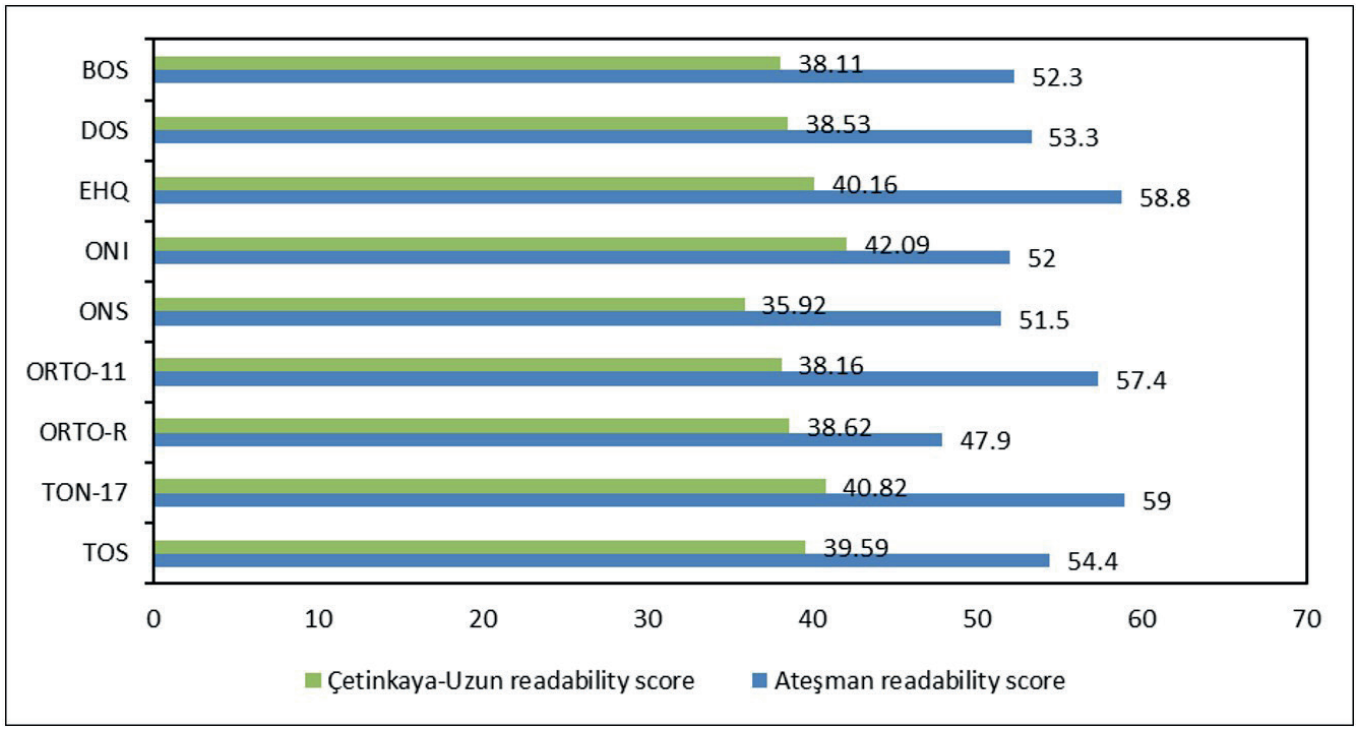

Figure 1. Readability score of the scales according to Ateşman and Çetinkaya-Uzun readability formulas

Table 4. Readability values of the scales

Scales	Ateşman Readability Level	Ateşman Education Level	Çetinkaya-Uzun Readability Level	Çetinkaya-Uzun Education Level
BOS	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
DOS	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
EHQ	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
ONI	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
ONS	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
ORTO-11	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
ORTO-R	Difficult	University level	Educational reading	8th–9th grade
TON-17	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade
TOS	Moderate difficulty	11th–12th grade	Educational reading	8th–9th grade

BOS: Barcelona Orthorexia Scale, DOS: Düsseldorf Orthorexia Scale, EHQ: Eating Habits Questionnaire, ONI: Orthorexia Nervosa Inventory, ONS: Orthorexia Nervosa Scale, TON-17: Test of Orthorexia Nervosa, TOS: Teruel Orthorexia Scale

Discussion

This study is one of the pioneering studies that examines the readability levels of Turkish adapted ON scales using objective criteria. The findings reveal that all scales examined have a generally "somewhat difficulty" readability level and are understandable by individuals with a high school education. However, when the average literacy level in Türkiye is considered the practical implication of these findings becomes particularly significant. The scales categorized as being of "moderate difficulty" may not be sufficiently comprehensible for

individuals with lower literacy levels, which could restrict their usability in community-based or clinical settings involving diverse educational backgrounds. This concern is further underscored by the close relationship between general literacy and health literacy, both of which are known to affect individuals' capacity to accurately interpret and respond to health related materials. A study conducted in Türkiye on the national health literacy level showed that three-quarters of individuals over the age of 18 have limited (insufficient or problematic) health literacy levels.[29] In conclusion, the moderate level of readability identified in this study may make it difficult to accurately assess orthorexic behaviors, particularly among individuals with low educational attainment and limited health literacy.

The differences in readability levels observed among the ON scales can be attributed to the methods used to develop these scales, the cultural contexts from which they originate, and strategic choices made during the translation process. For example, the ORTO-R scale, which has the lowest readability score, consists of short sentences but contains a language structure that is conceptually dense and loaded with technical terms. This situation may reduce the comprehensibility of the scale, especially for individuals with low educational levels and health literacy. Similarly, scales such as the BOS, which have a large number of words and sentences, may require more cognitive effort despite providing content richness. In contrast, scales such as the TON-17 and EHQ, which are structured with simpler and clearer expressions, increase comprehensibility. These results emphasize that the readability level of a scale is determined not only by the number of items but also by sentence structure, word choice, and conceptual clarity. Therefore, in the development of measurement tools, not only the content but also the linguistic presentation form should be considered. A similar pattern has been observed in various self-report instruments, particularly within the field of mental health, where readability analyses have shown that many commonly used scales demand literacy levels above the population average.[30] McHugh and Behar (2010) noted that the accessibility of such tools is often reduced due to the frequent use of technical terminology and complex sentence structures, potentially limiting their effectiveness among individuals with lower reading proficiency.[31]

When reviewing the validity and reliability studies of the Turkish adaptations of the ON scales, it is observed that these studies were largely conducted on university students or individuals with higher education. This situation has led to the samples consisting of individuals with generally high language proficiency, thereby limiting the generalizability of the evaluations of the scales' comprehensibility levels. For example, the Turkish adaptation studies of the EHQ, BOS, and ONS were conducted with university students; the average age of the participants was reported to be 21.26.[18] The TON-17 was tested on a sample with an average age of 30.2, 95% of whom were individuals with graduate or undergraduate education.[23] Similarly, the ONI was evaluated with a sample consisting of individuals with an average age of 30.15, 91.1% of whom had graduate and undergraduate education.[20] In the ORTO-R scale study, participants with an average age of 24 and 88% of whom had higher education were used.[22] It is noteworthy that in the adaptations of scales such as TOS, the majority of the samples consisted of individuals with a high level of education.[24] Although some studies have conducted comprehensibility tests and pilot applications, it is observed that these processes have not been systematically carried out for all scales and that they contain differences in terms of surface validity.[19-23] This situation highlights critical concerns regarding the functional applicability of existing scales, particularly for individuals with lower levels of education. In countries like Türkiye, where approximately 60% of the population are secondary school graduates,[32] scales validated predominantly on highly educated samples may not adequately represent or serve the broader population. As a result, the generalizability and inclusiveness of these scales are brought into question. The findings of the current study, which reveal moderate to difficult readability levels across scales, underscore the potential risk that these instruments may not be equally comprehensible to individuals with varying educational backgrounds. This disparity poses a threat to the early detection and proper assessment of ON, potentially leading to misinterpretations, omitted responses, or inaccurate self-reporting.

Readability is not only a linguistic concern but also a core determinant of a tool's effectiveness in accurately capturing user responses. In self-report psychological assessments, the clarity and accessibility of language directly influence the reliability and validity of the collected data. Scales with low readability are more likely to be misunderstood, improperly completed, or partially skipped, compromising both data quality and diagnostic accuracy. Moreover, when research tools are misaligned with the education level of their intended audience, they risk becoming exclusionary, thereby limiting both participation and the generalizability of findings.[30,33,34]

In clinical settings, such misalignments can result in diagnostic errors or delays, especially for emerging psychological conditions like ON, which lack standardized criteria yet demonstrate increasing prevalence. Therefore, it is essential that readability is systematically integrated into the scale development and adaptation process, alongside traditional psychometric evaluations. Doing so would enhance the inclusivity, clarity, and overall utility of assessment tools across diverse populations.

Limitations

This study has several limitations that should be acknowledged. First, the analysis was limited to nine self-report ON scales that have been adapted into Turkish and validated for adult individuals. Therefore, the results may not be generalizable to other scales that have not been included or to newly developed instruments. Additionally, the study focused solely on textual readability using two objective formulas (Ateşman and Çetinkaya-Uzun), without incorporating participant-based assessments such as user comprehension testing or qualitative feedback. Moreover, this study did not evaluate the readability of accompanying materials such as instructions, response formats, or scale administration procedures, which may also influence comprehension and usability. This study was conducted purely as a document-based analysis, and the scales were not pilot tested with participants from varying educational levels, which may limit the generalizability of the results. Finally, it is thought that the translation and adaptation processes of the scales evaluated differed and that not all of them followed a standard methodology, and that this situation may have indirectly affected the readability levels observed in the Turkish versions.

Conclusion

In this study, the readability levels of nine self-report scales adapted into Turkish for ON were evaluated using the Ateşman and Çetinkaya-Uzun Readability Formulas. The results obtained showed that most scales had a readability level suitable for high school students and were of moderate difficulty. Readability is as important a criterion as psychometric validity and reliability and should be considered for the proper and effective use of measurement tools. Low readability can negatively affect data quality by preventing participants from correctly understanding the scales and may lead to disruptions in the diagnostic process. Therefore, it is recommended that user focused criteria such as linguistic accessibility and readability be systematically evaluated in future scale development and adaptation studies. Furthermore, future research should prioritize conducting pilot testing and comprehensibility assessments with participants representing different educational levels to ensure that the scales are accessible and interpretable across diverse population groups. Additionally, the comprehensibility of scales should be tested through pilot applications and qualitative studies with participants from different educational and socio-cultural backgrounds. Ensuring that assessment tools for ON used in clinical practice and research are adequate from both psychometric and linguistic perspectives will enhance the effectiveness of early diagnosis and intervention processes. In conclusion, this study aims to contribute to future research and clinical practice by filling an important gap in the applicability of ON measurement tools.

Ethical approval

As this study involved document analysis of published materials and did not include human subjects or interventions, ethical committee approval was not required.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: SK; data collection: SK; analysis and interpretation of results: SK; draft manuscript preparation: SK. The author reviewed the results and approved the final manuscript.

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Conflict of interest

The author declares no conflict of interest.

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Factors affecting palliative care mortality after percutaneous endoscopic gastrostomy placement in non-cancer patients

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ABSTRACT

Objectives: The use of enteral route in nutritional support therapy is more physiological. It preserves the structural and functional intestinal integrity as well as the intestinal microbial diversity. Percutaneous endoscopic gastrostomy (PEG) is one of the enteral feeding routes. It is indicated for patients who cannot take oral food at all or cannot take oral food for more than 4 to 6 weeks.

Methods: Non-cancer patients who had PEG tube placement between November 1, 2024 and May 1, 2025 in the palliative care service were followed prospectively. Patients were divided into two groups: those who were discharged from the palliative care service after PEG tube placement and those who died in the palliative care service after PEG tube placement. It was examined whether the patients had an infection after PEG placement and, if so, what type of infection they had. The study was conducted with the 83 patients.

Results: According to the logistic regression analysis results, age and pneumonia after PEG tube placement were found to be risk factors affecting palliative care mortality after PEG tube placement in the palliative care service (respectively; p= 0.017, odds ratio [OR]=1.06, confidence interval [CI] of OR=1.012- 1.126; p=0.004, OR=5.32, CI of OR=1.697- 16.680).

Conclusion: Age and pneumonia after PEG tube placement were found to be risk factors affecting palliative care mortality after PEG tube placement in non- cancer palliative care patients.

Keywords: age, mortality, non-cancer, percutaneous endoscopic gastrostomy, pneumonia

Introduction

Maintaining adequate nutrient intake is important for health and quality of life in older people. However, older adults are at risk of malnutrition for many reasons.[1] Decreased cognitive and physical functions, depressive mood, poor oral hygiene, socioeconomic conditions, polypharmacy, dysphagia, some neurological diseases such as parkinson, dementia, cerebrovascular occlusion, and diseases that cause loss of appetite such as cancer can cause malnutrition in older people.[2]

The use of enteral route in nutritional support therapy is more physiological. It preserves the structural and functional intestinal integrity as well as the intestinal microbial diversity. Parenteral nutrition carries a risk of infective conditions, most likely due to hyperalimentation and hyperglycemia.[3] Therefore, if there is no contraindication in malnutrition treatment in older patients, we choose the oral or enteral route.

Percutaneous endoscopic gastrostomy (PEG) is one of the enteral feeding routes. It is indicated for patients

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who cannot take oral food at all or cannot take oral food for for more than 4 to 6 weeks.[4] Some types of cancer and some neurological diseases such as dementia, Parkinson's disease, motor neuron disease and stroke cause swallowing problems. Therefore, PEG may be indicated in those with these diseases.[5] This procedure can have many major and minor complications. Minor complications include: Wound infection, tube leakage to abdominal cavity, gastric outlet obstruction, inadvertent PEG removal, tube blockage, pneumoperitoneum, stoma leakage. Major complications include: Aspiration pneumonia, necrotizing fasciitis, buried bumper syndrome, perforation of bowel, hemorrhage, metastatic seeding.[4]

It is necessary to make the right decision in which patients and when the PEG tube will be placed. Complications can be much more serious, especially in older and frail patients. In patients with end-stage dementia, the risks of this procedure may outweigh its benefits. In such cases, the wishes of the patient's relatives also become important.

The aim of this study was to investigate the factors affecting palliative care mortality after PEG tube placement in palliative care patients without cancer.

Methods

Study participants

Patients who underwent PEG tube placement in the palliative care service were included in the study. Patients who had PEG tube placement between November 1, 2024 and May 1, 2025 were followed prospectively. Cancer patients, patients who had their PEG tube placement in another service, and patients who died or were not discharged but transferred to another unit during the study period were excluded from the study. There were 100 patients, 17 of whom were excluded from the study. The study was conducted with the remaining 83 patients.

Main Points

- Enteral nutrition is more physiological than parenteral nutrition and carries less risk in terms of infection.
- Percutaneous endoscopic gastrostomy (PEG) is one of the enteral feeding routes and is indicated in some patients.
- Pneumonia developing after PEG tube placement is one of the risk factors affecting palliative care mortality after PEG tube placement in non-cancer palliative care patients.

Data collection

Patients' age, medical history, and laboratory values were recorded. It was examined whether they had an infection after the PEG placement and, if so, what kind of infection they had. The patients' culture results and chest radiographs were followed to understand what type of infection they had. Urinary tract infection was diagnosed after urine culture was positive and an infectious disease specialist started antibiotics accordingly. Pneumonia was diagnosed after a positive sputum culture or infiltration on chest radiography and an infectious disease specialist started antibiotics accordingly. Bacteremia was diagnosed after the blood culture was positive and the infectious diseases specialist started antibiotics accordingly. Wound infection was diagnosed after culture positivity from the pressure ulcer or discharge around the PEG and appropriate antibiotics were started by an infectious disease specialist. Frailty status of patients was assessed using the clinical frail scale (CFS). Scoring is between 1 and 9. Frail is diagnosed at scores of 5 and above (score 5: mildly frail; score 6: moderately frail; score 7: severely frail; score 8: very severely frail and score 9: terminally ill).[6] The patient's daily living activities was evaluated using Katz activities of daily living (ADL).[7] Instrumental daily living activities was evaluated using Lawton-Brody instrumental ADL (IADL).[8] However, our patients received 0 points from the Katz ADL and Lawton-Brody IADL, meaning they were completely dependent in ADL and IADL.

Ethical statement

Informed consent was obtained from the patients. Approval from the local ethics committee was obtained (decision no: 2024/125).

Statistical analyses

IBM SPSS version 23 program was used for data statistics. The numerical variables were assessed by Kolmogorov-Smirnov test and histograms to determine whether their distributions were normal. Numerical variables were presented as mean ± standard deviation (SD) or median [interquartile range (IQR)] depending on normal or non-normal distribution. Categorical variables were presented

as numbers (percentages). For comparison of numerical variables Student's t-test or Mann-Whitney U test was used depending on normal or non-normal distribution. Chi-square (X^2) or Fisher's exact test was used to compare categorical variables. Logistic regression analysis was used to determine risk factors affecting mortality after PEG tube placement in palliative care. If the p value was ≤ 0.05, it was considered statistically significant.

Results

51.8 % (n=43) of patients were female, while the median age of patients was 84 [12]. 50.0 % (n=14) of patients who died after PEG tube placement had pneumonia after PEG tube placement. This rate was 20.0% (n=11) in patients who did not die, and this difference was statistically significant (p=0.005). Pressure ulcers were present in 89.3% of the patients who died, compared to 69.1% in the patients who did not die, and were statistically significant (p=0.042). While the mean prealbumin value of the non-survivor patients was 11.3±5.38, this value was 13.8±5.12 in the survivor patients, and this was statistically significant (p=0.041). The general characteristics of the patients are presented in Table 1.

In Table 1, those with a p- value below 0.20 and sex were included in the regression analysis (age, sex, albumin, prealbumin, procalsitonin, pneumonia, hemoglobin, pressure ulcer). Omnibus test for this model had a p-value of <0.001. Hosmer and Lemeshow test had a p-value of >0.050. Nagelkerke R square was 0.265 for this model. According to the logistic regression analysis results, age and pneumonia after PEG tube placement were found

Table 1. Characteristics of the patients

	Total, n=83	Non-survivor, n=28 (34%)	Survivor, n=55 (66%)	p-value
Sex				
Women; n (%)	43 (51.8)	14 (50.0)	29 (52.7)	0.814
Age; median [IQR]	84 [12]	85 [10]	84 [16]	0.126
CFS Score; median [IQR]	8 [0]	8 [0]	8 [0]	0.953
Pneumonia; n (%)	25 (30.1)	14 (50.0)	11 (20.0)	**0.005**
Bacteremia; n (%)	11 (13.3)	3 (10.7)	8 (14.5)	0.743
Urinary Tract Infection; n (%)	6 (7.2)	1 (3.6)	5 (9.1)	0.658
Wound infection; n (%)	15 (18.1)	6 (21.4)	9 (16.4)	0.571
Pressure Ulcer; n (%)	63 (75.9)	25 (89.3)	38 (69.1)	**0.042**
Bolus Feeding; n (%)	8 (9.6)	3 (10.7)	5 (9.1)	1.000
Continuous Feeding; n (%)	75 (90.4)	25 (89.3)	50 (90.9)	1.000
Albumin, g/dL; mean±SD	2.79±0.43	2.67±0.36	2.85±0.46	0.074
CRP, mg/dL; median [IQR]	50.8 [83]	66.5 [78.5]	47 [86]	0.340
Prealbumin, mg/dL; mean±SD	12.97±5.31	11.3±5.38	13.8±5.12	**0.041**
Procalcitonin, µg/L; median [IQR]	0.13 [0.17]	0.17 [0.28]	0.12 [0.14]	0.143
Hemoglobin, g/dL; mean±SD	10.37±1.72	9.98±1.57	10.56±1.78	0.150
Number of Follow-up Days; median [IQR]	16 [15]	18.5 [16]	16 [15]	0.531
Dementia, n (%)	50 (60.2)	19 (67.9)	31 (56.4)	0.312
CVD, n (%)	57 (68.7)	18 (64.3)	39 (70.9)	0.538
DM, n (%)	20 (24.1)	8 (28.6)	12 (21.8)	0.496
HT, n (%)	46 (55.4)	14 (50.0)	32 (58.2)	0.478

n:Number; IQR: Interquartile Ranges; CFS: Clinical Frail Scale; SD: Standard Deviation; CRP:C-Reactive Protein; CVD: Cerebrovascular Disease; DM: Diabetes Mellitus; HT: Hypertension

to be risk factors affecting palliative care mortality after PEG tube placement in the palliative care service. The results are presented in Table 2.

Table 2. Logistic regression analysis results*

	p-value	OR	CI of OR
Pneumonia	**0.004**	5.32	1.697- 16.680
Age	**0.017**	1.06	1.012- 1.126
Pressure Ulcer	0.075	3.69	0.875-15.626
Prealbumin	0.128	0.91	0.824- 1.025
Procalsitonin	0.540	1.36	0.508- 3.640
Albumin	0.581	1.52	0.340- 6.862
Hemoglobin	0.888	1.02	0.714- 1.476
Sex	0.930	0.95	0.314- 2.881

* Age, sex, albumin, prealbumin, procalsitonin, pneumonia, hemoglobin, pressure ulcer put in the equation. Omnibus test for this model had a p-value of <0.001. Hosmer and Lemeshow test had a p-value of >0.050. Nagelkerke R square was 0.265 for this model.
CI: Confidence Interval; OR: Odds Ratio

After PEG tube placement, 8 (9.6%) of the patients were bolus fed, while 75 (90.4%) were continuously fed. The rate of pneumonia in patients who were bolus fed after PEG tube placement was 38%, while this rate was 29% in patients who were continuously fed (p=0.692). 38% of patients who were bolus fed died, while this rate was 33% in patients who were continuously fed (p=1.000). Figure 1 shows pneumonia and mortality rates according to the feeding patterns.

Discussion

In this study, the most common infection type in both groups was pneumonia. Rates of pneumonia were higher in patients who died than in patients who did not die, but rates of other types of infections were higher in patients who did not die. It was found that pneumonia and age were the most important factors affecting mortality in the palliative care service after PEG tube placement.

Complications may occur after PEG tube placement. In the study conducted by Shehata et al., complications

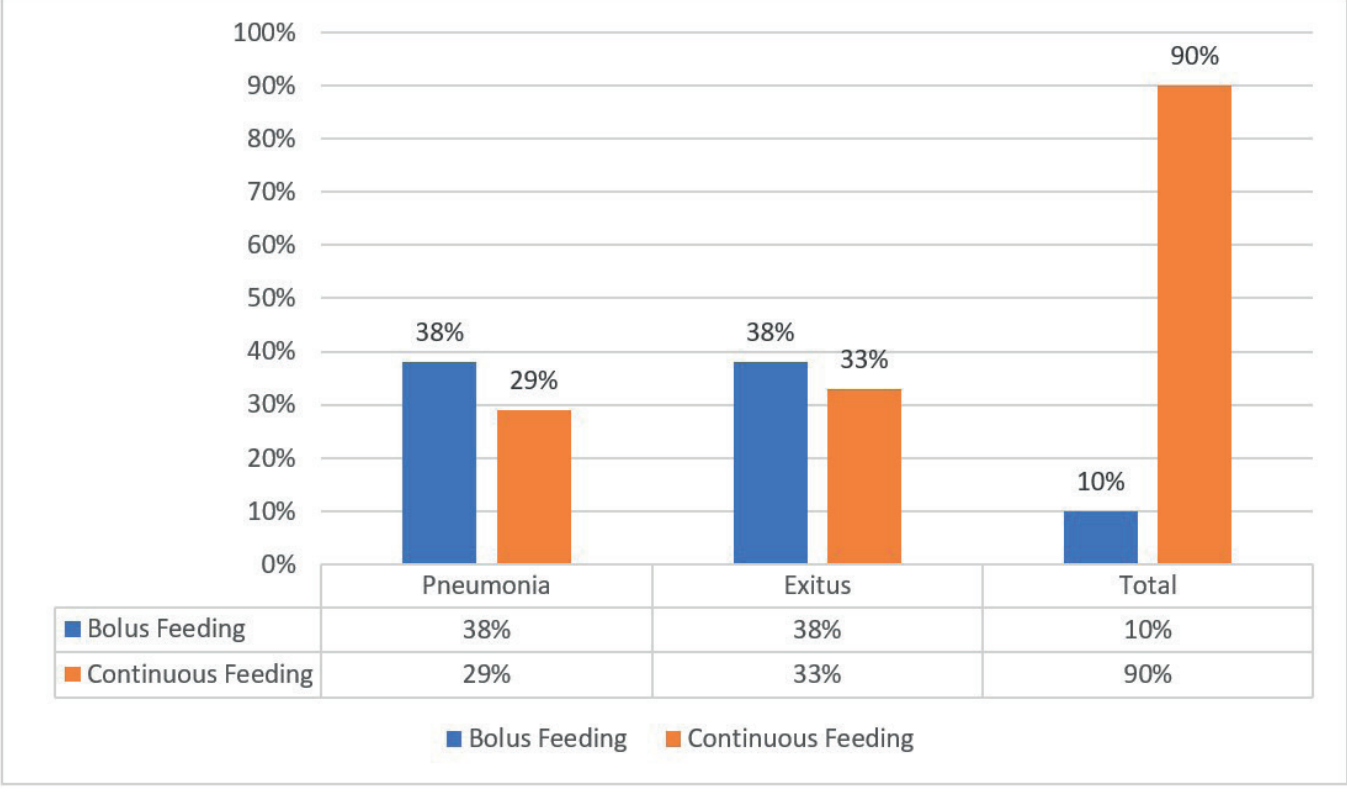

Figure 1. Pneumonia and mortality rates according to the feeding patterns

such as gastrointestinal bleeding were observed in 4.1% of patients, infection at the PEG site in 11.6% of patients, and peritonitis in 0.8% of patients within 30 days after PEG insertion. Complications were significantly higher in immunocompromised patients and in patients followed for non-neurological indications.[9] In the study conducted by Niu et al., higher mortality rates, longer hospital stays, and a higher incidence of septic shock were found in patients with PEG tubes who developed aspiration pneumonia.[10] In the study conducted by Deza et al., the most common complications after PEG tube placement were bronchoaspiration and rupture/dysfunction, respectively. The presence of early complications and age were found to be associated with shorter survival time.[11] The results of these studies also show that pneumonia following PEG tube placement is a serious problem.

In our study, infection developed in 69% of older patients after PEG tube placement. We can attribute this to the age of the patients, immunosuppression due to underlying diseases and long hospital stays. In this study, we found that infections such as urinary tract infection, bacterial infection, and wound infection that developed in patients with a peg tube were less life-threatening. But pneumonia developing after PEG tube placement is a serious, life-threatening risk factor. Half of the patients who died had pneumonia, and logistic regression analysis showed that pneumonia was a risk factor for palliative care mortality in older patients with PEG tubes. Considering that pneumonia is a serious risk factor for patients, we directed patients to continuous feeding rather than bolus feeding. We thought that the nutritional product given with a syringe during bolus feeding could pose a risk for aspiration due to the large and rapid administration of the product. We thought that administering small amounts of nutritional product continuously with a feeding pump would be better tolerated and less risky for aspiration. Eight of our patients received bolus feeding and pneumonia developed in 38% of these patients. 75 of our patients were fed continuously and pneumonia developed in 29% of these patients. This difference may be insignificant because our patient number is small, but this difference can be better understood in larger studies. Our patients were very old and immobile. Therefore, continuous feeding was suitable for them. Continuous feeding may be recommended to reduce the risk of pneumonia in such patients. When we examine the literature, there are generally studies comparing intermittent and continuous feeding in intensive care patients. In these studies, no significant difference was found in terms of negative outcomes in either nutritional group. A study by Lee et al in intensive care patients demonstrated that continuous enteral feeding significantly improved 80% of target nutritional requirements compared with intermittent enteral feeding. However, no difference was found between intermittent enteral feeding and continuous enteral feeding in terms of mortality or other important secondary outcomes such as length of hospital and intensive care unit stay, gastrointestinal intolerance, and organ support.[12] A meta-analysis by Heffernan et al compared continuous and intermittent enteral feeding in critically ill patients. Outcomes evaluated included bacterial colonization, gastrointestinal disturbance (diarrhea or constipation), increased gastric residual, incidence of pneumonia, and mortality. Patients receiving continuous infusion were found to have an increased risk of constipation. There were no statistically significant differences in other outcomes.[13] In our study, although not statistically significant, negative results were less frequent in continuous feeding. To obtain clearer results, multicenter studies with longer duration and larger patient numbers are needed in palliative care patients.

Age was one of the factors affecting palliative care mortality after PEG tube placement. If very older patients with dementia or cerebrovascular disease (CVD) cannot take oral food, enteral feeding via a nasogastric tube or nasoduodenal tube or parenteral nutrition may be a method of feeding these patients. Enteral feeding with a nasogastric tube or nasoduodenal tube is a short-term solution, not a long-term method. There are various problems with parenteral nutrition, including infection, and it is difficult for relatives of the patient to apply this method at home. Therefore, a PEG tube placement in these patients may be inevitable. However, it is important to explain to the patient's relatives that mortality from this procedure increases with age. In very old patients with end-stage dementia, the expectations of their relatives must be taken into account.

There were limitations in our study. First, the number of patients was small. Longer term studies with larger number of patients may be needed. Additionally, future multicenter studies are needed to generalize the study results. Second, some patients cannot tolerate some nutritional products. This intolerance may also cause aspiration. Therefore, studies can be conducted in which the nutritional product given to patients is also recorded. Third, No microorganisms were recorded growing in the patients' cultures. Mortality may also vary depending on the microorganisms grown in the culture.

Conclusion

Age and pneumonia after PEG tube placement were found to be risk factors affecting palliative care mortality after PEG tube placement in non- cancer palliative care patients. Continuous feeding may be recommended to reduce the risk of pneumonia in such patients.

Ethical approval

This study has been approved by the Ordu University Local Ethics Committee (approval date 27.09.2024, number 2024/125). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: İİ; data collection: İİ; analysis and interpretation of results: İİ; draft manuscript preparation: İİ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Comparison of pre-mixed multichamber bags versus compounded parenteral nutrition

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ABSTRACT

Objective: Parenteral nutrition (PN) is commonly used in patients with prolonged catabolic states when enteral feeding is not feasible. PN can be administered via pre-mixed multichamber bags (MCBs) or compounded bags (COBs). This study compares the biochemical, clinical effects, and complications of MCB and COB nutrition.

Methods: We retrospectively reviewed adult patients who received TPN in 2020 in an University Hospital. Patients were grouped based on receiving MCB or COB. Demographic data, lab values, hospital stay, and complications (hyperglycemia, refeeding syndrome, CRBSIs) were analyzed.

Results: A total of 235 patients were included. Hyperglycemia was more common in the MCB group, while CRBSI occurred more frequently in the COB group. COB patients more frequently met protein goals. Other biochemical and clinical outcomes were similar between groups.

Conclusion: MCB and COB both have unique advantages and drawbacks. Critically ill patients should be monitored closely regardless of PN formulation.

Keywords: parenteral nutrition, multichamber bags, compounded bags, critically ill, catheter-related infections

Introduction

Parenteral nutrition (PN) is defined as the intravenous provision of nutrients via a central or peripheral vein. It may be used as the stand-alone nutrition support or as an adjunct to enteral nutrition.[1] In patients severely ill with burns, acute pancreatitis, intestinal failure (such as extensive resection) and other reasons preventing adequate oral or enteral nutrition, PN prevents severe malnutrition and associated morbidity/mortality.[2]

There are two main types of parenteral nutrition preparation methods: hospital pharmacy–compounded bags (COBs) and commercial multichamber bags (MCBs). The COB can be standardized or tailored to the patient's specific needs.[3] As in our hospital, larger institutions with high acuity may use automated compounding devices to compound PN. These devices are used to customize a PN prescription for each patient. Due to limited stability of the compounded mixtures, COBs should be prepared every 24–48 hours in the case of inpatients requiring a daily delivery of PN; however, the exact frequency depends

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on the pharmacy service workload and on prescription changes. The commercial parenteral nutrition, known as "premixed or multichamber" PN, is a manufactured compounded, sterile product available in peripheral and central line formulations. In contrast to COBs, the shelf life of the MCBs is 12–24 months at room temperature.[4,5] For patients without relevant comorbidities, multi chamber bags as standard parenteral nutrition mixtures are often adequate to correct nutrient deficiencies and their related complications.[6] However, for patients with particular comorbidities (heart failure, chronic renal failure, hepatic failure), as well as for critically ill patients or for patients with benign chronic intestinal failure, compounded bags are often required.[7] Yet, there is no consensus on the clinical advantages and disadvantages of different PN preparation methods. During the management of certain shortages in compounded total parenteral nutrition (TPN), institutions like ours have utilized MCBs in place of COBs.[8,9]

This retrospective study aims to compare hospitalized patients' clinical data, biochemical values as serum electrolytes, blood glucose levels, prealbumin, kidney and liver function tests, length of hospital stay (LOS) and PN complications while they are receiving PN regimens as either MCBs or COBs. We hypothesized that patients who used different PN regimens (as MCBs or as COBs) had different risk of biochemical derangements, complications, different LOS and other clinical outcomes.

Materials and Methods

After ethical approval from the Hacettepe University Faculty of Medicine Ethics Committee (GO 21/272, 21.05.2021) files of all patients who had received PN products in Hacettepe University Adult Hospital in 2020, were analyzed retrospectively. We included all adult hospitalized patients who had been on PN consecutively for at least 3 days.

Main Points

- Both multichamber and compounded TPN methods are viable for critically ill patients.
- MCBs are associated with a higher risk of hyperglycemia.
- CRBSI is more frequent in COB group, influenced by infusion duration.
- No major differences were found in electrolyte or liver function outcomes.

In our institution, patients needing PN must be evaluated by a specialized nutritional team to establish their fluid, electrolytes, and macro and micronutrient requirements. Therapeutic decisions on using PN are taken by the attending physicians and the hospital nutrition support team (NST). Our NST consists of physicians (geriatricians, internists, surgeons, anesthesiologists, oncologists, gastroenterologists, pediatricians), dietitians, nurses, and pharmacists. After hospitalization, all patients are routinely screened for malnutrition with Nutritional risk screening (NRS 2002)[10] by the attending physician. The patients at malnutrition risk (NRS 2002≥4) or have contraindications to oral/enteral nutrtion (even if NRS 2002<4) are consulted to the NST for further assessment of their nutrition status. The contraindications to enteral nutrition are intestinal failure, intraabdominal infections, postoperative ileus, intestinal obstruction, severe burns, multiple trauma, or high output intestinal fistula. While providing nutrition assessment and determining nutritional needs, the NST aims to ensure appropriate and safe nutritional support to each patient. NST recommends oral or enteral nutrition initially. However, if the oral/enteral intake is inadequate or contraindicated, supplementary or total PN is recommended. Daily nutritional requirements were calculated as 20-30 kcal/kg/day for energy requirements and 1.2-2 g/kg/day for protein requirements. The patients who received a consultation with the NST for PN therapy for the first time were included into this study, while those who were already under nutritional therapy were excluded. Data about nutrition goals and the amount of nutrition actually received as well as PN associated complications were retrieved from NST files and electronic patient files.

All PN ordered were prepared by NST guided ACD (EM 2400 (Exacta Mix) automated compounding device to compound PN with aseptic technique. Patients were grouped according the PN product type they received: COBs or MCBs. The COB solution was prepared in a 2000-mL TPN bag (TPN EVA Bag, Kapsam Medical) with 10% Freselamin (Osel Pharmaceuticals), 20% Clinoleic (Baxter S.A.), 20%/30% dextrose, 0.9%/3% NaCl, 7.5% KCl, 10% Ca Picken (ADEKA Pharmaceuticals), 15% MgSO4, multivitamins (Todavit, Polifarma), and trace elements (Addamel N20, Fresenius Kabi). MCBs used were Oliclinomel N-4 550 E (Baxter S.A.), Oliclinomel N7-1000 E (Baxter S.A.), and Kabiven Peripheral (Fresenius Kabi). Multivitamins and trace elements were added into the MCBs with aseptic technique.

Patients' demographic data, comorbidities, causes of hospital admission, NRS 2002 score, Intensive Care Unit (ICU) stay, duration of hospital stay, survival status, serum sodium (normal levels 136-146 mEq/L), potassium (normal levels 3.5-5.1 mEq/L), magnesium (normal levels 1.8-2.5 mg/dL), chloride (normal levels 101-109 mEq/L), inorganic phosphorus (normal levels 2.5-4.5 mg/dL) and blood glucose levels (normal levels 70-100 mg/dL), albumin (normal levels 3.5-5.2 g/dL), prealbumin, creatinine (normal levels 0.51-0.95 mg/dL), blood urea nitrogen (normal levels 6-20 mg/dL) levels and liver function tests, and catheter related complications (catheter thrombosis, line obstruction or accidental removal of the catheter) were recorded. Data for the study were derived from Nucleus database of Hacettepe University Adult Hospital. Besides abnormal electrolyte levels, other PN related metabolic complications including hyperglycemia, refeeding syndrome, hyperlipidemia, hepatic disorders were observed after the administration of parenteral nutrition (PN). Hyperglycemia was defined as random blood glucose over 200 mg/dL[11] while on TPN infusion. Since refeeding syndrome can be defined as the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding, we set refeeding syndrome limits as hypophosphatemia, with a fall from baseline greater than 30% or more than 0.16mmol/l.[12] Hypertriglyceridemia was defined as plasma levels above 200 mg/dL. In accordance with a previous study[13], liver dysfunction (LD) was defined as: Cholestasis: alkaline phosphatase (ALP) > 280UI/L, gamma-glutamyltransferase (GGT) > 50UI/L and total bilirubin (TB) > 1.2 mg/dL; Hepatic necrosis: Aspartate aminotransferase (AST) > 40UI/L, alanine aminotransferase (ALT) > 42UI/L and Mixed pattern: ALP > 280UI/L, GGT > 50UI/L or TB > 1.2 mg/dL plus AST > 40 IU/L or ALT > 42UI/L.

Catheter related complications included phlebitis, catheter exit site infection, bacteremia and catheter related bloodstream infection (CRBSI) as defined by Infectious Diseases Society of America (IDSA). A definitive diagnosis of CRBSI required that the same organism grow from at least one percutaneous blood culture and from a culture of the catheter tip, or growth of microbes from the blood sample drawn from a catheter hub at least 2 hours before microbial growth is detected in a blood sample obtained from the peripheral vein.[14]

All analyses were performed using SPSS (Statistical Package for Social Sciences, version 22.0). Student's t-test was used to compare groups in terms of normally distributed quantitative variables (age, height, weight). Mann-Whitney U-tests were used to compare the groups in terms of nonparametric data. Normally distributed parametric data were presented as mean ± standard deviation (mean ± SD) and non-parametric data as median (minimum-maximum) values. The chi-square test was used to compare categorical data between the groups. The time dependent within group and between group analysis was performed by general linear model for repeated measures analysis. Parameters that were statistically significant at univariate analysis were included in multivariate logistic regression analysis. $p<0.05$ values were considered statistically significant.

Results

When the files of 239 patients who received parenteral nutrition in the Hacettepe Adult Hospital in 2020 were scanned, 4 patients were found to have missing data. Therefore, 235 patients were included in the study. Finally, Group I was constituted from 190 patients with COBs received, while Group II was constituted from 165 patients with MCBs received.

The baseline characteristics of the patients in the two groups are listed in Table 1. Moreover, protein and calorie goals per day, indications and duration of infusions of the two types of PN are presented in Table 2. There were no statistically significant differences in both groups regarding the indications to start and to stop the PN, the protein and calorie goals of nutrition and duration of the PN infusion. Patients received more proteins and hence, the nutrition protein goals were reached more commonly with COBs when compared to MCBs.

There was no significant difference between the groups regarding PN related mechanical complications (Table 3). There were no cases of catheter thrombosis, line obstruction or accidental removal of the catheter. PN related metabolic complications were also similar in the two groups except MCBs were associated with more hyperglycemia than COBs. When the group of patients with hyperglycemia was compared with the group of patients without hyperglycemia the differences other than the type of PN were the presence of diabetes (71% vs 14%, p=0.001), chronic renal failure (29% 3%, p=0.022), congestive heart failure (29% vs 4%, p=0.030). When the grouping variable and the presence of diabetes, chronic renal failure and congestive heart failure were entered into binary logistic regression analysis of the hyperglycemia as the dependent variable; the presence of diabetes (B=2.479, S.E.=0.959, p=0.010), and chronic

Table 1. Demographics and clinical characteristics of the two groups of patients who received different types of TPN (Compounded Parenteral Nutrition vs Pre-mixed Multichamber Bags)

Parameter	Compounded Parenteral Nutrition (n=190)	Pre-mixed Multichamber Bags (n=145)	P-value
Age, years	57.6 ± 16.2	59.1 ± 16.2	0.388
Gender, M/F	105/87	80/65	0.474
Height (cm)	166.8 ±8.4	164.9 ± 8.7	**0.043**
Weight (kg)	64.7 ± 14.3	65.1 ±13.6	0.792
NRS 2002	4 [3-7]	4 [1-7]	0.641
Comorbidities:			
Diabetes Mellitus	24 (13)	27 (19)	0.088
Chronic Obstructive Pulmonary Disease	5 (3)	6 (4)	0.321
Chronic Renal Failure	5 (3)	7 (5)	0.218
Coronary Artery Disease	17 (9)	16 (11)	0.325
Congestive Heart Failure	3 (2)	11(8)	**0.007**
Hypertension	34 (18)	42 (29)	**0.012**
Causes of hospital admission:			
Infection	7 (4)	10 (7)	0.316
Neurologic	7 (4)	6 (4)	
Gastrointestinal	20 (11)	24 (17)	
Cancer	146 (77)	99 (69)	
ICU patients	87 (46)	81 (56)	**0.043**
Duration of ICU stay (days)	0 [0-104]	1 [0-64]	0.135
Duration of hospital stay (days)	30 [4-455]	24 [4-143]	**0.025**
Mortality	36 (19)	34 (23)	0.192

Data is given as n (%), mean±SD or median [minimum-maximum] as appropriate.

renal failure (B=2.451, S.E.=1.157, p=0.034) were the statistically significant independent variables whereas the grouping variable (COB or MCB) (p=0.994) and congestive heart failure (p=0.523) were not statistically significant variables.

The only difference in PN related infectious complications between the two groups was the higher incidence of CRBSI in the COBs group. The most common microorganism associated with CRBSI was Candida albicans (6 cases), followed by Candia parapsilosis (3 cases) and Staphylococcus aureus (2 cases). When the group of patients with CRBSI was compared with the group of patients without CRBSI the only difference other than the type of PN was the duration of infusion (29[5-120] days vs 11[1-277] days, respectively) (Mann-Whitney U test, p<0.001). When the grouping variable and the duration of infusion were entered into binary logistic regression analysis of the CRBSI as the dependent variable; duration of infusion was the only statistically significant independent variable (B=0.018, S.E.=0.004, p=0.041) whereas the grouping variable (COB or MCB) was not (p=0.996).

Furthermore, patients' biochemical parameters are monitored at the initial day and 3, 7, 14, 21, 28 days after the start of PN nutrition (Figure 1). The time dependent within group and between group analysis was performed by general linear model for repeated measures analysis, which revealed statistically similar trends in the two groups regarding sodium, potassium, chloride, magnesium, ALT, AST, ALP, GGT, total bilirubin, BUN,

Table 2. Indications and clinical properties of the two types of PN

Parameter	Compounded Parenteral Nutrition (n=190)	Pre-mixed Multichamber Bags (n=145)	P-value
PN indication:			
Neurologic causes	5 (3)	10 (7)	0.797
Intestinal obstruction	53 (28)	39 (27)	
Perioperative support	23 (12)	7 (5)	
Intraabdominal infection	15 (8)	18 (12)	
Insufficient oral/EN intake	94 (50)	71 (49)	
EN during TPN	15 (8)	6 (4)	0.118
EN goal (kcal/day)	1500[1200-2190]	1775 [1250-1875]	0.424
EN protein goal (mg/day)	82 [67-110]	90 [75-112]	0.302
EN calories received (kcal/day)	700 [300-2300]	720 [200-1440]	0.677
EN protein received (mg/day)	40 [18-108]	35 [10-67]	0.424
EN calorie goal reached, n (%)	5 (33)	1 (17)	0.424
Central /peripheral TPN	90/100	**35/110**	**<0.001**
Type of the central catheter:			
Port/Hickman/IJV/SCV	22/8/54/6	7/5/22/1	0.911
PN calorie goal (kcal/day)	1625 [775-2630]	1625 [800-2500]	0.971
PN protein goal (mg/day)	78 [37-126]	78 [50-108]	0.923
PN calories received (kcal/day)	1000 [400-2200]	915 [910-1800]	0.578
PN protein received (mg/day)	50 [20-120]	33 [30-60]	**<0.001**
Duration of TPN infusion (days)	11 [2-777]	11 [1-131]	0.209
Reason to stop PN:			
Oral nutrition	101 (53)	73 (50)	0.255
Discharged from the hospital	9 (5)	11 (8)	
Home enteral nutrition	9 (5)	1 (1)	
Home TPN	7 (4)	5 (3)	
Clinical deterioration	28 (15)	21 (15)	

EN: Enteral nutrition IJV: Internal jugular vein, SCV: subclavian vein, PN: Parenteral nutrition, TPN: Total parenteral nutrition.
Data is presented as n (%) or median [minimum-maximum] and the two groups were compared with Chi-Square tests or Mann-Whitney U tests, respectively.

creatinine, albumin and prealbumin levels as shown in Figure 1. Of all the biochemical follow up measurements only the trends of the inorganic phosphorus levels were different between the two groups (p=0.002 for tests of between subject effects).

When subgroup analysis was performed for the ICU patients (n=168 total, 87 patients received COB, 81 patients received MCB), the diabetic, hypertensive, chronic heart failure patients, and hyperglycemia was more common with MCBs (25%, 36%, 10% and 6% respectively) when compared to COBs (12%, 17%, 2% and 0% respectively) whereas CRBSI was more common with COBs (6%) compared to MCBs (0%). In critically ill patients, COB PN was infused longer (median 14[2-277] days) than MCB PN (median 11[1-131] days) (p=0.009). Although the durations of ICU stay were similar (median 8[1-104] days in the COB group versus median 7[1-64]

Table 3. Complications of PN in the two groups

	Compounded Parenteral Nutrition (n=190)	Pre-mixed Multichamber Bags (n=145)	Chi-Square Test P-value
Insulin infusion required, n (%)	138 (80)	110 (77)	0.282
PN Hyperglycemia, n (%)	0 (0)	7 (5)	**0.003**
PN Hypertriglyceridemia, n (%)	5 (3)	3 (2)	0.241
PN Hypernatremia, n (%)	3 (1.6)	3 (2)	0.524
PN Hypophosphatemia, n (%)	22 (12)	11 (8)	0.151
PN Hypopotassemia, n (%)	3 (1.6)	4 (3)	0.354
Refeeding syndrome, n (%)	105 (60)	85 (60)	0.511
Liver dysfunction:			
Cholestasis, n (%)	21 (11)	14 (10)	0.195
Hepatic necrosis, n (%)	13 (7)	19 (13)	
Mixed pattern, n (%)	31 (18)	31 (22)	
Phlebitis, n (%)	2 (1)	3 (2)	0.375
Catheter insertion site infections, n (%)	5 (3)	8 (6)	0.143
Bacteremia, n (%)	22 (12)	21 (15)	0.272
CRBSI, n (%)	11 (6)	0	**0.002**

days in the MCB group) in these two subgroups, length of hospital stay was longer in the COB group than the MCB group (median 39[4-455] days and (median 26[4-143] days, respectively, P=0.004).

Discussion

In our study, we aimed to compare safety of two parenteral nutrition regimens (MCB vs COB) regarding the efficacy of nutrition support avoiding clinical side effects in hospitalized patients.

Despite the perceived benefits of premixed multichamber bag solutions, many hospitals have been slow to use them because they can't be tailored or customized to meet patients' individual medical needs. Multichamber bags tend to contain less protein and fewer electrolytes such as sodium, potassium, chloride, and acetate compared with personalized compounded solutions.[4] Our study confirmed that patients received less proteins and hence, the nutrition protein goals were reached less commonly with MCBs when compared to COBs probably due to the fact that COBs were preferred more commonly as central infusions than MCBs (47% vs 24% respectively). On the other hand, the trends in serum electrolytes were quite similar with these two types of PN. This can be explained by the close supervision and necessary replacement of the serum electrolytes by the physicians.

Although PN is an effective method of nutrition support, it has been associated with a range of mechanical, septic, and metabolic complications. Hyperglycemia is found in up to 50% of PN patients. In addition to long term complications, even short-lasting blood glucose values over 200 mg/dL appear unacceptable because they interfere with quality of life by inducing dehydration and polyuria.[15] In our study, almost 80% of patients in both groups received insulin infusion resulting in low incidence of hyperglycemia. All the TPN associated hyperglycemia cases were seen in the patients who received MCB PN. The presence of diabetes and chronic renal failure were found to be independent predictors of PN hyperglycemia. These two groups of patients may benefit from lower dextrose containing PN such as in COB.

Refeeding syndrome (RS) consists of a group of clinical signs and symptoms that occur in malnourished patients receiving nutrition support after a long fasting period. These signs and symptoms include electrolyte disorders, especially a reduction in intracellular electrolytes (potassium, magnesium, and phosphorus); altered

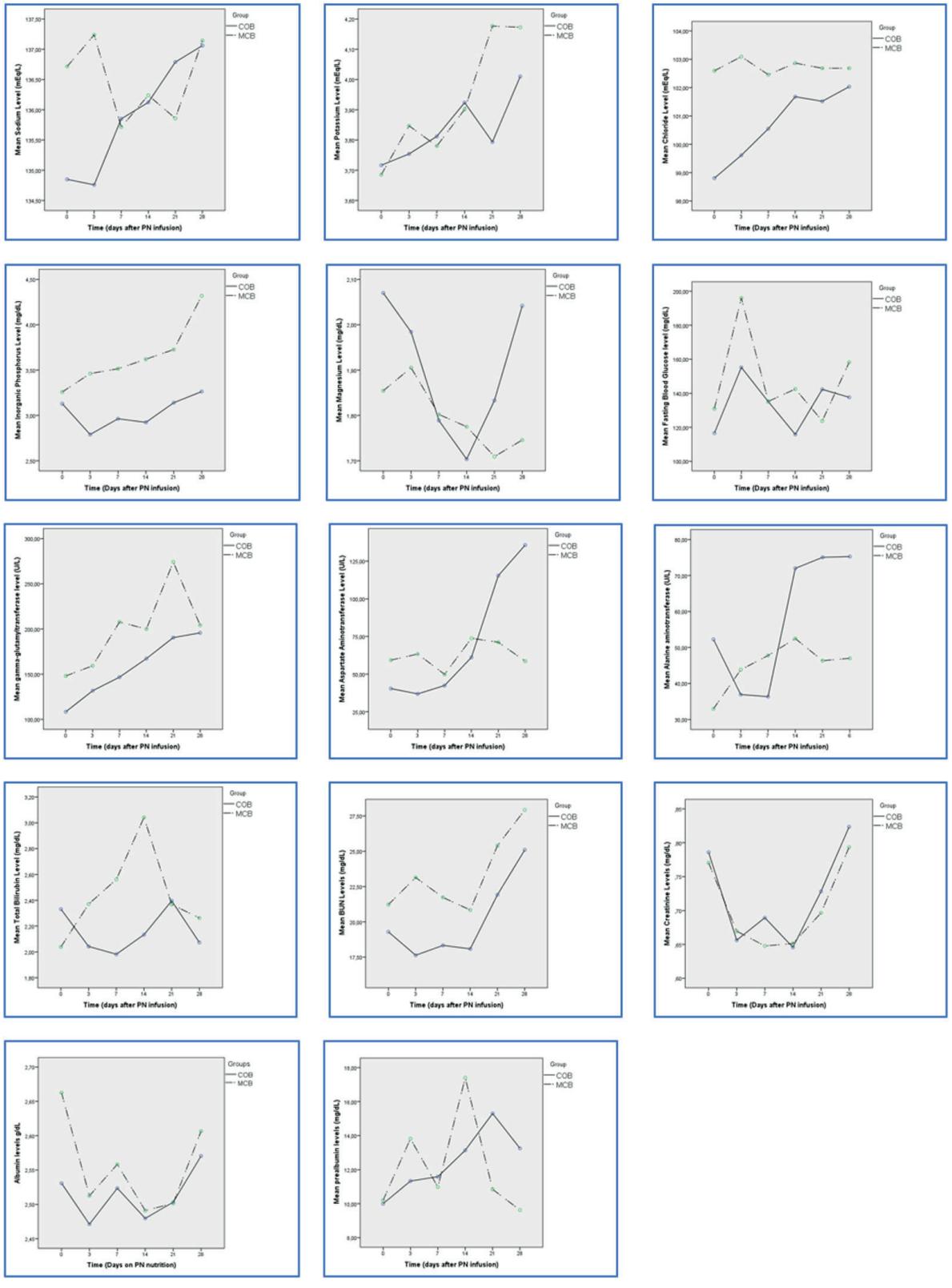

Figure 1. Periodic measurements of biochemical parameters in patients receiving PN as COB (Compounded Parenteral Nutrition) or M

CB (Pre-mixed Multichamber Bags).

glucose metabolism (hyperglycemia); and a deficiency of vitamins and oligoelements.[12,16,17] A systematic review and meta-analyses of literature reported an incidence of RS varying from 7% to 62% depending on the definition used and the population studied.[18] In our study, we found RS in 60% of our patients on PN. More than half of our patients had malnutrition (NRS 2002 ≥ 4), and more than half were in the ICU both of which are high risk factors for the development of RS. The high prevalence of patients with RS receiving PN highlights the need for the development of strategies for prevention and adequate nutrition approach for this population, which would require the implementation of specific protocols in the hospitals. Friedli et al.[19] proposed an evidence-based algorithm for the management and prevention of RS that encompasses the identification, prevention, management, and monitoring of RS, and it could be adapted for each PN team according to the particularities of the service and patients. In our study, refeeding incidence was similarly high in both groups (MCBs and COBs).

Hypertriglyceridemia is found in approximately 25–50% of PN patients.[1] One should aim for plasma triglyceride concentrations below 400 mg/dL during PN infusion. Severe hypertriglyceridemia (>1000 mg/dL and particularly >5000 mg/dL) can induce acute pancreatitis, similar to patients with severe hypertriglyceridemia without PN, and it can affect micro circulation.[20] In our study, 3% of our patients had elevated triglyceride levels and the type of the PN (MCBs or COBs, both of which contained olive oil) did not affect the triglyceride levels.

One of the other common complications of parenteral nutrition is LD, which is associated with a higher risk of mortality.[20] However, the causes of hepatic and biliary abnormalities induced by continuous PN have not been identified yet[20] even patients who receive PN for a short time frequently develop cholestasis.[21] Hepatic parameters should be continuously monitored in patients receiving PN to prematurely detect and treat any potential liver dysfunction. For this reason, our protocol included third day and the weekly monitoring of hepatic parameters. In both COB and MCB groups liver function tests were similar and tended to elevate as time passes on PN.

The use of the serum protein levels for nutritional assessment is well established. The relationship of serum albumin concentration ≤ 3.5 g/dl to an increased morbidity and mortality in medical and surgical patients is well documented.[22,23] However, it has also been suggested that a biochemical assessment of albumin is not a reliable marker of the nutrition status. The albumin concentrations slowly respond to protein restriction and are more a reflection of the patient's illness than the nutritional intake. Prealbumin responds quickly to the onset of malnutrition and rises rapidly with the adequate protein intake. Several studies have reported that patients with low prealbumin levels have a shorter length of stay in hospital stay and fewer complications, lower morbidity and possible mortality, if they are given either intravenous or oral hyperalimentation.[24,25] A prospective randomized study in five Chinese hospitals compared MCB parenteral nutrition to customized PN formulations. Among 240 patients, prealbumin levels rose more dramatically in the patients who received MCBs than the patients who received COB, but this difference could be attributed to the different types of the lipid compositions used in the two groups studied.[26] Reliability of prealbumin as a biomarker for nutrition state, however is also limited since prealbumin is a negative acute phase protein and serum levels are influenced not only by nutrition but also by the inflammatory state. However, prealbumin is still commonly used due to its small pool size and short half life.[27] We also monitored patients' prealbumin levels while they received TPN and found no statistical difference between the two groups (MCB vs COB).

In our study, there was no documented CRBSI among the patients in MCB group but 6% of patients had CRBSI in the COB group. The higher use of central catheters may explain the higher CRBSI in the COB group. The duration of PN infusion was the only statistically significant independent variable of CRBSI. Another study reported bloodstream infection percentage of 6.8% in the COB group, quite similar to our COB group (6%) whereas it reported a higher ratio of bloodstream infection (5.6%) in the MCB groups than our MCB group.[28]

The main limitation of our study is its retrospective design and that not all relevant variables were available in the electronic health record. On the other hand, it is worth mentioning that PN and follow-up data were registered prospectively by the nutrition support team, which minimized measurement bias. Close supervision by the nutrition support team helped earlier detection and proper management of complications in both types of PN (COB and MCB).

In line with the notion of standardization of medications/formulations whenever possible to improve patient safety, multichamber bag solutions are closed systems premade by a manufacturers and are considered low risk for harboring contaminants and bacteria.[5,29,30] Moreover, compounding, labeling, and administration

errors are significantly higher when hospital staff use compounded bags vs premixed multichamber bag solutions. As a result, the American Society for Parenteral and Enteral Nutrition (ASPEN) established best practices for compounding PN and determined that premixed formulations or multichamber bag solutions would be valuable alternatives.[8]

We conclude that MCBs and COBs have both different pros and cons in terms of clinical outcomes; specifically, critically ill patients should be closely monitored for the effects of parenteral nutrition with either MCB or COB. MCB can be an alternative to COB with vigilant monitoring and appropriate management of metabolic complications, especially hyperglycemia. Patients with diabetes and chronic renal failure may benefit more with COB as dextrose content can be adjusted. It should be noted that specific illnesses such as renal failure, liver dysfunction, electrolyte imbalances, and patients with increased and /or spesific metabolic needs may also benefit more from personalized compounded solutions compared to premixed solution.

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Ethical approval

This study has been approved by the Hacettepe University Faculty of Medicine Ethics Committee (approval date 21.05.2021, number GO 21/272). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: SBA, CES; data collection: CES, ZŞ, ND, MYS; analysis and interpretation of results: SBA, MH; draft manuscript preparation: SBA, CES. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Medication administration via feeding tube for older adults

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ABSTRACT

Older adults are particularly vulnerable to medication administration errors, especially when malnutrition coexists with polypharmacy, highlighting the need for tailored healthcare approaches in this population. In this narrative review, it is aimed to emphasis the importance of medication administration via feeding tube in older adults and provide the list of appropriate administration of common medications in older adults. Feeding tubes used primarily for enteral nutrition and water administration, however when the patient needs medication administration feeding tubes considered as an administration route even though feeding tubes generally not design for medication administration. Therefore, this approach is prone to administration errors. Appropriate administration of medication is important in order to provide optimum pharmaceutical treatment for the older patients, prevent negative outcomes, complications and adverse medication events. However, appropriate administration of medication via feeding tube is challenging due to limited evidence and generally based on best practice. Pharmacists play an important role in providing comprehensive information regarding medication characteristics, the suitability of dosage forms, potential drug interactions, physicochemical stability, and appropriate administration techniques. The recommendations should be made for individual patients and medications with the contribution of multidisciplinary nutrition support team in order to maintain comprehensive evaluation of patient.

Keywords: medication administration, drug administration, feeding tube, enteral nutrition, older adults

Introduction

Medication administration via feeding tubes is critical process in clinical practice, especially for older adults who are unable to take medications orally due to dysphagia, neurological disorders, or other medical conditions affecting swallowing.[1,2] Comorbidities, geriatric syndromes, and polypharmacy should be taken into consideration while managing treatments of older adults, because aging is an unavoidable process, along with changes in pharmacokinetic/pharmacodynamic parameters.[1] Polypharmacy which is defined as the routine use of at least 5 medication continues to be a significant global problem for the health of the older adults.[3] The polypharmacy rates in older adults vary widely in between 40-90%[3,4] and dysphagia is estimated to affect 15-40% of adults aged 60 years and above, with significant consequences for their health status and overall quality of life. [2] Optimizing medication treatment with specific actions such as appropriate administration of medications, deprescribing and regular monitoring should be one of the main duties for healthcare workers.[1] The majority of patient harm and deaths in the medication incident reports are related with inappropriate administration of medications.[5] In general, medication errors that result in patient harm are estimated to occur in 1–2% of hospitalized patients and of all types of medication errors, medication administration errors are hard to recognized which require special attention.[5]

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Older adults generally are at increased risk of malnutrition due to many factors such as chronic diseases, loss of appetite, poor diet or swallowing problems.[6,7] These factors can be observed up to 25% of those living in the community, up to 62% of those hospitalized, and 85% of those living in nursing homes.[7] Malnutrition in older adults has a major concern similar with other life-threatening diseases due to increased rates of infections, sarcopenia, frailty, length of hospital stays and mortality.[6]

Combination of malnutrition and polypharmacy in older adults can lead to medication administration errors and in order to provide optimum healthcare services special attention should be given in this patient group. In this review, it is aimed to emphasis the importance of medication administration via feeding tube in older adults and provide the list of appropriate administration of common medications in older adults.

Swallowing Problems and/or Need of a Feeding Tube

In the process of aging, patients become frailer and complex. Awareness about specific diseases, malnutrition risk, malnutrition, xerostomia and swallowing problems can help to determine the appropriate medical or nutritional treatments.[8,9] Advanced dementia, neurological disorders, stroke or head and neck cancers are commonly seen conditions that require modification in the medical treatment due to swallowing difficulties and eventually mostly require feeding tube for both medical and nutritional treatment.[8,10,11] As more people are being diagnosed with swallowing difficulties, the prevalence of feeding tube use linked to these issues may rise.[12] However, choosing appropriate medications for these conditions and knowledge about safe administration of medications are generally underestimated during the medical treatment process.[10,12]

Main Points

- Safe and individualized medication administration via feeding tubes is important for older adults.
- Age-related changes in gastrointestinal, hepatic, and renal functions require detailed examination.
- Pharmacists can make valuable contributions within the multidisciplinary nutrition support teams in terms of medication adminstration via feeding tube.

Swallowing difficulties can impact quality of life (QoL), hydration, nutrition, and medication administration.[12] Studies showing that almost 15% of the community dwelling older adults experiencing difficulty with swallowing oral dosage forms.[11] In addition to altering the texture of fluid and food intake medication administration must also be considered when the swallowing difficulty detected.[12] Those who have difficulty swallowing or need to administer medications via feeding tube may need to crush or suspend the solid dosage forms, open capsules or switch to liquid dosage forms. Inappropriate modifications in the process of altering dosage type can cause inadequate medical treatment or advers effects. Some solid dosage forms due to its nature can not be crushed such as extended-release formulation, enteric coated tablets or medication with carcinoid properties. Sometimes the bitter taste also can play a role for not altering the dosage type. Another concern related with altering the dosage type is tube clogging. Some medications do not dissolve into fine particles when crushed and increasing the risk of clogging a feeding tube.[12,13] Cost of certain dosage forms besides the stability, bioavailability, viscosity, particle size or toxicity also be considered when it comes to change the dosage type.[12,13]

When the patient has swallowing difficulties, but the feeding tube was not placed, crushed solid dosage forms, liquids or opened capsules generally crushed and suspended with combination of liquid and thickener products. Studies indicating that thickened liquids can impact gastric emptying rate and therefore the absorption rate of medications. It should be taking into consideration Xanthan gum will have a different impact than starch-based thickeners on some medications.[12]

European Society of Clinical Nutrition and Metabolism (ESPEN), suggest that if oral intake is expected to be impossible for more than three days or expected to be below half of the energy requirements for more than one week, despite interventions to ensure adequate oral intake for older adults, feeding tube shall be offered.[6] When the patient has feeding tube, all the medications should be carefully evaluated in terms of appropriate and safe administration.[3,14,15]

On the other hand, polypharmacy itself can be associated with malnutrition or dysphagia.[3,16] Due to some side effects of some medications such as loss of appetite, dry mouth, nausea, and vomiting, malnutrition or dysphagia can occur in a long-term period.[15,17] Therefore, both polypharmacy and nutritional status need to be taken into account in clinical practice concomitantly.

Physiological Changes in Aging and Their Impact on Drug Administration

Significant physiological changes associated with aging have a direct impact on the efficacy and safety of administering medications via feeding tubes. The deterioration of gastrointestinal function is among the most significant changes. The dissolution, absorption, and transit time of drugs administered via enteral tubes can be changed by decreased intestinal motility, delayed gastric emptying, and decreased gastric acid production (hypochlorhydria).[18,19] Drug selection and dosage decisions may become more difficult as a result of these alterations, which may also affect the bioavailability of medications, especially those that need an acidic environment for best absorption.[20]

A reduction in liver and kidney function, which affects drug metabolism and excretion, is another significant age-related change. Age-related decreases in liver mass and blood flow frequently lead to a decline in hepatic first-pass metabolism, while a decrease in glomerular filtration rate causes a decline in renal clearance.[21,22] These modifications raise the possibility of drug accumulation and toxicity, particularly when medication is administered through enteral tubes in liquid or crushed tablet form, bypassing some of the barriers that oral intake modifies absorption. Therefore, when selecting drug formulations and routes for older adults undergoing enteral nutrition therapy, age-related pharmacokinetic shifts must be taken into account.[22,23]

Furthermore, the volume of distribution for many medications is altered by age-related changes in body composition, such as decreased lean body mass, increased fat mass, and decreased total body water. This may also have an impact on the pharmacologic profile of drugs given through a feeding tube. For instance, hydrophilic drugs may exhibit lower peak concentrations, whereas lipophilic drugs may have longer half-lives.[24] All of these age-related physiological changes highlight how crucial customized medication planning, careful observation, and multidisciplinary teamwork are important to ensure older adults receive safe and efficient enteral medication therapy.[22]

Medication Administration via Feeding Tube

Older adults often experience polypharmacy and multiple comorbidities, which increase their vulnerability to adverse drug events, drug-drug and drug-nutrient interactions, and altered pharmacokinetics.[3] The administration of medications through feeding tubes adds layers of complexity, including considerations related to the physical and chemical compatibility of drugs with feeding tube materials, potential tube occlusions, and changes in drug absorption and efficacy.[14]

Feeding tubes are used primarily for enteral nutrition and water administration, however when the patient needs medication administration feeding tubes considered as an administration route even though feeding tubes generally not design for medication administration. Therefore, this approach is prone to administration errors.[11,13,14,25,26]

There are some concerns about medication administration via feeding tube such as tube clogging, loss of dose, medication-nutrient interaction, reduction of the medication efficacy or increase of the medication toxicity.[14,25,26] When older adults have polypharmacy, inappropriate medication administration via feeding tube and medication interactions, which occur 20–40% of the time, can result in adverse medication events.[27]

Medication administration errors as a part of medication related problems can be seen more frequently in patients with feeding tube.[28] In a study conducted in England, the risk of a medication administration error was significantly higher in patients with enteral tubes than in patients without (56% vs 25.3%, $p<0.001$) and mostly caused by inadequate flushing of the tube.[9] In another study conducted in care facilities almost one-third of the dosage form modifications performed inappropriately and this leads to increased risk of medication administration errors.[11]

American Society for Parenteral and Enteral Nutrition (ASPEN) and one study underline that inappropriate administrations of medications may lead to severe negative outcomes, increase morbidity and mortality.[14,28] Appropriate administration of medication is important in order to provide optimum pharmaceutical treatment for the patients, prevent negative outcomes, complications and adverse medication events.[11,14,26] In general, most oral medications are not designed for modifying the dosage type and feeding tube administration.[14,27,29] Inappropriate administrations of medications may result physical and chemical incompatibilities, precipitation, flocculation, adsorption, color changes, chelation and medication-nutrient interactions, changes in drug bioavailability and medication loss.[14,27,29] Medication loss while crushing

is a neglected issue by many practitioners. Medication loss is frequently observed when solid dosage forms are crushed in a container and transferred to syringe for feeding tube administration.[30] One study showing that crushing tablets with a mortar and pestle and transfer was associated with 5.5–13.3% loss of tablet weight[30], in another study it is reported that at least 5–10% of every dose is not delivered to the patient while crushing and administrating the medication via feeding tube.[31] Practitioners generally not rinsing the device that used for crushing and lead to medication loss.[31] The following recommendations are derived from the work of Boullata et al., as part of the ASPEN publication, which aims to ensure the safety of the entire enteral nutrition process through evidence-based practices and expert consensus.

Practice Recommendations by ASPEN[32]:

- Establish comprehensive policies and standardized procedures such as checklists, bundles and protocols to guarantee safe enteral medication preparation and delivery by all departmental staff.
- Ensure the prescriber's order clearly specifies the drug name, dosage, formulation, administration route (such as enteral), and the type of access device (e.g., nasoduodenal tube).
- Each medication prescribed for enteral use must be reviewed by a pharmacist to ensure it is safe, stable, and appropriate for the intended route.
- Establish and implement nursing procedures that promote safe handling and delivery of all medications.
- Avoid mixing medications directly into enteral feeding formulas.
- Do not mix medications; administer each separately through the appropriate route of access.
- Use liquid formulations only when they are suitable for enteral administration.
- Follow the pharmacist's instructions when preparing approved immediate-release solid dosage forms for enteral administration.
- Ensure that enteral medications are measured and prepared using suitable instruments only.
- Before administering any medication, pause enteral feeding and flush the feeding tube with at least 15 mL of water. Dilute solid or liquid medications as appropriate and administer them using a clean oral syringe of at least 20 mL in size. Following administration, flush the tube again with a minimum of 15 mL of water, considering the patient's fluid status. If additional medications are to be given, repeat the same steps for each. Conclude the process with a final flush of at least 15 mL of water.
- Resume enteral feeding promptly to prevent any negative impact on the patient's nutritional status. Feeding should be withheld for 30 minutes or longer only when a medication-nutrient interaction is present in order to prevent altered drug bioavailability.

Appropriate administration of medication via feeding tube is challenging due to limited evidence and generally based on best practice.[9] Making a list can be helpful but not easy due to different excipients in every commercial medication, condition of patient, different ingredients of nutrition products.[33] In order to make comprehensive research about which medication can be given via feeding tube, some factors should be known such as distal tip of feeding tube, the internal diameter and length of the tube, enteral nutrition product information, medication preparation (dosage form liquid or solid, crushing of solid form and dilution), volume restriction, the size of the oral syringe, medication-nutrient interaction and patient conditions (such as the length of a patient's functional bowel).[14,34,35]

During medication administration via feeding tube, in order to avoid the drug-nutrient interactions, enteral nutrition infusion should hold temporarily (30 minutes or more for some medication).[35]

In general liquid medications may easily administered via feeding tube. However even the medications with low viscosity should further diluted with sterile water prior to the administration.[26] The volume of dilution is determined by viscosity and osmolality of the liquid dosage form, the internal diameter and length of the tube, and the location of the distal tip.[26] For liquid medication containing sorbitol amount should be checked due to risk of diarrhea when daily intake over 20g.[14,25,36]

Special attention should be given to the enteral nutrition products, because those characterized by a high protein concentration, especially containing caseinates, interact with numerous drugs, and, due to the high viscosity,

cause tube clogging.[37] Some solid dosage forms such as conventional tablets are suitable for administration via feeding tube on the other hand due to alteration of medication effectiveness or clogging risk, modified-release, film coated or enteric coated tablets are not suitable for crushing.[14,25,26,37,38] It is hard to assure accurate doses with the soft gelatin capsules administration and it is generally not recommended to administer injectable medications via feeding tube due to different design comparing to oral tablets.[26] The information's about some medications administration via feeding tube is shown in Table 1.

Tube obstruction is under responsibility of pharmacist and nurse together. Pharmacist should carefully evaluate all the medications for tube administration and nutritional product formulation to avoid or minimize tube obstruction.[37] One study shown that the risk of feeding tube occlusion is 4.8 times more likely in patients who has more than five medications and 5.3 times more likely when the medication doses number is more than 13 daily. Furthermore, it is reported that if the patient administered the medications via feeding tube for longer than 10 days, they become 2.6 times more susceptible for feeding tube occlusion.[9] In another study it is reported that tube occlusion incidence varies between 12.5 to 45% and mostly caused by wrong medication preparation or administration techniques.[27] Among medications that cause tube obstruction, it is mostly by crushed modified released tablets (10%).[14] In order to avoid tube obstruction and possible interactions solid dosage forms should crushed separately and administer separately with adequate water. Rinsing of the crushing device plays an important role not only to prevent drug loss but also to prevent chemical interactions between remaining medications in the crushing device and new medication.[33] It should be noted that stopping nutrition infusion and flushing the tube before and after every medication is the key component for tube obstruction prevention as well as possible medication-nutrient interaction.[13,26,28] It is best to avoid feeding tube occlusion rather than trying to open clogged ones due to negative outcomes such as delayed administration of nutrients and medications, lack of therapeutic benefits, increased health related costs and even hospitalization.[14,26] The use of warm water to open the clogged feeding tubes is recommended in most cases. Besides the warm water alternating pressure with syringe with an appropriate syringe size, sodium bicarbonate and water mixture or for some conditions pancreatic enzymes, sodium bicarbonate and water mixtures may be preferable.[39]

Role of a Clinical Pharmacist in the Clinical Nutrition Support Team

A multidisciplinary approach was essential to optimize the effectiveness and safety of clinical nutrition treatment. It has been demonstrated that clinical nutrition support teams enhance patient outcomes, safety, and the quality of healthcare organizations. The key members of a nutrition support team are usually a physician (director), a dietician, a pharmacist and a nurse.[40] Pharmacists have a well-established position in nutrition support teams. Medication delivery presents special difficulties for patients undergoing nutrition therapy. All medications frequently need to be given intravenously or through enteral feeding tubes, which necessitate stability and compatibility assessments by pharmacists.[41] When it comes to the changed pharmacokinetics, pharmacodynamics, and bioavailability of drugs, pharmacists have additional problems from common comorbidities which require entire nutrition support team to get involved.[41] When administering medication via a feeding tube, the clinical pharmacist is responsible for controlling many parameters besides medication's characteristics such as the length of the patient's functional bowel region, the internal diameter and length of the tube, the composition of the tube, the routine flushing regimen, the distal end position of the feeding tube and the content of the feeding formula.[36] The clinical pharmacist role throughout the entire process to ensure the safety and effectiveness of both nutritional and pharmaceutical treatments. This includes oversight of the product used, evaluation of the selected medications, monitoring of the route and techniques of administration, assessment of the clinical response, and management of potential complications.

Conclusion

Enteral nutrition treatment plays an important role for those who has malnutrition, however one of the important aspects of enteral nutrition treatment is the need of medication treatment concomitantly. Appropriate medication administration via feeding tube should be provided in order to maintain safe and effective treatment of both nutritional and pharmaceutical. Pharmacists may provide the information's about characteristics of medications, appropriateness of dosage forms, interactions, stability or administration techniques. The recommendations should be made for individual patients and medications with the contribution of multidisciplinary nutrition support team in order to maintain comprehensive evaluation of patient.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Acarbose	Tablet	Tablets are suitable for crushing and suspending with water.	Interaction with nutrients should be considered.
Acetylsalicylic acid	Tablet	Enteric-coated tablets generally not suitable for crushing.	Administer after nutrients.
Aciclovir	Tablet Suspension Injection	Tablets can be dispersed in 50 ml of water. Feeding tube administration of suspension should be avoided due to lack of data.	A specific site of absorption is not documented.
Alendronate	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known. Tablet must be taken on empty stomach.
Allopurinol	Tablet	Tablets are suitable for crushing and suspending with water.	Careful monitoring for malnourished patients is needed due to the risk of toxicity.
Amiodarone hydrochloride	Tablet	Tablets are suitable for crushing and suspending with water.	Administer without regard to meals.
Amlodipine	Tablet	Tablets are suitable for crushing and suspending with water.	Administer without regard to meals. Administration via jejunum is not known.
Ampicillin+sulbactam	Tablet Suspension Injection	Feeding tube administration of tablets should be avoided due to lack of data.	Administer without regard to meals.
Apixaban	Tablet	Tablets can be crushed and may be suspended in 60 mL of water.	Administer without regard to meals
Atorvastatin	Tablet	Tablets are suitable for crushing and suspending with water.	Administer without regard to meals.
Betahistine dihydrochloride	Tablet	The tablets are very soluble in water and can be crushed also.	Administration via jejunum is not known.
Candesartan cilexetil	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administer without regard to meals.
Captopril	Tablet	Tablets are suitable for crushing and suspending with water.	The presence of nutrients in the GI tract reduces absorption by 30–40%.
Carvedilol	Tablet	The tablets will disperse in 10 mL of water if shaken for 5 minutes	The absorption rate decreases in jejunum.
Cholestyramine	Sachet	Contents of one sachet should be mixed with 120–180 mL fluid.	Administer without regard to meals.
Cilazapril	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Ciprofloxacin	Tablet	Tablets are suitable for crushing and suspending with water.	Avoid dairy products within 1-2 hours of ciprofloxacin.
Citalopram	Tablet	Tablets are suitable for crushing and suspending with water.	Administer without regard to meals.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Clarithromycin	Tablet Granule	Feeding tube administration of tablets should be avoided due to lack of data. Granules can be suspended and administered via feeding tube.	Can be administered into jejunum.
Clopidogrel	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Co-amoxiclav (amoxicillin+clavulonic acid)	Tablet Suspension Injection	Feeding tube administration of tablets should be avoided due to lack of data. Suspension should be diluted 1:1 or 1:1/2 with water.	Administer without regard to meals.
Colchicine	Tablet	Tablets will disperse in 10 mL of water.	Administration via jejunum is not known.
Dabigatran	Capsule	Do not break or open capsules. Opening capsule will lead to 75% increase in absorption and serious adverse reactions.	Administration via jejunum is not known.
Dapagliflozin	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Dexamethasone	Tablet	Tablets will disperse in 10 mL of water.	Tablets may contain lactose.
Diclofenac	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Parenteral formulation is available.
Digoxin	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Tablets may contain lactose. Absorption of digoxin is slowed and reduced by concurrent intake of high-fiber, plasma levels should be monitored. Can't be administered via jejunum.
Diltiazem hydrochloride	Tablet	Feeding tube administration of modified release tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Domperidone	Tablet Capsule Oral suspension	Tablets are suitable for crushing and suspending with water. Oral suspension dosage form should be diluted 1:1 or 1:1/2 with water.	Suspension contains sorbitol.
Donepezil	Tablet Oro-dispersible tablet	Tablets are suitable for crushing and suspending with water. Tablets will disperse in 10 mL of water. Oro-dispersible tablets are not suitable for administration via an enteral feeding tube.	Administration via jejunum is not known.
Duloxetine hydrochloride	Capsule	Contents of capsule can be added to 50 mL of water. Do not crush the microgranules.	Nutrients decreases absorption by 11%, however this is not considered clinically relevant.
Edoxaban	Tablet	Tablets may crush and mixed with 60 to 90 mL water. Suspension should be administered immediately.	Administration via jejunum is not known.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Empagliflozin	Tablet	Feeding tube adminstration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Enalapril maleate	Tablet	Tablets are suitable for crushing and suspending with water.	Administer without regard to meals.
Escitalopram	Tablet	Feeding tube adminstration of tablets should be avoided due to lack of data.	Administer without regard to meals.
Esomeprazole	Tablet Capsule	Tablets can be dissolved in water. Enteric-coated microgranules shouldn't be crushed.	Hold the feeding 1 hours before and after medication administration.
Ezetimibe	Tablet	Tablets will disperse in 10 mL of water if shaken for 5 minutes.	Administer without regard to meals.
Famotidine	Tablet	Tablets are suitable for crushing and suspending with water.	Administration via jejunum is not known.
Fenofibrate	Tablet Capsule	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Fluoxetine	Capsule	Capsules can be opened and the contents mixed with water.	Administer without regard to meals.
Fluvastatin	Tablet	Modified-release tablets are not suitable for crushing.	Administration via jejunum is not known.
Furosemide	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Food reduces the bioavailability of furosemide by 30%. Can be administered into jejunum.
Gabapentin	Capsule Oral solution	Contents of capsule can be added to 10 mL of water.	Administer without regard to meals.
Galantamine	Capsule Oral solution	Modified-release capsules are not suitable for crushing. Oral solution is sugar free; does not contain sorbitol, can be mixed with water.	Administration via jejunum is not known.
Gliclazide	Tablet	Tablets will disperse in 10 mL of water quickly. Modified release tablets are not suitable for crushing.	Administration via jejunum is not known.
Glipizide	Tablet	Modified-release tablets are not suitable for crushing.	Administration via jejunum is not known.
Granisetron	Tablet	Tablets are suitable for crushing and suspending with water.	May contain lactose. Administer without regard to meals.
Haloperidol	Tablet Oral drops	Feeding tube administration of modified release tablets should be avoided due to lack of data. Oral drops can be administered.	Administer without regard to meals.
Ibuprofen	Tablet Capsule Oral solution	Tablets are suitable for crushing and suspending with water. Oral solution dosage form should be diluted 1:1 or 1:1/2 with water.	Peak plasma concentrations are reduced and delayed when administered with nutrients.
Irbesartan	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administer without regard to meals.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Lansoprazole	Capsule	Microgranules of capsule can be added to 10 mL of 8.4% sodium bicarbonate.	Nutrients decreases the bioavailability by about 50%, hold the feeding 1 hour before and after medication administration. Administration into jejunum is not known.
Levetiracetam	Tablet Solution	Tablets are suitable for crushing and suspending with water. Oral solution dosage form should be diluted 1:1 or 1:1/2 with water.	Can be administered via jejunum.
Levodopa+Benserazid	Capsule Dispersible tablet	Feeding tube adminstration of capsule should be avoided due to lack of data. Dispersible tablets will disperse in 10 mL of water if shaken.	Protein amount in the diet should be calculated. 1–2 hour break might needed due to nutrient-drug interaction.
Levodopa+Carbidopa	Tablet	Conventional tablets disperse in 10 mL of water quickly.	Protein amount in the diet should be calculated. 1–2 hour break might needed due to nutrient-drug interaction.
Levodopa+Karbidopa	Tablet Intestinal gel	Tablets will disperse in 10 mL of water if shaken for 5 minutes. Modified-release tablets are not suitable for administration via enteral feeding tube. Intestinal gels are suitable for feeding tube.	Protein amount in the diet should be calculated. 1–2 hour break might needed due to nutrient-drug interaction.
Levofloxacin	Tablet	Film-coated tablets can be crushed but it takes few minutes for the coating to dissolve when placed in the water.	1–2 hour break might needed due to nutrient-drug interaction. Tablets can be administered via jejunum.
Levothyroxine sodium	Tablet	Tablets are suitable for crushing and suspending with water.	Can be administered via jejunum. Protective equipment must be used during the crushing process.
Linagliptin	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Lisinopril	Tablet	Tablets disperse in 10 mL of water within 2 minutes.	Administration via jejunum is not known.
Lorazepam	Tablet	Tablets are suitable for crushing and suspending with water.	Administration via jejunum is not known.
Losartan potassium	Tablet	Film coated tablets are suitable for crushing and suspending with water.	-
Memantine hydrochloride	Tablet Oral solution	Feeding tube administration of tablets should be avoided due to lack of data. Solution should be added to water then drawn into enteral syringe.	Solution contains sorbitol.
Metformin hydrochloride	Tablet Modified release tablet	Tablets are suitable for crushing and suspending with water. Modified released tablets are not suitable for enteral feeding tube administration.	Avoid administering tablets via jejunum.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Metildopa	Tablet	Tablets are suitable for crushing and suspending with water.	
Metoclopramide hydrochloride	Tablet Oral solution	Tablets can be crushed, but use of a liquid preparation is recommended.	Administration via jejunum is not known.
Metoprolol tartrate	Tablet Modified release tablet	Tablets are suitable for crushing and suspending with water. Modified released tablets are not suitable for enteral feeding tube administration.	Can be administered via jejunum.
Metronidazole	Tablet	Tablets are suitable for crushing and suspending with water.	Nutrients reduces the bioavailability this medication. Admini stration via jejunum is not known.
Mirtazapine	Tablet Orodispersible tablet Oral solution	Feeding tube administration of tablets or orodispersible tablets should be avoided due to lack of data. Solutions may be diluted with water prior to administration.	Administer without regard to meals.
Naproxen sodium	Tablet	Tablets are suitable for crushing and suspending with water.	Absorption is delayed but not reduced by nutrients
Nebivolol	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administer without regard to meals.
Olanzapine	Tablet Orodispersible tablet	Feeding tube administration of tablets should be avoided due to lack of data. Orodispersible tablet can be disperse in water.	Administer without regard to meals.
Olmesartan medoxomil	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Food has minimal effect on absorption of Olmesartan medoxomil
Omeprazole	Capsule	Capsules can be opened and the contents mixed with water.	Can be administered via jejunum.
Ondansetron	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Food has minimal effect on the bioavailability of ondansetron.
Pancreatin admixtures	Capsule Tablet	Capsules can be opened and the contents mixed with water, apple juice or sodium bicarbonate solution. Enteric-coated, sugar-coated tablets; must be swallowed whole.	The pharmacological response is based on the interaction with food.
Pantoprazole	Tablet	Tablet can be crushed and dissolved in at least 10 mL of 8.4% sodium bicarbonate.	Administration via jejunum is not known.
Paracetamol	Tablet	Conventional tablets can be crushed/ suspended with water. Modified release tablets are not suitable for crushing.	Administer without regard to meals.
Perindopril arginine	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Perindopril should be taken before food.
Phenytoin sodium	Capsule	Contents of capsule can be added to the water.	Administration via jejunum is not known.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Pioglitazone	Tablet	Tablets are suitable for crushing and suspending with water.	Administration via jejunum is not known.
Piracetam	Tablet Capsule Oral solution	Feeding tube administration of tablets or capsules should be avoided due to lack of data.	Administration via jejunum is not known.
Prasugrel	Tablet	Tablets are suitable for crushing and suspending with water.	Administration to jejunum may result in reduced bioavailability of prasugrel
Pravastatin	Tablet	Tablets are suitable for crushing and suspending with water.	Nutrients may reduce the systemic bioavailability of the drug by 35–40%. Avoid administering to the jejunum.
Pregabalin	Capsule	Capsules can be opened and the contents mixed with water.	Administer without regard to meals. Can be administered via jejunum.
Quetiapine	Tablet	Film-coated tablets are poorly soluble in water. Manufacturer recommends crushing and mixing in yogurt. Flush the tube with 25 mL of sterile water prior and 50 ml of sterile water after administration.	Hold tube feeds for 30 minutes before administration.
Quinapril	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Peak plasma concentration may be delayed by approximately 30 minutes with nutrients.
Rabeprazole	Tablet	Do not crush. Not suitable for enteral tube administration.	Administration via jejunum is not known.
Ramipril	Tablet	Tablets will disperse in 10 mL of water.	Administration via jejunum is not known.
Risperidone	Tablet	Tablets will disperse in 10 mL of water if shaken for 5 minutes.	Administration via jejunum is not known.
Rivaroxaban	Tablet	Tablets are suitable for crushing and suspending with 50 mL of water.	Avoid administration distal to the stomach; a decrease in the AUC and Cmax (29% and 56%, respectively) was observed when rivaroxaban was delivered to the proximal small intestine; further decreases may be seen with delivery to the distal small intestine.
Rivastigmine	Capsule	Feeding tube administration of capsules should be avoided due to lack of data.	Administration via jejunum is not known.
Rosuvastatin	Tablet	Tablets will disperse in 10 mL of water if shaken for 5 minutes.	Administration via jejunum is not known.
Sertraline	Tablet	Tablets are suitable for crushing and suspending with water.	Administer without regard to meals. Administration via jejunum is not known.
Simvastatin	Tablet	Tablets are suitable for crushing and suspending with water.	Administration via jejunum is not known.

Table 1. Medication Administration via Feeding Tube[9,26,42]

Active Ingredient	Dosage Forms	Information for Administration via Feeding Tube	Additional Information
Sodium valproate	Tablet Oral solution	Modified released tablets/capsules are not suitable for enteral feeding tube administration. Solutions may be diluted with water prior to administration.	Nutrients may delay the absorption of valproate.
Spironolactone	Tablet	Tablets will disperse in 10 mL of water if shaken for 5 minutes.	Can be administered via jejunum.
Tamsulosin	Capsule Tablet	Modified-release preparation; do not crush. Not suitable for enteral tube administration.	Administration via jejunum is not known.
Telmisartan	Tablet	Tablets are suitable for crushing and suspending with water.	Food delays absorption and significantly reduces telmisartan absorption
Ticagrelor	Tablet	Tablets are suitable for crushing and suspending with water.	Crushed tablets comparing to the whole tablets may result in increased concentrations of ticagrelor
Tramadol	Capsule Tablet	Modified released tablets/capsules are not suitable for enteral feeding tube administration.	Administration via jejunum is not known.
Trandolapril	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Trazodone hydrochloride	Tablet	Modified released tablets/capsules are not suitable for enteral feeding tube administration.	Administration via jejunum is not known.
Trimethoprim + sulfamethoxazole	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Valsartan	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Nutrients decreases the AUC by 40% and peak levels by 50%.
Verapamil hydrochloride	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Vildagliptin	Tablet	Feeding tube administration of tablets should be avoided due to lack of data.	Administration via jejunum is not known.
Warfarin sodium	Tablet	Tablets are suitable for crushing and suspending with water.	There is nutrient-drug interaction with warfarin. Can be administered via jejunum. Protective equipment must be used during the crushing process.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: BKÇ, CB, KD, MH; data collection: BKÇ, CF; analysis and interpretation of results: BKÇ, CB; draft manuscript preparation: BKÇ, CB, KD, MH. Supervision KD, MH All authors reviewed the results and approved the final version of the article.

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Pediatric patients have specific nutritional needs different than adult-designed products

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Parenteral nutrition (PN) is indicated when oral or enteral nutrition is not possible, insufficient, or contraindicated to correct or prevent nutritional deficiencies. The Case Report of Mohd Johari et al.[1] illustrated several key benefits of commercial multi-chamber bags (MCBs) in patients requiring home PN administration. These advantages include ease of administration, fewer line manipulations, reduced caregiver burden, and cost savings. The authors showed that PN switching administration from pharmacy compounded 2-in-1 binary admixtures with separate intravenous lipid emulsion to commercial MCBs improved safety and convenience by reducing the frequency of lipid syringe changes, lowering infection risk, and simplifying infusion with a single pump. They also showed that the transition to MCBs decreased consumable use and pump maintenance expenses, reducing annual costs by 52%.[1] These characteristics are important because PN is a vital therapy for many patients but also represents a significant burden for patients and their caregivers during home PN. Several authors have already confirmed the observations of Mohd Johari et al.[1] showing that the stability at room temperature and the long shelf life of MCBs offer more flexibility and quality of life than pharmacy-compounded PN bags that need to be stored in temperature-controlled refrigerators for up to one week.[2-4]

Beside these important considerations, the authors did not discuss the nutritional inadequacies of adult-designed MCBs in pediatric patients, which is a major limitation of these in pediatric patients, especially during long-term PN. Pediatric patients have different nutritional needs because of their growth requirements (i.e., statural growth, organ development, bone accretion, etc.).[5] Adult-designed MCBs are obviously not designed for pediatric patients, even if they often include an indication for children over two years of age and are sometimes used in pediatric patients.[3,6,7] The adult-designed MCBs do not allow to meet all the pediatric nutritional requirements, mainly because of low energy content, inadequate protein to energy ratio, low mineral content, low electrolyte content, low calcium to phosphorus ratio, and insufficient essential and semi-essential nutrient contents.[5,8-10] It explains why the PN regimens described in this case report showed poor growth and suboptimal nutrient intake intakes when referring to recent PN guidelines.[1,11,12] It suggests that enteral/oral supplements may be considered when using adult MBCs to compensate for any deficits, when possible and for limited periods, due to the inadequacies of current adults MCBs. In this case report, the calorie intakes from adult-designed MCBs can be considered appropriate but the amino acids intakes were much higher than recommended (~2 g/kg/d), varying between 3.0 and 3.75 g/kg/day. These

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high amino acid intakes implied that the total energy to amino acid ratio was close to 20 kcal per gram of amino acid while it is usually recommended to provide 30-40 kcal total energy per gram of amino acid.[8,13,14] This has probably impaired the amino acid utilization during PN and restricted the growth of lean body mass. The calcium intakes were also lower than recommended in the case report, between 0.12 and 0.19 mmol/kg/day, while recent guidelines recommend more than 0.25 mmol/kg/d, up to 0.5-2 mmol/kg/d.[8,11,12] The calcium to phosphorus ratio was around 0.2 mol/mol in the case report while recent guidelines recommend a ratio of 0.5 mol/mol or higher.[15]

Interestingly, the authors included in their references the publication of Colomb et al.[16] that discussed the new availability of pediatric-designed MCBs in 2013. Unfortunately, the authors did not discuss the opportunity and the potential use of such pediatric MCBs in their case report.[1] This might have been quite relevant for healthcare professionals who participate in multidisciplinary nutrition therapy teams and take care of pediatric patients requiring PN. Colomb et al.[16] discussed the use of two commercial pediatric-designed MCBs that allows to supply of 40-50 kcal per gram of amino acids and 0.35-0.5 mmol/kg/d of calcium when providing 2 g/kg/d of amino acids, with a 0.4-0.7 mol/mol calcium to phosphorus ratio.

The role and value of commercial MCB for providing safe and efficient PN in pediatric patients have been reviewed recently.[5] The authors acknowledged that PN practice remains a high-risk and challenging therapy in pediatric patients and highlighted that actual practice should be regularly audited for compliance with recommendations and good practices. As Mohd Johari et al.[1], they confirmed that recent guidelines recommend the use of standardized PN with validated stability data in pediatric patients to improve both safety and efficacy. Such practice may not only reduce the risk of suboptimal PN and poor growth, but also reduces the complexity of prescribing, preparing, and administering PN. The full manufacturing license of commercial MCBs offers safety advantages over unlicensed compounded PN because of high-quality manufacturing standards, validated compatibility/stability, and continued safety insurance while on-market because of worldwide pharmacovigilance.[5]

There are few pediatric-designed MCBs on the market and they are not available in every country yet. The current evidence showed they are easy to use, improve nutritional outcomes, reduce workload, and reduce costs. Nutritional improvement was not observed in the case report of Mohd Johari et al. because of using adult-designed MCBs. Therefore, the development and use of pediatric-designed MCBs represents an opportunity for improving PN practices in pediatric patients globally.[5]

Author contribution

The author declares contribution to the paper as follows: Draft manuscript preparation: TS; Review and approval of the final version of the article: TS. The author reviewed the results and approved the final version of the article.

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