EISSN 2667-6230

KEPAN
SOCIETY OF CLINICAL ENTERAL PARENTERAL NUTRITION-TURKEY

CLINICAL SCIENCE OF NUTRITION

VOLUME 5
ISSUE 2
AUGUST 2023

AVES

clinscinutr.org

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CLINICAL SCIENCE OF NUTRITION

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Contact:
Address: Büyükdere Cad. 199/6 34394
Mecidiyeköy, Şişli, İstanbul
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
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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.

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The journal's target audience includes academicians, practitioners, specialists and students interested in nutrition and dietetics.

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OPEN ACCESS

Editor in Chief: Prof. Sadık Kılıçturgay
Address: Department of General Surgery, Uludağ University School of Medicine, Bursa, Turkey
E-mail: skturgay@gmail.com
Publisher: Society of Clinical Enteral Parenteral Nutrition – Turkey
Address: Gazi Üniversitesi Çocuk Sağlığı ve Hastalıkları Gastroenteroloji Bölümü, Ankara, TURKEY

Publishing Service: AVES
Address: Büyükdere Cad. 199/6 34394 Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
E-mail: info@avesyayincilik.com
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ORIGINAL ARTICLES

CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.22059

Does the Level of Vitamin D in COVID-19 Patients Affect the Survival and Duration of Hospital Stay?

Sevan Çetin Özbek[1], Selen Özsoy[2], Levent Öztürk[3]

[1]Nutrition and Dietetics, Yüksek İhtisas University, Faculty of Health Sciences, Ankara, Turkey
[2]Department of Clinical Nutrition Units, Ankara City Hospital, Ankara, Turkey
[3]Department of Anesthesiology and Reanimation, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara, Turkey

Cite this article as: Çetin Özbek S, Özsoy S, Öztürk L. Does the level of vitamin D in COVID-19 patients affect the survival and duration of hospital stay? *Clin Sci Nutr.* 2023;5(2):41-49.

ABSTRACT

Objective: This study aimed to evaluate the effect of categorized and normal vitamin D levels on hospital stay and mortality in adult patients with COVID-19.
Methods: One hundred sixty-eight hospitalized patients due to coronavirus disease 2019 were retrospectively evaluated. The study data were collected from medical records (age, gender, comorbidity, vitamin D level, duration of hospital stay, mortality/survival status). Serum 25(OH) vitamin D level ≥ 30 ng/mL is defined as normal, 20-29 ng/mL is an insufficiency level, and less than 20 ng/mL is defined as a deficiency level.
Results: The mean vitamin D level of 168 patients was 18.72 ± 11.18 ng/mL, and 79.4% of patients with vitamin D deficiency had comorbidity. When vitamin D levels were categorized, there was no difference between the groups regarding hospital stay and survival ($P > .05$). However, when the mean vitamin D levels between the deceased and surviving patients were assessed, vitamin D levels were significantly higher in the survivors ($P = .019$). Vitamin D significantly affected survival compared to the univariate model ($P = .044$), while there was no significant effect on the multivariate model ($P > .05$). Even when the factors affecting the vitamin D level were adjusted, no significant results were found.
Conclusion: Among hospitalized COVID-19 patients, vitamin D levels did not support an association between the duration of hospital stay and mortality.

Keywords: COVID-19, duration of hospital stay, mortality, vitamin D

INTRODUCTION

While the new COVID-19 continues its adverse effects globally, the lack of an effective pharmacological treatment in the fight against the disease complicates the process.[1,2] COVID-19 disease causes severe respiratory symptoms and acute respiratory syndrome.[3,4] Age, ethnicity, poverty, crowded environments, medical conditions, and certain occupational groups have been considered risk factors for developing the disease.[5] In addition, comorbidity (e.g., diabetes-hypertension) presence is one of the other factors that adversely affect the course of the disease.[6] The relationship between COVID-19 and vitamin D is based on the fact that vitamin D reduces the risk of infection by various (anti-inflammatory pathways and its role as an immunomodulator) mechanisms.[7,8] The risk groups for COVID-19 disease are also at risk for vitamin D deficiency/insufficiency.[9] Based on the fact that no food is miraculous, vitamin D is not also miraculous to prevent COVID-19 and fight against the disease; it is a component of optimal health.[10,11] However, the increasing pandemic in the winter months and the quarantine period have increased the risk factors for vitamin D deficiency.[12]

Vitamin D, which has chemical forms of ergocalciferol and cholecalciferol, is a micronutrient and prohormone in which intake is limited with foods.[7,13] Vitamin D synthesis is associated with exposure to sunlight, and synthesis occurs through the skin.[7,10,13] The synthesized vitamin D is converted to 25-hydroxyvitamin D in the liver and converted to the active form 1,25-dihydroxy-vitamin D in the kidneys (by the enzyme 25-hydroxyvitamin D-1α hydroxylase).[14] Therefore, hepatic and renal pathologies are among the

Corresponding author: Sevan Çetin Özbek, e-mail: sevancetin@yiu.edu.tr

Received: January 8, 2023 Accepted: February 20, 2023
Publication Date: March 24, 2023

regulatory factors for vitamin D.[15] In addition, vitamin D deficiency is associated with many diseases such as cancer, cardiovascular, and infectious diseases.[14] Vitamin D deficiency/insufficiency is a silent but complex public health problem.[4,16] The elderly, pregnant women, different ethnic groups, obese people, children,[16] and people living in the Northern latitudes in winter are among the risk groups for vitamin D deficiency/insufficiency.[1,7] Seasons, time of sun exposure during the day, clothing style, use of sunscreen cream, skin pigmentation, gastrointestinal tract malabsorptions, obesity, and chronic conditions affect vitamin D synthesis and/or bioavailability.[15] In a Turkish study in which a vitamin D level of 108 742 patients was evaluated, the average level was reported as 21.6 + 13.3 ng/mL.[17] In a meta-analysis, the level of vitamin D deficiency in the Turkish population was stated as 63%.[18] Vitamin D insufficiency has brought different actions to the agenda of the countries in geographical locations that cannot benefit from sunlight. These countries use food enrichment and supplementation to eliminate vitamin D deficiency/insufficiency.[12,16,19]

Vitamin D has primary functions in calcium and phosphate metabolism and development of the musculoskeletal system and secondary functions in immune-modulatory, anti-inflammatory, and anti-oxidant pathways.[20,21] Vitamin D reduces viral replications through cathelicidins and defensins,[7,13] decreases proinflammatory cytokines, and increases anti-inflammatory cytokines.[7] In addition, it has immune homeostasis protective properties while performing the immunomodulatory role.[7,8] Especially in patients with COVID-19, the cytokine storm associated with a poor prognosis is affected through these pathways,[7] which encouraged the scientists to find the answer to the question "Can there be hope?"[13] In a retrospective study conducted in the USA in 2020, a relationship between COVID-19 disease and vitamin D level in terms of clinical outcomes was not supported in hospitalized patients due to COVID-19.[3] However, a recent systematic review and meta-analysis showed that vitamin D supplementation during the COVID-19 pandemic was associated with favorable clinical results, especially in patients supplemented after the COVID-19 diagnosis.[2] This study aims to assess the effect of vitamin D level (deficiency/insufficiency/normal level) on mortality and duration of hospital stay in adults with COVID-19.

MAIN POINTS

- The mean vitamin D levels of the deceased patients were deficient, and they had a more extended hospital stay.
- Age and comorbidity (especially neurological diseases and renal failure) were among the factors affecting mortality in COVID-19 disease.
- Supplementation of Vitamin D deficiency/insufficiency is an easy, inexpensive, and cost-effective method.

METHODS

The Design of the Study and the Patient Groups

This retrospective and descriptive study was conducted on adult patients who applied to Ankara City Hospitals Neurology-Orthopedics Hospital between 01 August and 31 October 2021 and had positive COVID-19 PCR tests. The study included (n = 181) patients whose serum 25(OH) vitamin D level was analyzed and patients who used drugs that would affect vitamin D absorption, such as corticosteroids, cholesterol-lowering agents, phenytoin-containing agents were excluded (n = 13) from the study (Figure 1). The research was approved by the Ministry of Health of the Republic of Turkey (Approval Number: (Date: May 30, 2021, Approvel Number: 2021-05-28T15_24_52) and the Ethics Committee of Yüksek İhtisas University (2021/07/07) University. Research procedures were conducted based on the Declaration of Helsinki. Since the study was retrospective, verbal consent was obtained by calling the registered phone numbers of the patients/parents/relatives.

Collection of Data

The study data were collected from medical records. The collected data included age, gender, comorbidity, vitamin D level, duration of hospital stay, and mortality/survival situations. The hospital stay duration was calculated by subtracting the date of hospitalization from discharge. Mortality data showed deaths occurring during hospitalization.

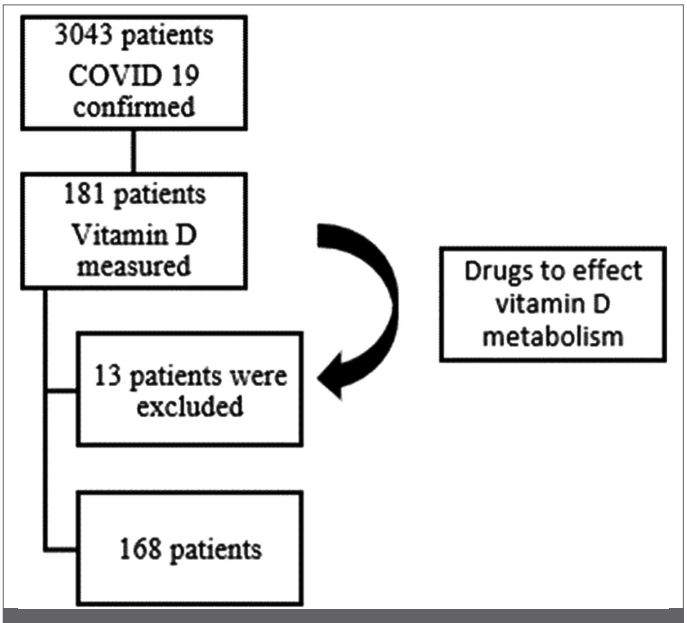

Figure 1. Research design.

Measurement of Serum 25(OH) Vitamin D Levels and Vitamin D Groups

In the study, vitamin D ranges in the pandemic hospital biochemistry laboratory reflected the vitamin D levels of the patients; as of hospitalization, the first measured serum 25(OH) vitamin D level was recorded. Serum 25(OH) vitamin D level was defined as ≥30 ng/mL normal, 20-29 ng/mL insufficient, and less than 20 ng/mL as deficiency level.

Statistical Analysis

In the data of 168 patients included in the study, mean ± SD, median (IQR: 25th-75th percentiles) minimum–maximum values were given for numerical variables, and number and per cent values were given for categorical variables. The vitamin D level is categorized into 3 groups (deficiency, insufficiency, and normal level). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to determine the suitability of the characteristics for the normal distribution. After comparing the quantitative features with normal distribution between the 3 groups with the ANOVA test, the Tukey test was used as the post hoc test. The Kruskal–Wallis test and the Mann–Whitney *U*-test with Bonferroni correction were used to compare the characteristics that did not have a normal distribution. The chi-square test was used to assess differences between the groups regarding the distribution of qualitative variables. The relationship between 25(OH) vitamin D level and 20 ng/mL deficiency status with independent variables were examined by logistic regression analysis. The Statistical Package for the Social Sciences Windows version 25.0 package program was used for statistical analysis, and $P < .05$ was considered statistically significant.

RESULTS

Patient Characteristics and Vitamin D Status

According to vitamin D levels, the patient characteristics are shown in Table 1. Of the patients, 90 (53.6%) were male and 78 (46.4%) were female. The vitamin D level of patients was 63.7% (n=107) deficiency, 25.6% (n=43) insufficiency, and 10.7% (n=18) normal. According to the patient's categorized vitamin D (deficiency/insufficiency/normal) levels, the mean age was 63.44 ± 16.9 years, 59.88 ± 15.1 years, and 60.39 ± 12.2 years, respectively. The main reasons for admission to the hospital were dyspnea (53.2%) and cough (38.3%). Eighty-five (79.4%) patients with deficient vitamin D levels and 29 (67.4%) patients with insufficient vitamin D levels had comorbidity. The most common comorbidities were hypertension, diabetes mellitus (DM) and cardiovascular diseases (CVD). Although the duration of hospital stay and vitamin D levels were not significantly associated, it was primarily observed in the deficiency group; the median was 13 (IQR:6-23) days ($P > .05$). There was no difference between the groups in terms of categorized vitamin D levels and duration of hospital stay ($P > .05$) (Table 1).

The clinical characteristics of the patients according to their survival and exitus status are shown in Table 2. During the research period, 32 out of 168 patients (19%) lost their lives, and the mean mortality age was 72.97 ± 11.93 (75 years; IQR: 65-81.75 and $P=.0001$). When the deceased and surviving patients were compared regarding mean vitamin D levels, the vitamin D levels of the surviving patients were significantly higher in their favor ($P=.019$). In addition, it was observed that the presence of comorbidity (especially DM, CVD, chronic renal failure (CRF), and neurological disease) and the duration of hospital stay were significantly higher in the patients who lost their lives compared to the survivors ($P < .05$). According to vitamin D level, the exitus was highest in the deficiency group (76.6%), and it was shown that there was no difference between the groups when compared to the patients who died ($P > .05$). However, when vitamin D levels were categorized, there was no difference between the groups in terms of survival and hospital stay ($P > .05$).

When the factors that impact survival are assessed using the logistic regression method, it has been observed that increasing age and comorbidities such as CRF, DM, CVD, and neurological diseases have a significant and elevating effect on the exitus (Table 3). Vitamin D significantly affected survival compared to the univariate model ($P=.044$), with no significant effect on the multivariate model ($P=.323$).

When the patients' vitamin D levels, age, gender, duration of hospital stay, and survival factors were adjusted, there was no significant difference ($P > .05$) (Table 4).

DISCUSSION

The results of this study, in which we retrospectively examined the effect of vitamin D deficiency/insufficiency on hospital stay and mortality in adult patients diagnosed with COVID-19, are presented later.

In this study, we retrospectively analyzed the association between vitamin D deficiency/insufficiency and duration of hospital stay and mortality of adult COVID-19 patients.

In the COVID-19 patients included in the study, vitamin D insufficiency was 25.5%, deficiency level was 63.6%, and vitamin D level was below normal in 89.2% of the patients. In a study by Campi et al.[22] 35% of the entire cohort had vitamin D deficiency.[22] In two studies in Turkey on vitamin D and COVID-19, the deficiency rate was determined by

Table 1. Characteristic Features of Patients According to Vitamin D Levels				
	Vitamin D Level			
	Deficiency < 20 ng/mL (n = 107)	**Insufficiency 20-29 ng/mL (n = 43)**	**Normal ≥ 30 ng/mL (n = 18)**	***P*****
Age				
Mean ± SD	63.44 ± 16.9	59.88 ± 15.1	60.39 ± 12.2	.417
Med (IQR)	65 (52-77)	61 (51-71)	61 (52.75-65.25)	
	n/%	n/%	n/%	
Gender				
Female	53/49.5	16/37.2	9/50	.37
Male	54/50.5	27/62.8	9/50	
Reason for hospitalization				
Dyspnea	57 (53.2%)	17 (39.5%)	8 (44.4%)	.19
Cough	41 (38.3%)	13 (30.2%)	6 (33.3%)	.51
Fever	40 (37.3%)	14 (32.5%)	6 (33.3%)	.73
Weakness	21 (19.6%)	17 (39.5%)	7 (38.8%)	**.02**
Nausea-vomiting	12 (11.2%)	5 (11.6%)	3 (16.6%)	.74
Myalgia	8 (7.4%)	7 (16.2%)	3 (16.6%)	.23
Diarrhea	5 (4.6%)	2 (4.6%)	3 (16.6%)	.19
Sore throat	5 (4.6%)	2 (4.6%)	1 (5.5%)	.97
Comorbidity†	85/79.4	29/67.4	16/88.8	.13
HT	57/53.2	17/39.5	11/61.1	.20
DM	43/40.1	10/23.2	8/44.4	.11
CVD	26/24.3	11/25.5	6/33.3	.73
Thyroid disease	15/14.0	3/6.9	0	.05
Cancer	10/9.3	3/6.9	1/5.5	.79
Neurological	9/8.4	4/9.3	1/5.5	.88
CRF	9/8.4	1/2.3	3/16.6	.13
Asthma	8/7.4	3/6.9	4/22.2	.18
Other*	18/16.8	10/23.3	4/22.2	.62
Duration of hospital stay (days)				
Med (IQR)	13 (6-23)	9 (6-14)	11.5 (6.5-17)	.24

CRF, chronic renal failure; CVD, cardiovascular diseases; DM, diabetes mellitus; HT, hypertension; Med (IQR), median (25th-75th percentiles).
*Other: liver, gout, dermatological, inflammatory bowel diseases, transplantation, rheumatologic, psychiatric diseases.
** $P < .05$, χ^2, chi-square test; kw, Kruskal–Wallis; *z*, Mann–Whitney *U*-test f: One Way Analysis of Variance
†More than 1 answer given.

Table 2. Comparison of Clinical Characteristics of Survival and Deceased Individuals				
	Survival (n = 136)	**Deceased (n = 32)**	***P****	
Age				*t*
Mean ± SD	59.67 ± 15.88	72.97 ± 11.93	**.0001***	
Med (IQR)	61 (51- 69)	75 (65- 81.75)		
Vitamin D level (ng/mL)				***z***
Mean ± SD	19.54 ± 11.67	15.25 ± 8.06	**.019***	
Med (IQR)	17 (13-23.75)	14 (10-17)		
Duration of hospital stay (days)				***z***
Mean ± SD	15.13 ± 16.19	21.06 ± 18.22	**.027***	
Med (IQR)	10.5 (6-17)	18.5 (7.25-26.5)		
	n (%)	n (%)		
Gender	136 (81)	32 (19)		
Female	63 (46.3%)	15 (46.9%)		χ^2
Male	73 (53.7%)	17 (53.1%)	.955	
Comorbidity	100 (73.5%)	30 (93.7%)	**.014***	χ^2
HT	64 (47.0%)	21 (65.6%)	.059	χ^2
DM	44 (32.3%)	17 (53.1%)	**.028***	χ^2
CVD	30 (22.0%)	13 (40.6%)	**.03***	χ^2
Thyroid disease	13 (9.5%)	2 (6.2%)	.739	χ^2
Cancer	10 (7.3%)	4 (12.5%)	.309	χ^2
Neurological	9 (6.6%)	9 (28.1%)	**.002***	χ^2
CRF	7 (5.1%)	7 (21.8%)	**.006***	χ^2
Asthma	10 (7.3%)	3 (9.3%)	.715	χ^2
Other	26 (19.1%)	6 (18.8%)	.962	χ^2
Vitamin D level				χ^2
≥30 ng/mL	15 (83.3%)	3 (16.7%)	.109	
20-29 ng/mL	39 (90.7%)	4 (9.3%)		
<20 ng/mL	82 (76.6%)	25 (23.4%)		
Duration of hospital stay (days) according to vitamin D level				
Med (IQR)	12.4 ± 9.5	15.67 ± 10.07	.574	*z*
≥30 ng/mL	11 (7- 5)	17 (5-25)		
Med (IQR)	13.1 ± 15.47	16 ± 9.09	.299	*z*
20-29 ng/mL	9 (6-14)	18 (6.5-23.5)		
Med (IQR)	16.58 ± 17.42	22.52 ± 19.99	.095	*z*
<20 ng/mL	11.5 (6-19.5)	20 (7.5-29.5)		

χ^2, chi-square test; CRF, chronic renal failure; CVD, cardiovascular diseases; DM, diabetes mellitus; HT, hypertension; Med (IQR), median (25th-75th percentiles); *t*, independent samples *t*-test; *z*, Mann–Whitney *U*-test.
**P* < .05 is statistically significant.

Table 3. Logistic Regression Analysis of Factors Affecting Mortality

Logistic Regression Analysis				
	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender (female)	1.02 (0.47-2.21)	.955		
Age	1.07 (1.03-1.10)	**.0001***	1.05 (1.01-1.09)	**.012***
Comorbidity	5.4 (1.22-23.75)	**.026***		
HT	2.14 (0.96-4.79)	.062		
DM	2.37 (1.08-5.17)	**.031***	2.03 (0.80-5.11)	.131
CVD	2.41 (1.07-5.45)	**.033***	1.98 (0.74-5.26)	.169
Thyroid disease	0.63 (0.13-2.94)	.558		
Cancer	1.8 (0.52- 6.15)	.349		
Neurological	5.52 (1.98-15.39)	**.001***	4.27 (1.25-14.57)	**.02***
CRF	5.16 (1.66-16.00)	**.004***	4.16 (1.36-15.61)	**.014***
Asthma	1.30 (0.33-5.03)	.701		
Other diseases	0.97 (0.36-2.61)	.962		
Vitamin D level (ng/mL)	0.94 (0.89-0.99)	**.044***	0.97 (0.91-1.02)	.323
Hospital stay (days)	1.01 (0.99-1.03)	.085		

CI, confidence interval; CRF, chronic renal failure; CVD, cardiovascular diseases; DM, diabetes mellitus; HT, hypertension.
**P* < .05 statistically significant; logistic regression analysis; Absent class was accepted as reference class in all examinations.

Table 4. Examination of Factors Affecting the Vitamin D Level

Outcome	Unadjusted Std. B_{vitD}	Standard Error	*P**	95% CI Lower	95% CI Upper
Age	−0.131	0.054	.09	−0.197	0.015
Gender	−0.151	1.715	.051	−6.765	0.008
Duration of hospital stay (days)	−0.096	0.052	.214	−0.167	0.038
Survival	−0.151	2.178	.051	−8.588	0.014
Outcome	Adjusted Std. B_{vitD}	Standard Error	*P*	95% CI Lower	95% CI Upper
Age	−0.55	0.058	.512	−0.153	0.077
Gender	−0.154	1.726	**.048***	−6.842	−0.025
Duration of hospital stay (days)	−0.081	0.053	.310	−0.16	0.51
Survival	−0.121	2.29	.135	−7.959	1.085

CI, confidence interval; Std. B, standardized beta coefficient.
**P* < .05 statistically significant; linear regression analysis.

Karahan et al.[23] by 69.1%, Demir et al[24] found to be 44% (0-10 ng/mL) and 32% (10-20 ng/mL).

Vitamin D sufficiency is essential for health maintenance at every stage of life, due to its effects on optimal muscle strength, bone mineral density, risk reduction in some types of cancer, and its role as an immune modulator.[11,25] Vitamin D deficiency is an essential public health problem,[13] and its optimal dose is controversial.[26] Therefore, deprivation of sunlight, the major primary source of vitamin D, due to quarantine conditions has raised concerns about inadequate vitamin D intake in the body.[10] However, the latitude of the place of residence, the duration and time of sun exposure, the incidence of sunlight, and genetic and ethnic characteristics play a role in ensuring the optimal dose of vitamin D level.[10] A study specific to Turkey showed that the difference between seasonal transitions (increase with the summer season and decrease with autumn) rather than gender is essential.[27] On the other hand, vitamin D deficiency in acute-inflammatory response is associated with a decrease in vitamin D carrier receptors, hemodilution, and increasing conversion from 25(OH) D to 1,25-dihydroxy vitamin D.[28]

Of the patients included in the study (n=168), 77.3% (n=130) had at least 1 comorbidity, and 19% lost their lives. The diseases contributing to mortality (DM, CVD, neurological, CRF) were also compatible with the literature.[29] More than half of the patients who died (n=32) were due to circulatory disorders (56.25%) and due to respiratory diseases (34.38%). Decreased induction of antimicrobial peptides, decreased pulmonary vascular barrier, and increased lung inflammation through

neutrophils are thought to cause this situation.[22] On the other hand, excessive increase in immune activation and induction of cytokine storm in infected cells are among the other causes.[13] The increase in the risk of thrombosis in infections and the low level of vitamin D affecting vascular resistance and extracellular fluid homeostasis via the renin–angiotensin system are among the factors affecting circulation.[13]

Low vitamin D levels are associated with increased disease severity, morbidity, and mortality in intensive care patients.[26] Most deaths from COVID-19 disease are associated with at least 1 comorbidity.[30] Diabetes, CVDs, cancer, chronic obstructive pulmonary disease, chronic kidney failure, and some neurological diseases are risk factors for COVID-19.[5] In addition, it is stated that the presence of hypertension concurrently with CVD in a patient increases the mortality odds ratio 40 times.[30] The presence of advanced age and comorbidity in this study (respectively, $P < .0001$ and $P = .014$) confirm the above hypothesis. However, the 19% mortality rate despite advanced age, presence of comorbidities, and low vitamin D levels suggest that the severity of the disease, the effectiveness of the treatment methods, and appropriate interventions (intubation, parenteral/enteral nutrition/appropriate pharmacological therapy) at the right time are important factors affecting this outcome. In addition, this result is based on the fact that the study was carried out in the summer, the latitudes of the geography we are in, the quarantine process is partially alleviated, and more sunlight is benefited.

The mean vitamin D level ($P = .019$) was higher in survivors with COVID-19 than in individuals who died. It suggests a potential protective effect of vitamin D on survival. However, when vitamin D levels were categorized, the difference between serum 25(OH) vitamin D level and duration of hospital stay and survival was insignificant.

Karahan and Katkat,[23] in a study with moderate and critical COVID-19 patients, showed that the results of both categorical and mean vitamin D levels of patients who survived and died were significant ($P < .001$). In a study conducted with 329 COVID-19-positive patients, it was shown that there was a meaningful relationship between vitamin D levels and duration of hospital stay ($P = .007$).[31] However, Pecina et al[32] found results that support the converse of this theorem. In a multicenter, prospective study, while there was no relationship between decategorized 25(OH) vitamin D and duration of hospital stay ($P = .120$), vitamin D levels in patients below <10 ng/mL 9 days (95% CI:6.4-11.6)) has been shown that there is a greater tendency for ($P = .057$), but this has not reached statistical significance in modeling.[33] In this study, there was no significant relationship between categorized vitamin D levels and duration of hospital stay. It is thought that COVID-19 disease (need for mechanical ventilation, the severity of the disease, inflammatory responses) and patient-related factors (age, gender, ethnicity, obesity, pregnancy, comorbidities) may be effective in this situation rather than vitamin D level.

In the multivariate model, age effected on mortality (OR:1.05 95% CI: 1.01-1.09; $P < .05$) from due to COVID-19, while vitamin D level had no effect (OR: 0.97, 95% CI: 0.91-1.02; $P > .05$). It supports the hypothesis that the elderly have a higher mortality rate for COVID-19 disease.[13]

As a result, the elderly are at risk for vitamin D deficiency,[16] and it is based on the fact that with age, the synthesis decreases due to lifestyle and physiological changes.[11] Szeto et al.[3] in a retrospective study conducted with 93 patients, found that individuals with vitamin D deficiency did not show any significance in any outcomes (deceased and duration of stay, discharge status) compared to individuals with normal vitamin D levels. A meta-analysis by Chen et al[34] showed that vitamin D level did not affect disease-related mortality (OR: 0.65, 95% CI: 0.40-1.06, $I^2 = 79\%$). However, a meta-analysis (OR: 1.80; 95%CI: 1.72-1.88) also shows that vitamin D deficiency/insufficiency is 80% more likely to get COVID-19 infection than individuals with adequate levels.[35]

Contrary to our study, there is evidence regarding the relationship between vitamin D and COVID-19.[22,31] This heterogeneity might be attributed to the different categorizations of vitamin D levels and the inability to adjust the influencing factors.

Many confusing factors such as age, obesity, ethnicity, genetic polymorphism, geography, and comorbidities will affect the prognosis and clinical results between vitamin D deficiency/insufficiency and COVID-19 disease.[3]

Vitamin D reduces the pro-inflammatory response by suppressing inflammatory cytokines, increasing the production of anti-inflammatory cytokines. The production of antimicrobial peptides forms a line of defense by up-regulating the angiotensin-converting enzyme 2, a receptor mediator, in the placement of the virus in the host.[28,36] On the other hand, the effect of vitamin D on COVID-19 disease has not yet been clarified. The difference in sample groups, the disease severity, the dose, and the duration of vitamin D supplementation have also led to heterogeneity in the studies. In addition, the socioeconomic status of the countries, the number of health professionals, and the quality of health care are other factors that affect the whole process of the disease.

Study Limitations

Our study has some limitations. The limited number of vitamin D level data did not allow us to determine the situation in individuals with COVID-19 and normal vitamin D levels. The study's other limitations are the severity of the disease, vitamin D level in patients who need mechanical ventilation, pre-hospitalization vitamin D levels, and lack of data on the use of supplements.

In this study, we retrospectively investigated the association between vitamin D deficiency/insufficiency, duration of hospital stay, and mortality of adult COVID-19 patients. The categorized vitamin D level does not impact the hospital stay and mortality. However, the mean vitamin D level supports this hypothesis regarding mortality. Considering the inflammatory, immunomodulatory, and antiviral effects of vitamin D, it is crucial to screen COVID-19 patients for vitamin D levels. In terms of being a cheap, feasible, and accessible method of eliminating vitamin D deficiency, the patient's health would benefit the triangle of the workforce of health professionals and the national economy. In addition, the inclusion of vitamin D in countries' nutrition policies through food enrichment should take its place among other applicable methods.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yüksek İhtisas University (Date: July 7, 2021, Number: 2021/12/01).

Informed Consent: Written informed consent was obtained from patient and patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Ç.Ö., S.Ö.; Design – L.Ö., S.Ö., S.Ç.Ö.; Supervision – L.Ö., S.Ö.; Resources – S.Ç.Ö., S.Ö.; Materials – S.Ö.; Data Collection and/or Processing – S.Ç.Ö., S.Ö.; Analysis and/or Interpretation – L.Ö., S.Ö., S.Ç.Ö.; Literature Search – S.Ç.Ö., S.Ö.; Writing Manuscript – L.Ö., S.Ö., S.Ç.Ö.; Critical Review – L.Ö., S.Ö.; Other – L.Ö., S.Ö., S.Ç.Ö.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.23077

Use of NUTrition Risk in the Critically Ill and Modified NUTrition Risk in the Critically Ill with C-Reactive Protein Scores as a Prognostic Indicator in COVID-19 Patients

Gülbahar Çalışkan[1], Pınar Küçükdemirci Kaya[2], Mustafa Dikici[1], Nermin Kelebek Girgin[1]

[1]Department of Anesthesiology and Intensive Care, Ministry of Health, Bursa City Hospital, Bursa, Turkey
[2]Department of Anesthesiology and Intensive Care, Bursa Uludağ University, Faculty of Medicine, Bursa, Turkey

Cite this article as: Çalışkan G, Küçükdemirci Kaya P, Dikici M, Kelebek Girgin N. Use of NUTrition risk in the critically ill and modified NUTrition risk in the critically ill with C-reactive protein scores as a prognostic indicator in COVID-19 Patients. *Clin Sci Nutr.* 2023;5(2):50-57.

ABSTRACT

Objective: This study aimed to investigate the applicability of the NUTrition Risk in the Critically Ill and modified NUTrition Risk in the Critically Ill with C-reactive protein scores for assessing nutritional risks and predicting outcomes of these critically ill coronavirus disease 2019 patients.
Methods: This retrospective study included 246 adult patients admitted to the intensive care unit between March 15, 2020, and August 15, 2021, diagnosed with coronavirus disease 2019 which was confirmed with real-time-polymerase chain reaction, and who received invasive mechanical ventilation. Treatments in the intensive care unit and clinical outcomes of the patients were recorded. The nutritional risk for each patient was assessed using both the NUTrition Risk in the Critically Ill and the modified NUTrition Risk in the Critically Ill with C-reactive protein scores. If the NUTrition Risk in the Critically Ill and modified NUTrition Risk in the Critically Ill with C-reactive protein scores were ≥6, and the nutritional risk was considered to be high.
Results: The median age was 68 (21-93) years, and 61% of them were male. The median duration of invasive mechanical ventilation was 9 (1-62) days, the median length of stay in intensive care unit was 15 (1-65) days, and the mortality rate in 28 days was 77.2%. Most of the patients had low nutritional risk according to NUTrition Risk in the Critically Ill score (75.2%) and modified NUTrition Risk in the Critically Ill with C-reactive protein score (69.1%). High NUTrition Risk in the Critically Ill and modified NUTrition Risk in the Critically Ill with C-reactive protein scores were not significantly associated with the duration of invasive mechanical ventilation, length of stay in intensive care unit, and mortality at 28 days.
Conclusion: It was shown that NUTrition Risk in the Critically Ill and modified NUTrition Risk in the Critically Ill with C-reactive protein scores were not correlated with the duration of invasive mechanical ventilation, length of stay in intensive care unit, and 28-day mortality in critically ill coronavirus-19 patients. NUTrition Risk in the Critically Ill score was not an appropriate nutrition risk assessment tool as a prognostic marker in patients with severe acute respiratory syndrome coronavirus 2 infection, which is correlated to interleukin-6 and C-reactive protein levels.

Keywords: Intensive care, nutrition, NUTRIC score, modify NUTRIC score, prognosis

INTRODUCTION

The nutritional status of patients in the intensive care unit (ICU) is affected not only by chronic and acute starvation but also by the severity of the underlying pathophysiological conditions leading to ICU admission. Malnutrition is associated with poor outcomes such as wound healing, high hospital-acquired infection rates, and increased mortality in critically ill patients.[1-3] Nutritional therapy can improve malnutrition-related outcomes in these patients.[1] However, when and how to implement nutrition therapy is still controversial.[1,3] Validated scoring systems are needed to determine the likelihood that ICU patients will benefit most from nutritional support. Therefore, it is recommended to use variables related to current metabolic status instead of traditional screening tools (body mass index, weight loss, etc.) to assess nutritional risk in the ICU.[4-6] There are many assessment tools such as Nutritional Risk Screening (NRS-2002), Malnutrition Universal Screening Tool (MUST), and Mini Nutritional Assessment (MNA) to measure nutritional risk.[2,3] Unfortunately, these tests have not been validated specifically for patients followed in the ICU. Heyland et al[4] presented a new screening tool called NUTrition Risk in the Critically Ill (NUTRIC) score, which was

Corresponding author: Gülbahar Çalışkan, e-mail: alkanbahar@yahoo.com

Received: April 23, 2023 Accepted: June 5, 2023
Publication Date: July 14, 2023

validated for ICU patients. Although the NUTRIC score is based on variables such as acute inflammation and severity of underlying disease, measurement of interleukin (IL)-6 levels is not routinely obtained in critical care clinical practice. Therefore, the NUTRIC score was later validated without the use of IL-6, yielding the modified NUTRIC (mNUTRIC) score. Rahman et al[7] demonstrated the validity of an mNUTRIC score that included all variables except the IL-6 level. In addition, there are publications in the literature showing the effectiveness of using C-reactive protein (CRP), which is measured more widely, instead of IL-6 values in nutritional risk assessment in ICUs.[6,8] On the other hand, ESPEN guidelines suggest that all patients who stay in the ICU for longer than 48 hours are at risk of malnutrition and that we should consider all critically ill patients as malnourished until a special scoring system is developed.[2]

Coronovirus disease 2019 (COVID-19) is a respiratory illness caused by the severe acute respiratory syndrome coronavirus 2. It can cause a range of symptoms, from mild to severe, and can lead to death. Severe COVID-19 can lead to malnutrition, which can further worsen the patient's condition.[9,10] Therefore, management and prevention of malnutrition should be considered in the treatment of COVID-19 patients.[10-12] However, the clinical evidence for the association between nutritional risk assessment tools and clinical outcomes in patients with COVID-19 is limited.[10,13] In addition, the number of studies are insufficient to suggest that NUTRIC and the modified NUTRIC, calculated without including IL-6, the score can be used as a suitable tool in critically ill COVID-19 patients.[12-16] Besides, a study evaluating the prognostic efficiency of NUTRIC score calculated with CRP, which has prognostic importance in terms of infection conditions that are frequently followed during critically ill patients with a diagnosis of COVID-19, also has not been found in the literature.

We aimed to investigate the applicability of the NUTRIC and modified NUTRIC with C-reactive protein scores for assessing nutritional risks and predicting outcomes and 28-day mortality of critically ill COVID-19 patients undergoing invasive mechanical ventilation.

Main Points

- The mNUTRIC-CRP score can provide insights into the nutritional status of the patients diagnosed with COVID-19, especially when IL-6 measurements are not available.
- Patients with higher NUTRIC and mNUTRIC-CRP scores had a higher prevalence of hypertension, heart failure, and chronic kidney disease. These results highlight the importance of considering nutritional status in the management of critically ill patients with comorbidities.
- The association between nutritional risk scores and clinical outcomes in COVID-19 patients remains controversial.

METHODS

Ethical Considerations

This retrospective study was given approval by the Clinical Research Ethics Committee of Bursa City Hospital (September 1, 2021, No: 2021-15/10).

Study Participant and Protocol

Patients above 18 years of age who were admitted to Bursa City Hospital, Anesthesiology Intensive Care Units between March 15, 2020, and August 15, 2021, were diagnosed with COVID-19 which was confirmed with real-time-polymerase chain reaction (RT-CPR) and patients who received invasive mechanical ventilation (IMV) and treated longer than 24 hours were enrolled in this retrospective study. Patients whose IL-6 level was not measured, whose hospital stay was <24 hours, who were not performing IMV, and who were pregnant were excluded.

Data Collection

Demographic data, comorbidities, the time between the onset of COVID-19-related symptoms and admission to the hospital and ICU, Acute Physiological and Chronic Health Assessment (APACHE) score II, Glasgow coma score (GCS), Sequential Organ Failure Assessment (SOFA) score, laboratory data (urea, creatinine, hemoglobin, CRP, aspartate aminotransferase, alanine aminotransferase, bilirubin, and IL-6), ICU, and hospitalization length of stay (LOS) were recorded. Treatments (vasopressor, renal replacement therapies [RRT] s, etc.) and complications that developed in the ICU period (acute respiratory distress syndrome [ARDS], shock, acute myocardial infarction, and acute hepatic or renal failure) also were recorded. The 28-day mortality rate was calculated.

The nutritional risk for each patient was assessed using both the NUTRIC and the mNUTRIC-CRP score. Laboratory data and individual health status characteristics were used for both score assessments. The NUTRIC score was calculated using age, APACHE II, and SOFA scores, number of comorbidities, number of days from admission to hospital admission, and serum IL-6 value within the first 72 hours after admission to the ICU. The NUTRIC score, modified with CRP, was calculated by using CRP values within the first 5 days after admission to the ICU. Modified NUTRIC-CRP score was performed according to the cut off value found as a result of the analysis of the CRP results. If the NUTRIC score was ≥6 and the mNUTRIC-CRP score was ≥6 the nutritional risk was considered to be high. If the NUTRIC score was <6 and the mNUTRIC-CRP score was <6, the nutritional

risk was considered to be low. Both scores were compared in terms of ICU-LOS and predictability of mortality.

Statistical Analysis

The data were analyzed with the statistical software IBM Statistical Package for the Social Sciences Statistics for Windows version 20.0 (IBM SPSS Corp., Armonk, NY, USA). The descriptive statistics were presented as number (n), percentage (%), and median (minimum–maximum). The normal distribution of the data of numerical variables was evaluated using the Shapiro–Wilk normality test. Comparisons between groups were performed using Student's *t*-test for variables with normal distribution and Mann–Whitney *U* test for variables not showing normal distribution. The relationship between categorical data was evaluated using chi-square test statistics. Multivariate logistical regression was conducted to identify independent risk factors. The accuracy of each independent predictor was determined by each Area Under the receiver operating characteristic (ROC) Curve (AUC). A *P*-value of <.05 was considered statistically significant.

RESULTS

Patient Population and Characteristics

During the study period, a total of 246 critically ill COVID-19-PCR (+) patients were included in the study (Figure 1). The median age of patients was 68 (21-93) years, and 150 (61%) of them were males. Median APACHE II and SOFA scores were 13 and 4, respectively. One or more comorbidities were frequently seen, the most common of which were hypertension (56.9%) and diabetes mellitus (DM) (37.8%). A total of 137 patients (55.7%) received at least 1 vasoactive drug, and 31 patients (12.6%) required RRT. The mortality rate was 77.2% on the 28th day. Demographic and clinical characteristics of the patients are shown in Table 1.

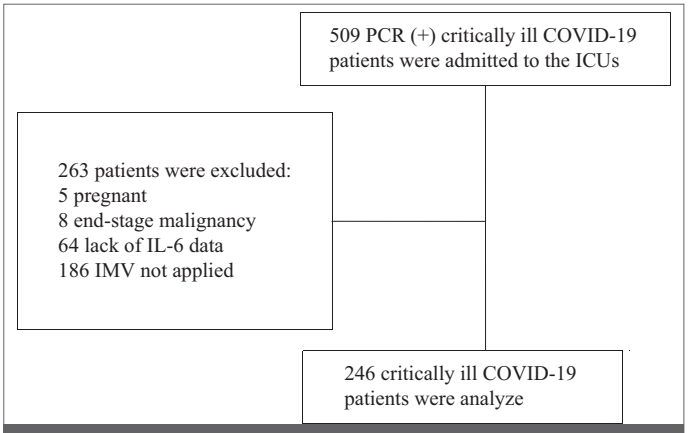

Figure 1. Flow diagram of the study. ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; PCR, polymerase chain reaction.

Table 1. Demographic and Clinical Characteristics of the Patients

	Total (n = 246)
Age (years), median (min-max)	68 (21-93)
Gender, male, % (n)	61 (150)
APACHE II score, median (min-max)	13 (3-42)
SOFA score, median (min-max)	4 (2-12)
Comorbidities, % (n)	
Hypertension	56.9 (140)
Diabetes mellitus	37.8 (93)
Coronary artery disease	23.6 (58)
Heart failure	15.9 (39)
COPD	6.5 (16)
Chronic kidney disease	6.5 (16)
Complications during ICU stay, % (n)	
Secondary infection	65.9 (162)
Shock	55.7 (137)
Acute kidney injury	35.8 (88)
Acute myocardial injury	21.1 (52)
Acute liver dysfunction	6.9 (17)
Treatments in ICU, % (n)	
Vasopressors	55.7 (137)
CRRT	12.6 (31)
Ferritin ng/mL, median (min-max)	889 (16-4552)
Interleukin-6 level, pg/mL, median (min-max)	155 (5-5000)
C-reactive protein, mg/L, median (min-max)	124 (1-415)
Duration of IMV, median (min-max)	9 (1-62)
Length of ICU stay, median (min-max)	15 (1-65)
Length of hospital stay, median (min-max)	18 (2-99)
Outcomes	
Death at ICU 28 days, % (n)	77.2 (190)

APACHE, Acute Physiological and Chronic Health Evaluation; COPD, Choronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation; SOFA, sequential organ failure assessment; min-max, minimum-maximum.

Nutritional Risk and Outcomes

Most of the critically ill COVID-19 patients had low nutritional risk according to NUTRIC (75.2%) and

mNUTRIC-CRP score (69.1%) at the ICU admission (Tables 2 and 3).

C-reactive protein was identified as an independent risk factor of mortality in critically ill COVID-19 patients. The AUCs of CRP was 0.663 (95% CI: 0.600-0.721) ($z=4.13$, $P<.001$), with a cutoff value of 141, CRP showed sensitivity of 53.6%, specificity of 76.7% (Figure 2).

NUTrition Risk in the Critically Ill and mNUTRIC-CRP scores were significantly higher in patients with older age, with higher APACHE II and SOFA scores (for all $P<.001$) (Tables 2 and 3).

The patients with high NUTRIC scores had more hypertension, DM, heart failure, and chronic kidney disease than those with low NUTRIC scores ($P=.001$, $P=.042$, $P<.001$,

Table 2. Comparison of Clinical Characteristics and Initial Laboratory Indices among Patients with High and Low Nutritional Risk According to NUTRIC Score

	Low Nutritional Risk Group (n=185)	High Nutritional Risk Group (n=61)	*P*
Age (years), median (min-max)	66 (21-93)	79 (52-92)	**<.001**
Gender, male, % (n)	63.2 (117)	54.1 (33)	.227
APACHE II score, median (min-max)	15 (3-31)	23 (11-42)	**<.001**
SOFA score, median (min-max)	4 (2-8)	7 (4-12)	**<.001**
Comorbidities, % (n)			
Hypertension	50.8 (94)	75.4 (46)	**.001**
Diabetes mellitus	38.9 (72)	34.4 (21)	**.042**
Coronary artery disease	22.7 (42)	26.2 (16)	.603
Heart failure	9.7 (18)	34.4 (21)	**.000**
COPD	4.9 (9)	11.5 (7)	.079
Chronic kidney disease	3.2 (6)	16.4 (10)	**.001**
Complications during ICU stay, % (n)			
Secondary infection	64.9 (120)	68.9 (42)	.642
Shock	50.3 (93)	72.1 (44)	**.003**
Acute kidney injury	35.1 (65)	37.7 (23)	.759
Acute myocardial injury	18.4 (34)	29.5 (18)	.072
Acute liver injury	7.6 (14)	4.9 (3)	.575
Treatments in ICU, % (n)			
Vasopressors	50.3 (93)	72.1 (44)	**.003**
CRRT	10.3 (19)	19.7 (12)	**.049**
Duration of IMV, days, median (minimum-maximum)	9 (1-62)	9 (1-47)	.695
Length of ICU stay, days, median (min-max)	15 (2-65)	15 (1-55)	.305
Length of hospital stay, days, median (min-max)	19 (2-99)	18 (4-66)	.573
Outcomes			
Death at ICU 28 days, % (n)	76.2 (141)	80.3 (49)	.599
Ferritin ng/mL, median (min-max)	882 (16-4552)	1017 (63-3705)	.338
C-reactive protein, mg/L, median (min-max)	123 (1-358)	133 (7-415)	.223
Interleukin-6 level, pg/mL, median (min-max)	143 (5-5000)	220 (15-5000)	**.030**

APACHE, acute physiological and chronic health evaluation; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation; SOFA, sequential organ failure assessment; min-max, minimum-maximum. <0.05 was considered statistically significant.

Table 3. Comparison of Clinical Characteristics and Initial Laboratory Indices among Patients with High and Low Nutritional Risk According to Modified NUTRIC Score (mNUTRIC-CRP)

	Low Nutritional Risk Group (n=170)	High Nutritional Risk Group (n=76)	*P*
Age (years), median (min-max)	65 (21-93)	76 (51-92)	**<.001**
Gender, % (n)	62.9 (107)	56.6 (43)	.396
APACHE II score, median (min-max)	14 (3-31)	22 (11-42)	**<.001**
SOFA score, median (min-max)	4 (2-9)	6 (3-12)	**<.001**
Comorbidities, % (n)			
Hypertension	48.8 (83)	75 (57)	**<.001**
Diabetes mellitus	37.1 (63)	39.5 (30)	.092
Coronary artery disease	24.1 (41)	22.4 (17)	.871
Heart failure	11.2 (19)	26.3 (20)	**.004**
COPD	5.3 (9)	9.2 (7)	.270
Chronic kidney disease	3.5 (6)	13.2 (10)	**.009**
Complications during ICU stay, % (n)			
Secondary infection	64.1 (109)	69.7 (53)	.467
Shock	48.8 (83)	91.1 (54)	**.001**
Acute kidney injury	35.9 (61)	35.5 (27)	1.000
Acute myocardial injury	17.6 (30)	28.9 (22)	.062
Acute liver dysfunction	8.8 (15)	2.6 (2)	.103
Treatments in ICU, % (n)			
Vasopressors	48.8 (83)	71.1 (54)	**.001**
CRRT	9.4 (16)	19.7 (15)	**.036**
Duration of IMV, median days, median (min-max)	9 (1-62)	9 (1-47)	.887
Length of ICU stay, days, median (min-max)	15 (2-65)	15 (1-55)	.239
Length of hospital stay, days, median (min-max)	19 (2-99)	18 (4-66)	.495
Outcomes			
Death at ICU 28 days, % (n)	75.3 (128)	81.6 (62)	.198
Ferritin ng/mL, median (min-max)	902 (16-4552)	775 (63-3705)	.820
C-reactive protein, mg/L, median (min-max)	116 (1-358)	146 (7-415)	**.001**
Interleukin-6 level pg/mL, median (min-max)	146.5 (5-5000)	179 (15-5000)	.900

APACHE, acute physiological and chronic health evaluation; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ICU, intensive care unit; IMV, invasive mechanical ventilation; SOFA, sequential organ failure assessment; min-max, minimum-maximum.

P=.001, respectively). Patients with higher NUTRIC scores also required RRT and vasopressor treatment than the low NUTRIC score group (*P*=.003, *P*=.049, respectively) (Table 2).

In the high mNUTRIC-CRP score group, the ratio of hypertension, heart failure, and chronic kidney disease was higher than in the low mNUTRIC-CRP group (*P* < .001, *P*=.004, *P*=.009, respectively). In this group also need for

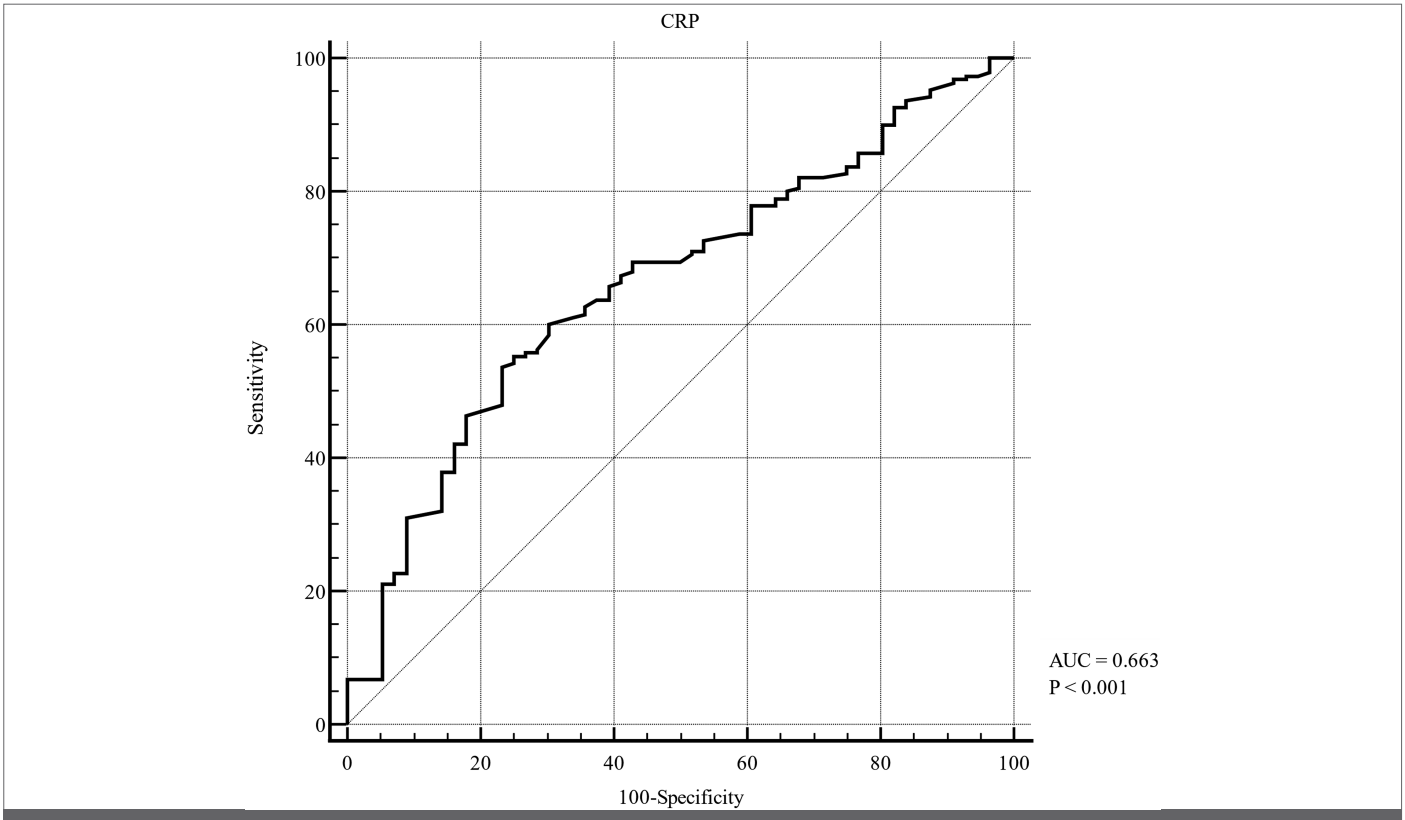

Figure 2. Prognostic accuracy of C-reactive protein to predict the outcome.

RRT and vasopressor drug use was higher than in the low-score group ($P = .001$, $P = .036$, respectively) (Table 3).

The high nutritional risk group of both NUTRIC and mNUTRIC-CRP scores had statistically significantly higher shock rates as a complication during ICU stay than the low nutritional risk group ($P = .003$, $P = .001$, retrospectively) (Tables 2 and 3).

High NUTRIC and mNUTRIC-CRP scores were not significantly associated with the duration of IMV, LOS of the ICU, and mortality at 28 days (Tables 2 and 3).

DISCUSSION

Coronavirus disease 2019 caused the death of millions of people in the world from 2019 to the present. Many studies published about risk factors, clinical outcomes, morbidity, and mortality of the disease.[9,17-19] It is suggested that the nutritional risk status affects clinical outcomes of the critically ill COVID-19 patients in ICU.[10-13,20]

In this study, we evaluated nutrition status with both NUTRIC and mNUTRIC-CRP in COVID-19 patients treated in ICU and detected that most of the patients were low nutritional risk group. Liberti et al[16] also detected that 43 COVID-19 patients in ICU had low nutritional risk with NUTRIC score. Whereas Osuna-Padilla et al[20] study included 112 patients with a diagnosis of COVID-19 who required mechanical ventilation was found that most of the patients had a high NUTRIC score (66%). The age of the patients in the studies may have contributed to these different results. Patients in Liberti's[16] and our study were at a similar age (64-68 years old, respectively), while those in Osuna's study[20] were younger (56 years old).

Comorbidities such as cardiovascular disease, hypertension, and DM were found to be significantly associated with admission to the ICU and mortality in COVID-19 patients.[9,17,19] In our study, most of the patients have at least 1 chronic disease and the most common comorbidities were hypertension, DM, and cardiovascular disease. Although the percentages varied in other studies, this triple was the most common comorbidities.[14,16,20]

Using of vasopressor for hemodynamic instability and the requirement for RRT were present in 55.7% and 12.6%, respectively, in our study. Zang et al[13] detected that the proportion of patients who were treated with vasopressor and RRT were 66% and 21%, respectively. Kucuk et al[14] detected that vasopressor drugs were required by 45% and CRRT was applied to 22% of the patients. Using of vasopressor drugs was significantly higher in patients with

high NUTRIC (72.1%) and mNUTRIC-CRP (54%) scores compared to those with low scores (50.3% and 48.8%, respectively) in our study. In the different studies, the prevalences of using vasopressors varied between 45% and 66% in the high nutrition risk groups.[12-14,20] Also, the requirement for RRT was significantly higher in patients with high NUTRIC and mNUTRIC-CRP scores compared to those with low scores in our study. Kucuk et al[14] also detected similar results in high NUTRIC scores in their study. But, Zang et al[13] did not find any differences in the requirement of RRT between high and low modified NUTRIC scores not including IL-6.

In this study, prognostic performance in COVID-19 patients treated in the ICU of both NUTRIC and mNUTRIC-CRP was evaluated, and it was detected that these scores may not be appropriate to show the requirement for IMV, LOS of hospital, and ICU and to use as a prognostic indicator in this patients. However, Li et al[10] reported a high rate of in-hospital mortality for COVID-19 patients with a high mNUTRIC score. Additionally, another study[14] also detected that the requirement for IMV, length of stay in ICU, and the mortality rates of patients were significantly higher in patients with high NUTRIC and mNUTRIC (without IL-6) scores compared to those with low scores. The authors suggested that the NUTRIC and mNUTRIC scores were effective scoring systems in COVID-19 patients in the ICU, and due to the lower cost and ease of calculation of the mNUTRIC score, it could be considered in preference to the NUTRIC score. Osuna-Padilla et al[20] detected that the patients with COVID-19 who required mechanical ventilation with a high NUTRIC score had a higher 28-day mortality, and the author suggested that high nutritional risk using NUTRIC score is associated with increased mortality risk. We think that the low number of patients included in the study was the reason why high NUTRIC scores and developing complications were not found to be associated with mortality in our study. In these studies, only high and low mNUTRIC scores or both the NUTRIC score and the mNUTRIC have been evaluated, whereas NUTRIC and mNUTRIC-CRP scores were evaluated in COVID-19 patients in our current study. In literature, values of ≥6 for both the NUTRIC[14] and mNUTRIC-CRP score[6] have been defined as high scores. We accepted the same level in both scores and detected that 61 patients had a high NUTRIC score and 76 had a high mNUTRIC-CRP in our study included a total of 246 patients. The patients with high scores were older and had higher APACHE II and SOFA scores than low scores. Zhang et al[13] compared high mNUTRIC scores with those with a low score in 136 COVID-19 patients, and they detected a statistically significant difference in respect of age, APACHE II score, SOFA score, the use of vasopressors, and mortality in high- and low-score groups. Kucuk et al[14] also detected a high NUTRIC score in older patients with COVID-19 in ICU. Additionally, in Kucuk's study, APACHE II and SOFA scores were higher in the high NUTRIC and mNUTRIC (without IL-6) score groups than in the groups with low scores. In our study, we calculated the mNUTRIC score with CRP instead of IL-6 which is an inflammation marker too.

C-reactive protein is an important marker of inflammation. Therefore, if clinicians consider or want to exclude an infectious or inflammatory etiology, CRP is mostly evaluated in ICUs.[3] Whereas, in pandemic or normal routine clinical time, IL-6 is not routinely examined in all ICUs. Therefore, in our research, we compared the NUTRIC score and the mNUTRIC-CRP score in COVID-19 critically ill patients. The only difference between the 2 scoring systems is the inclusion of CRP instead of IL-6 in the NUTRIC score calculations. According to our knowledge, there are 2 studies evaluating nutrition via NUTRIC score with CRP.[6,8] Oliveria et al[6] evaluated the concordance between the modified NUTRIC (without IL-6) and NUTRIC with CRP in identifying nutritional risk and predicting mortality in patients at ICU. The authors detected that both scores were positively associated with mortality, and the risk of death was increased in patients with a high mNUTRIC score. Moretti et al[8] also researched the same scores and found that these scores behaved similarly to the original NUTRIC score, and they suggested that the addition of the CRP improves the score performance and may be an alternative to IL-6 if it is not available. Evaluation of nutritional status using CRP values in patients with COVID-19 has never been investigated before. In our study, while the CRP level was detected to be significantly higher in patients with the high mNUTRIC-CRP group than in patients with low mNUTRIC-CRP, there was no difference between the high and low NUTRIC score groups. Additionally, the 2 scores (NUTRIC or mNUTRIC-CRP) were not superior to each other in the prediction of mortality, the difference was not statistically significant.

Strengths

To our knowledge, this study is the first to evaluate nutrition conditions via mNUTRIC-CRP score for COVID-19 patients in the ICU.

Study Limitations

This study was conducted at a single center and retrospective design. It has also a limited number of patients. Besides, it was conducted among the Turkish population. Therefore, the results of the study may not be suitable for different ethnic patients.

We found that NUTRIC and mNUTRIC-CRP scores are not correlated with the mechanical ventilation time, length of stay at the hospital and ICU, and 28-day mortality in critically ill COVID-19 patients. We think that the NUTRIC score is not an appropriate nutrition risk assessment tool as a prognostic marker in patients with SARS-CoV-2 infection, which is correlated to IL-6 levels. More studies including a larger number of patients are needed to establish the relationship between the NUTRIC score and mortality in COVID-19 patients.C-reactive protein is an independent risk factor for mortality in critically ill COVID-19 patients.

Ethics Committee Approval: Ethics committee approval was received for this study from Clinical Research Ethics Committee of Bursa City Hospital (September 9, 2021, No: 2021-15/10).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.Ç., P.K.K., M.D., N.K.G.; Supervision – G.Ç., P.K.K., N.K.G.; Resources – G.Ç., P.K.K., M.D., N.K.G.; Materials – G.Ç., P.K.K., M.D., N.K.G.; Data collection and/or Processing – G.Ç., P.K.K., M.D., N.K.G.; Analysis and/or Interpretation – G.Ç., P.K.K., M.D., N.K.G.; Literature Search – G.Ç., M.D., N.K.G.; Writing Manuscript – G.Ç., P.K.K., M.D., N.K.G.; Critical Review – G.Ç., P.K.K., M.D., N.K.G.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

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CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.23062

Investigation of the Effect of the Modified Nutrition Risk in Critically Ill Score on the Length of Stay in the Intensive Care Unit

Burhan Sami Kalın[1], Koray Altun[1], Ali İhsan Sert[1], Nevin Kurt Çelebi[1], Esra Aktiz Bıçak[2], Bahattin Savuşma[3]

[1]Division of Critical Care, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[2]Department of Anesthesiology and Reanimation, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[3]Division of Critical Care, Clinical Nutrition Nurse Specialist, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

Cite this article as: Kalın BS, Altun K, Sert Aİ, Kurt Çelebi N, Aktiz Bıçak E, Savuşma B. Investigation of the effect of the modified nutrition risk in critically ill score on the length of stay in the intensive care unit. *Clin Sci Nutr.* 2023;5(2):58-62.

ABSTRACT

Objective: Modified Nutrition Risk in Critically Patients is a classification scale that has been widely used all over the world recently to determine the level and degree of nutritional risk in individuals treated in intensive care units. It was analyzed whether the length of stay in the intensive care units as different in individuals classified according to the Modified Nutrition Risk in Critically score level.

Methods: In this retrospective study, which included 100 patients, the age and gender of the patients, the laboratory parameters at the time of first admission to the intensive care units, the prognostic indicators including the Acute Physiologic and Chronic Health Evaluation Score II, Sequential Organ Failure Assessment, and Modified Nutrition Risk in Critically scores calculated in the first day, the need for invasive mechanical ventilation, and if ventilated duration of invasive mechanical ventilation, intensive care units length of stay, comorbid conditions, and death rate were recorded.

Results: Sixty (60%) patients were male. The median age was 66 (48-79) years. The patients with high Modified Nutrition Risk in Critically score were 26 (26%). Intensive care units length of stay was 19 (10-38) days. Acute Physiologic and Chronic Health Evaluation II score was 18 (11-24). Mortality rate was 39%. High Modified Nutrition Risk in Critically score group had higher Acute Physiologic and Chronic Health Evaluation II score, the necessity of invasive mechanical ventilation, length of stay in the critical care unit, and death rate as compared to low Modified Nutrition Risk in Critically score group (for all $P > .05$) and need of invasive mechanical ventilation and Modified Nutrition Risk in Critically score ≥ 5 were shown to have a remarkable influence on length of stay in the critical care unit.

Conclusion: The need for invasive mechanical ventilation and Modified Nutrition Risk in Critically score ≥ 5 were shown to have remarkable influence on intensive care units length of stay.

Keywords: mNUTRIC score, intensive care unit, length of stay

INTRODUCTION

In line with diagnosis, disease severity, additional diseases, and disease processes, the patients are planned to be accepted to intensive care units (ICUs) and their treatment is carried out. Furthermore, malnutrition and related problems are frequently encountered in this group whose condition is evaluated as critically ill. It was determined that the prevalence of malnutrition in critical care units varied from 39% to 50%, depending on patient populations and nutritional scores.[1,2] The evaluation of nutritional status, creation of a nutrition plan, and providing appropriate nutritional support in ICU patients constitute an important part of the treatment and are of vital importance. Adequate and appropriate nutritional support should be given without delay in patients who be necessary to stay in the ICU for more than 2 days, and nutritional status and risk assessment should be performed within the first day after admission to the ICU.[3] Clinical, anthropometric, chemical, and immunological parameters can be used to define malnutrition in ICU patients. However, there is no ideal test that can identify malnutrition in ICU patients both sensitively and specifically. In the follow-up of nutritional therapy, many laboratory parameters (such as prealbumin) are useful, and more valuable information can be obtained with a good anamnesis and physical examination, by allocating a certain time to the patient in defining the nutritional condition of the individuals.[4,5] In 2011, Heyland and colleagues introduced the Nutrition Risk in Critically Ill (NUTRIC) score, which is specifically designed to screen for

Corresponding author: Burhan Sami Kalın, e-mail: bskalin@windowslive.com

Received: February 5, 2023 Accepted: April 29, 2023
Publication Date: May 31, 2023

critically ill to state nutritional risk status and degree.[6] The NUTRIC score includes 6 important parameters: age, Acute Physiologic and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), the number of comorbid situations, days from hospital admission to critical care unit admission, and IL-6 level. However, IL-6 used as an inflammatory marker is not routinely used in most hospitals. When calculating the NUTRIC score, if one of the parameters, IL-6, is not included in the result, the scoring tool to be obtained is called the modified NUTRIC (mNUTRIC) score. Patients are divided into low- (0-4) and high (5-9)-risk groups according to mNUTRIC score, and high mNUTRIC score is associated with poor prognosis.[7] The goal of the study is to retrospectively explore whether there is a relationship among length of stay (LOS) in the ICU, which is considered a poor prognosis for patients, and mNUTRIC score.

METHODS

This retrospective study included patients hospitalized in the tertiary ICU of a state hospital between January 2022 and August 2022. This study protocol was ratified by the ethics committee (December 9th 2022; no. 267) and since the data of the study were obtained from the old medical files, written or verbal consent was not obtained from the patients and their relatives for the use of their information. If the age of the patient planned to be included in the study was younger than 18 years and if the patient was hospitalized in the intensive care unit for less than 24 hours, the person was not included in the patient list. One hundred patients were joined in this study. Age and gender of the patients participating in the study, APACHE II, SOFA, and mNUTRIC scores which were calculated in the first day after admission to the ICU, the patient's need for invasive mechanical ventilation (IMV) and how long time the patient remained on IMV, the total ICU LOS, diagnosed chronic diseases of the patients, the status of the blood parameters taken at the first-day admission to the ICU (white blood cell (WBC), c-reactive protein (CRP), arterial lactate level, procalcitonin, albumin, and prealbumin values) and death status were recorded.

Main Points

- The mNUTRIC score is an important and easily calculated scoring tool that has been validated in terms of showing malnutrition and prognosis for patients hospitalized in the ICU.
- The advantage of mNUTRIC score is that, unlike the NUTRIC score, IL-6, which cannot be studied in every hospital, is not included in the calculation.
- In addition, the high mNUTRIC score correlates with ICU LOS.

Statistical Analysis

Shapiro–Wilk test was used to analyze the normality of continuous variables, and the data obtained were presented as median and interquartile range or mean ± SD. Mann–Whitney *U*-test was used to analyze the differences between groups for data that were not normally distributed. To compare the differences between groups of normally distributed data, statistical analysis was performed with the Student's *t*-test. Differences between percentile data identified as categorical variables were statistically analyzed using the chi-square test or Fisher's exact test. Linear regression analysis was applied to identify independent risk factors for length of stay in the critical care unit. Patients were divided into 2 groups as high and low mNUTRIC score, and the differences between each of 2 groups were analyzed for all parameters. While the data obtained in the results of the regression analysis were presented as odds ratio (OR) and 95% confidence interval (CI), *P* value less than .05 was statistically meaningful. Statistical analyses were performed with IBM Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) version 22.0.

RESULTS

Sixty (60%) were male and the median age was 66 (48-79) years. The patients with high mNUTRIC score were 26 (26%). Death rate was 39%. Intensive care units LOS was 19 (10-38) days. Acute Physiologic and Chronic Health Evaluation II score was 18 (11-24), and SOFA score was 5 (3-6). The need for IMV was 61 (61%) and IMV duration 7 (1-22) days. Median lactate value was 2.1 (1.4-2.9) mmol/L, CRP value 90 (67-105) mg/dL and procalcitonin was 0.6 (0.2-3) µg/L. The mean level of serum albumin on day 0 was 2.8 ± 0.6 g/L, and median serum prealbumin level on day 0 was 12 (8-19) g/dL. In this study, 30 (30%) patients had hypertension (HT), 20 (20%) patients had diabetes mellitus (DM), and 20 (20%) patients had chronic obstructive pulmonary disease (COPD). The patients with low mNUTRIC score had higher age, APACHE II score, need for IMV, procalcitonin, cerebrovascular disease (CVD), DM, IMV duration day, and death ratio as compared to the patients with low mNUTRIC score (for all $P < .05$). Sex, SOFA score, IMV duration day, WBC, lactate, CRP, albumin and prealbumin (on day 0) values, COPD, coronary artery disease (CAD), and HT were not different among patients (for all $P > .05$). High mNUTRIC score group had higher APACHE II score [25 (2-30) vs. 14 (9-21), $P=.025$], age [81 (66-85) vs. 60 (38-73), $P=.001$], need for IMV [22 (84.6%) vs. 39 (52.7%), $P=.004$], LOS in ICU [23 (10-39) vs. 15 (9-29), $P=.04$], and death ratio [17 (65.3%) vs. 22 (29.7%), $P=.009$] as compared to low mNUTRIC score group (data of the participants are shown in Table 1). The need for IMV ($P=.011$) and mNUTRIC score ≥ 5 ($P=.008$)

Table 1. Demographic and Clinical Characteristics of the Patients

Variables	Total, n = 100	mNUTRIC score ≥5, n = 26	mNUTRIC score <5, n = 74	*P*
Age (years)	66 (48-79)	81 (66-85)	60 (38-73)	**.001**
Sex, n (%)				
Male, n (%)	60 (60)	15 (57.7)	45 (60.8)	.780
Female, n (%)	40 (40)	11 (42.3)	29 (39.2)	
APACHE II score	18 (11-24)	25 (2-30)	14 (9-21)	**.025**
SOFA score	5 (3-6)	7 (5-9)	4 (2-5)	.581
Need for IMV, n (%)	61 (61)	22 (84.6)	39 (52.7)	**.004**
IMV duration, day	7 (1-22)	8 (4-20)	6 (1-23)	.256
WBC (10^3/μL)	12 (8.6-16.8)	12 (8-14.7)	13 (10-17)	.581
Lactate (mmol/L)	2.1 (1.4-2.9)	2.3 (1.4-3)	2 (1.3-2.9)	.277
CRP (mg/dL)	90 (67-105)	69 (20-162)	64 (5-134)	.905
Procalcitonin (μg/L)	0.6 (0.2-3)	1.6 (0.5-6)	0.4 (0.1-2)	**.004**
Albumin (g/dL), 0 day	2.8 ± 0.6	2.6 ± 0.6	2.8 ± 0.6	.175
Prealbumin (mg/dL), 0 day	12 (8-19)	11 (8-19)	13 (8-19)	.614
Comorbidities, n (%)				
COPD	20 (20)	6 (23.1)	14 (18.9)	.648
CAD	14 (14)	6 (23.1)	8 (10.8)	.185
HTN	30 (30)	11 (42.3)	19 (25.7)	.111
CVD	9 (9)	5 (19.2)	4 (5.4)	**.04**
DM	20 (20)	9 (34.6)	11 (14.9)	**.03**
LOS in ICU, days	19 (10-38)	23 (10-39)	15 (9-29)	**.04**
Mortality, n (%)	39 (39)	17 (65.3)	22 (29.7)	**.009**

APACHE II, Acute Physiologic and Chronic Health Evaluation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; NRS, nutritional risk screening; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; y, year.
Since the *P* values were less than 0.05 and statistically significant, these numbers were expressed in bold values.

Table 2. Linear Regression Modeling of Parameters for Length of Stay in Intensive Care Unit

Variables	Unstandardized Coefficient		Standardized Coefficient		
	B	Standard Error	Beta	*t*	*P*
Constant	30.831	13.658		2.257	.226
Age	–0.184	0.207	–0.122	–0.889	.377
APACHE II score	–0.950	0.712	–0.239	–1.334	.185
Need for IMV	18.752	7.252	0.269	2.586	**.011**
mNUTRIC score	8.008	4.256	0.470	1.881	.063
mNUTRIC score ≥5	–31.065	11.458	–0.400	–2.711	**.008**

APACHE II, Acute Physiologic and Chronic Health Evaluation; IMV, invasive mechanical ventilation; mNUTRIC, Modified Nutrition Risk in Critically Ill; OR, odds ratio.
Since the *P* values were less than 0.05 and statistically significant, these numbers were expressed in bold values.

was shown to have significant effects on LOS ICU (data of the participants are shown in Table 2).

DISCUSSION

Patients who are nutritionally deficient before hospitalization may experience worse clinical outcomes than patients who do not have nutritional problems. This relationship is more pronounced in the case of serious illness leading to ICU admission. While malnutrition status and degree of deterioration are slower in the case of lack of oral intake, it occurs more rapidly with disease severity.[8] A severe catabolic process occurs in patients in the ICU, depending on the degree of the illness compared to a normal individual. This process leads to increased calorie and protein needs. Severe deterioration of nutritional status leads to complications such as increased mortality, decreased physical function, and increased hospital stay. It is substantial to determine the risk of malnutrition to diminish the unfavorable consequences that may develop. It is no consensus on the ideal way for determining this risk, especially in the ICU. Parameters such as weight, body mass index, clinical diagnosis, laboratory findings, amount of food and energy intake, and functional status are used in these measurement methods.[9-11] These were generally defined by studying hospital inpatients outside the ICU.[12]

While there was no scale specifically developed for ICU, the NUTRIC score was evolved in 2011 with the determination of the importance of inflammation in malnutrition.[6] Since IL-6 did not make a clinically and statistically significant difference, the mNUTRIC score was formed by removing it from the original scoring. Leoni et al[13] demonstrated that diagnosed COVID-19 patients with NUTRIC score ≥ 5 have upward death ratio than same diagnosis patients with NUTRIC score < 5 (80.5% vs. 21.1%; *P* < .001). Kucuk et al[14] showed that a high mNUTRIC score poses a risk for mortality for COVID-19 patients hospitalized to critical care unit (the area under the curve value was 0.786 and *P* < .0001). In a meta-analysis by Ibrahim et al.[15] which included 4076 patients in total, it was observed that ICU LOS was prolonged in patients with high mNUTRIC score (*P* < .001). In the retrospective cohort by Zeng et al.[16] ICU LOS was found higher in patients with upward of mNUTRIC score among the patients who underwent cardiothoracic surgery. In a study conducted by Lin et al.[17] hospitalized in the surgical ICU patients who connected to IMV for at least 24 hours, ICU LOS was found higher in patients with modified NUTRIC score ≥ 5 (7.3 ± 9.5 vs. 3.4 ± 4.7, *P* < .001). Although there are many studies showing positive results between a high mNUTRIC score and the length of stay in the ICU, there are also contradictory studies. In a study conducted by Tripathi, in 115 patients with cirrhosis, there was no difference in the length of ICU stay between the patients when they were separated according to the mNUTRIC score.[18] Tseng et al[19] investigating the prognostic importance of the mNUTRIC score in patients with community-acquired pneumonia, no relationship was found between the ICU LOS and the mNUTRIC score. Considering the outcomes of our study, the ratio of malnutrition was determined as 26% according to mNUTRIC score. The patients with an mNUTRIC score > 5 were included in the malnutrition category, and both mortality and the ICU LOS were found to be higher in the malnutrition group. The ICU LOS is affected by multiple parameters. Infection status of the patients, comorbidities, need and duration of invasive mechanical ventilation, electrolyte imbalance, albumin and prealbumin values, nutritional support status, high intensive care score, and age can be included in these parameters. mNUTRIC score includes 5 of these counted parameters. Studies have found that these 5 parameters are highly correlated with the LOS in the ICU. We analyzed 4 parameters from these 5 values, and only the duration of hospitalization before admission to the intensive care unit was not examined. While the parameters alone could not be established as a risk factor for ICU LOS, the mNUTRIC score was determined as a risk factor. There were some limitations in the study. Some parameters that may affect the ICU LOS were not included in the study. Energy and protein support and requirements given to patients, the route of application of nutritional support, unquestioned diseases (such as neurological, muscle, and liver diseases), body mass index, IL-6 level, sedation and vasopressor drugs given, and renal replacement therapy can be counted. In addition, being planned in a single intensive care unit, restricted of participants, heterogeneity of the group and being a retrospective study can be included in the limitations of the study.

Although there is no gold standard for the determination of nutritional risk, the mNUTRIC score, which is determined without the need for IL-6, has been shown many times to be a reliable parameter especially in terms of determining the risk of mortality. Although studies sometimes show negative results in terms of ICU LOS, the mNUTRIC score, which has been shown to be effective in our study and has been previously validated and can be easily calculated, may be appropriate to calculate in critically ill patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi Yaşargil Training and Research Hospital (Date: December 9, 2022, Number: 267).

Informed Consent: Informed consent from patients was not procured because of the retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.S.K., A.İ.S., K.A., N.K.Ç., E.A.B.; Design – B.S.K., A.İ.S., K.A., N.K.Ç., B.S.; Supervision – A.İ.S., K.A., N.K.Ç.; Resources – B.S.K., A.İ.S., K.A.; Materials – B.S.K., K.A., B.S.; Data Collection and/or Processing – K.A., B.S.K., B.S.; Analysis and/or Interpretation – A.İ.S., K.A., N.K.Ç.; Literature Search – B.S.K., A.İ.S., K.A., N.K.Ç.; Writing Manuscript – B.S.K., A.İ.S., K.A., N.K.Ç., E.A.B.; Critical Review – B.S.K., A.İ.S., K.A., N.K.Ç., E.A.B.

Declaration of Interests: The authors did not report any conflict of interest in any matter related to the article.

Funding: The authors declared that this study has received no financial support.

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CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.23090

Is Immunonutrition Effective on Surgical Site Infection and Length of Hospital Stay in Pancreaticoduodenectomy Patients?

Pınar Taşar, Sadik Kılıçturgay

Department of General Surgery, Bursa Uludağ University, Faculty of Medicine, Bursa, Turkey

Cite this article as: Taşar P, Kılıçturgay S. Is immunonutrition effective on surgical site infection and length of hospital stay in pancreaticoduod enectomy patients? *Clin Sci Nutr.* 2023;5(2):63-69.

ABSTRACT

Objective: Studies emphasize the importance of nutritional support in pancreatic cancer patients with malnutrition and suggest that immunonutrition products reduce postoperative morbidity compared to standard products. In this study, we evaluated the effect of standard nutritional support and immunonutrition on surgical site infection and postoperative length of hospital stay in patients undergoing pancreaticoduodenectomy for malignancy.

Methods: Patients who underwent pancreaticoduodenectomy between 2018 and 2022 were divided into 3 groups: those who received no nutritional support, those who received standard nutritional support, and those who received immunonutrition. Patients' age, gender, body mass index, weight loss, Nutritional Risk Screening-2002 score, preoperative prealbumin and albumin values, whether they received nutritional support or not, the period of nutritional support use and whether standard nutritional support or immunonutrition was applied, postoperative surgical site infection development and length of hospital stay were evaluated.

Results: The study included 114 patients, 66 of whom were male. The mean age of the patients was 63.8 ± 10.45 years, the mean body mass index was 26.53 ± 5.29 kg/m^2, and the median Nutritional Risk Screening-2002 score was 4 (2-6). Weight loss was observed in 57% of the patients. Of the 65 patients with weight loss, 14 (21.5%) did not receive nutritional support. In total, 49 patients received immunonutrition. There were 31 patients in the no nutritional support group. When the groups were compared, the difference in the incidence of surgical site infection was significant (P=.030). However, there was no difference between the groups regarding length of hospital stay (P=.147). When the groups were compared among themselves, there was no difference in surgical site infection between the standard nutritional support or immunonutrition groups (P=.128). In those with weight loss, surgical site infection was highest in the no nutritional support group with 71.4%, while it was 23.3% and 23.8% in the immunonutrition and standard nutritional support groups, respectively (P=.004). Length of hospital stay was similar. In those without weight loss, there was no difference between the groups regarding surgical site infection and length of hospital stay (P=.057, P=.271, respectively).

Conclusion: In malnourished or at risk of malnutrition patients undergoing pancreaticoduodenectomy for periampullary site malignancy, nutritional support positively affects the development of surgical site infection, whereas specifically, immunonutrition does not reduce postoperative surgical site infection or length of hospital stay.

Keywords: Immunonutrition, morbidity, periampullary cancer

INTRODUCTION

Tumors of the periampullary region (PAT) localized within 2 cm of the major papilla, including the ampulla vateri, distal choledochal, pancreatic head-uncinate process, and duodenum, account for 0.5%-2% of all gastrointestinal cancers.[1] Pancreaticoduodenectomy (PD) is considered the most effective treatment in these patients. Although mortality after PD gradually decreases, morbidity is still around 50%. A significant portion of the morbidity is caused by surgical site infection (SSI).[2] Among the causes of SSI, malnutrition is an important factor.[3] Cancer patients are immunosuppressive and severe malnutrition may be encountered in 50%-80% of patients due to impaired oral intake, malabsorption, and the effects of the catabolic process.[4] In pancreatic cancer, impairment in both endocrine and exocrine function of the pancreas leads to alterations in food digestion and glucose hemostasis, resulting in increased caloric requirements and malabsorption, leading to weight loss in 80%

Preliminary data for this study were presented as a oral presentation at the Turkish Society of Clinical Enteral & Parenteral Nutrition Congress, March 2023.

Corresponding author: Pınar Taşar, e-mail: pinartasar@gmail.com

Received: June 17, 2023 Accepted: July 17, 2023
Publication Date: July 31, 2023

of patients at diagnosis.[5] This has been demonstrated to decrease the immune response in surgical patients, increase postoperative complications, length of hospital stay (LoHS), and cost, and has a negative impact on quality of life.[6,7] Therefore, the nutritional status of patients and the presence or risk of malnutrition should be evaluated preoperatively and supported with patient-based nutrition protocols. For this purpose, immunonutrition (IN) products can be used in addition to standard nutritional support (SNS) products. Immunonutrition containing specific nutritional products can be administered enteral and parenteral. These products contain arginine, glutamine, dietary nucleotides, and omega-3 fatty acids. Therefore, both preoperative and postoperative IN is founded in European Society for Clinical Nutrition and Metabolism (ESPEN) 2017[8] and 2021[9] for patients undergoing upper gastrointestinal surgery. However, some recent studies have not shown that IN is more effective on postoperative infectious complications than SNS.[10-15] At the same time, while the Enhanced Recovery After Surgery (ERAS) guideline in 2012 found the use of IN for 5-7 days preoperatively in PD patients,[16] the revised guideline in 2019 showed that the use of IN did not affect complications when industry-sponsored studies were excluded.[17] Thus, ERAS does not find the use of IN in PD patients with a high level of evidence and a strong level of recommendation.[17]

This study evaluates the effect of IN or SNS on postoperative SSI and LoHS in patients undergoing PD for PAT.

Main Points

- Weight loss appears to be an effective factor on length of hospital stay (LoHS).
- In patients with malnutrition and/or malnutrition, nutritional support is effective on early postoperative outcomes such as surgical site infection (SSI) and LoHS.
- Although most of the studies have shown the effectiveness of the use of immunonutrition products on postoperative infections complications for cancer patients, conflicting results still remain.
- In our study, the superiority of specialized nutritional support products over standard products in terms of SSI and LoHS, especially in patients with malnutrition and at risk of malnutrition, could not be demonstrated.
- The retrospective nature of the study also enabled us to evaluate the results of nutritional approaches of different surgical teams, regardless of the type of nutritional support used (immunonutrition-standard nutritional support). This is weight loss, and it is also significant in terms of showing the effect of malnutrition on early postoperative outcomes in patients who are on a standard diet and who do not receive nutritional support.

METHODS

The data of patients who underwent PD for PAT in our clinic between 2018 and 2022 were retrospectively analyzed. Ethics committee date January 11, 2023, approval numbered 2023-1/45 of Bursa Uludag University, Faculty of Medicine was obtained. Patients with non-malignant pathologic diagnoses and patients with missing data were excluded from the study. Patients' age, gender, weight loss (>10% within 6 months), body mass index (BMI), Nutritional Risk Screening-2002 (NRS-2002) score (Table 1),[18] prealbumin and albumin values, preoperative biliary drainage (as a factor that increases infectious complications), preoperative and postoperative nutritional support (NS) and IN were analyzed from file data. Patients with NRS-2002 score ≥ 3 and >10% within weight loss were considered at nutritional risk. Patients were divided into 3 groups as "No NS (NNS)," "SNS," and "IN." The preoperative nutritional support (NS) decision was taken according to the personal preferences of 3 different surgeon teams who performed these surgeries. For this reason, it was observed that NS was not given to a group of patients who could need perioperative NS. immunonutritional support (IN), on the other hand, was given according to the physician's decision. In a small number of patients, although IN was started due to intolerance, taste problems (too much sugar), and more difficult control of diabetes, it could not be continued and standard nutritional support (SNS) was applied. Oral Impact Powder® (Nestle, Vevey, Switzerland)) (3 packets-711 mL/day-1023 kcal/day and 54 g/day of L-arginine-milk protein) and glutamine (Resource glutamine (Nestle, Vevey, Switzerland) 30 g/day) were used as IN products. These products were administered orally for 7 days preoperatively and enteral/orally for 7 days postoperatively. In the IN group, SNS products containing calorie 1.0 kcal/mL and 14 g protein were added to patients who could not meet the daily calorie requirement of 25-30 kcal/kg and 1-1.2 g/kg protein requirement. In the postoperative period, patients were started on a nasojejunal (NJ) tube with 10 mL/h at the 6th hour, and it was aimed to increase the dose to 50 mL/h on the third day. Oral intake was then started based on clinical findings. The group receiving standard NS provided similar caloric and protein support as the IN group. Surgical site infection and LoHS were evaluated in the postoperative period. Surgical site infection was classified as superficial, deep, and organ-cavity infection.[19]

Statistical Analysis

Whether the numerical data fit the normal distribution was tested by the Shapiro–Wilk test. Numerical variables fitting the normal distribution were given as mean ± standard deviation, and those not fitting the normal distribution

Table 1. NRS 2002 (Nutritional Risk Score)[18]

Deterioration in Nutritional Status			Severity of Disease	
Score			Score	
Normal Nutrition	0 (None)		Normal Nutrient Requirement	0 (None)
>5% weight loss in 3 months or food intake in the last week is below 50%-75% of normal requirements	1 (mild)	+	Hip fracture, especially in chronic patients with acute complications: liver cirrhosis, COPD, chronic hemodialysis, diabetes, cancer	1 (mild)
Weight loss > 5% within 2 months or BMI 18.5-20.5 + general condition disorder or food intake in the last week is 25%-50% of normal requirements	2 (moderate)		Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy	2 (moderate)
Weight loss > 5% within 1 month (>15% in 3 months) or BMI <18.5 + general impairment or last week's food intake was 0%-25% of normal needs	3 (severe)		Head trauma, bone marrow transplantation, intensive care unit patients (APACHE > 10)	3 (severe)

Patient age ≥ 70 years + 1 point.
Point ≥ 3: Nutritional risk exists, and a nutrition plan is initiated.
Point < 3: An NRS 2002 assessment should be performed once a week. If a major surgical intervention is planned, a nutritional plan should be implemented as a precaution against possible risks.

were given as median (minimum–maximum) values. In the comparison of numerical variables between 2 independent groups, the independent sample *t*-test was used for the comparison of independent groups if the data were normally distributed, 1-way analysis of variance was used for the comparison of more than 2 independent groups, Mann–Whitney *U* test was used for the comparison of 2 independent groups if the data were not normally distributed, and Kruskal–Wallis test was used for the comparison of more than 2 Independent groups. Categorical variables were expressed as n and percentages. Fisher's exact chi-square and Fisher–Freeman–Halton tests were used to compare categorical variables between groups. The Spearman correlation coefficient was used to analyze the relationships between variables. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics 23.0 package program.

RESULTS

The study included 114 patients, 66 of whom were male. The mean age of the patients was 63.8 ± 10.45 years. The mean BMI was 26.53 ± 5.29 kg/m^2, and 57% of the patients had weight loss. The median NRS-2002 score was 4 (2-6). The median prealbumin was 0.19 g/L (0.07-0.32), and the median albumin was 38.0 (23.0-48.0) g/L. Postoperative LoHS was 12 (6-75) days. Of the 65 patients with weight loss (>10%), 14 (21.5%) did not receive NS. There were a total of 31 patients who did not receive NS. In total, 49 patients received IN. While 48 of these patients received both preoperative and postoperative IN, 1 patient received only postoperative IN because blood glucose regulation could not be achieved in the preoperative period. Of a total of 34 patients who received SNS, only one-fourth (8 patients) received both preoperatively and postoperatively, whereas 26 patients received SNS only postoperatively. Weight loss was present in 21 (61.8%) of the patients who received SNS. Biliary drainage was performed in 20 patients (64.5%) in the NNS group, 21 patients (42.9%) in the IN group, and 16 patients (47.1%) in the SNS group. The distribution of all these parameters in the groups was similar and showed no statistically significant difference (Table 2).

The study showed SSI developed in 32.5% (37 patients) (Table 3). Of these patients, 54.05% (20 patients) developed organ cavity infection, 32.4% (12 patients) developed deep SSI, and only 5 (13.51%) developed superficial SSI. The difference between the groups regarding SSI development was significant (P=.030). The incidence of SSIs in the group that did not receive NNS (48.4%) was significantly higher than in the SNS group (17.6%) (P=.008). In contrast, the rate of SSI in the IN group (32.7%) was similar to both the NNS group and the SNS group (P=.159, P=.128, respectively). When the types of SSI were evaluated, superficial SSI developed in 1 patient, deep SSI in 9 patients, and organ-cavity infection in 5 patients in the NNS group. Among the patients who received NS, 2 patients in the SNS group developed superficial SSI, 1 deep SSI, and 3 organ cavity infections,

Table 2. Comparison of the Preoperative Characteristics of the Cases				
	NNS (n=31)	**SNS (n=34)**	**IN (n=49)**	***P***
Age (years)*	65 (31-79)	65.5 (43-81)	65 (39-82)	.866
>10% Weight loss**	14 (45.2)	21 (61.8)	30 (61.2)	.295
BMI*	26.6 (20.7-35.5)	24.7 (19.2-45.8)	25.8 (16.9-43.9)	.625
NRS-2002*	3 (2-5)	4 (2-6)	4 (2-6)	.245
Albumin (g/L)#	38.45 ± 6.57	35.76 ± 5.06	36.41 ± 5.18	.131
Prealbumin (g/L)	0.18 (0.10-0.32)	0.15 (0.07-0.29)	0.19 (0.07-0.27)	.179
Presence of biliary drainage**	20 (64.5)	16 (47.1)	21 (42.9)	.155

BMI, body mass index; IN, immunonutritional support; NNS, no nutritional support; SNS, standard nutritional support.
*Median (minimum-maximum).
**n (%).
#Mean ± SD.

while 2 patients in the IN group developed superficial SSI, 2 patients developed deep SSI, and 12 patients developed organ cavity infections. It was statistically significant that 9 (75%) of the 12 patients with deep SSI were in the NNS group (*P*=.014), while it was not statistically significant that 12 (60%) of the 20 patients with organ cavity infections were in the IN group (*P*=.070).

Of the 17 patients who developed superficial or deep SSI, 10 (58.8%) were in the group not receiving NS. The difference was statistically significant compared to 7 patients in the standard or IN group (*P*=.037).

When the groups were compared among themselves, there was no difference between the SNS or the IN group regarding SSI (*P*=.128). When the patients with weight loss were analyzed, SSI was observed in the NNS group with a rate of 71.4%, while SSI was observed in the IN and SNS groups with rates of 23.3% and 23.8%, respectively (*P*=.004). In patients with weight loss, there was no difference in SSI infection between those who received IN and those who received SNS (*P*=1.000), while SSI was significantly lower in both the IN and SNS groups compared to the NNS group (*P*=.002, *P*=.005, respectively). Surgical site infection developed in 30.6% of those without weight loss. There was no difference between the groups in terms of SSI in those without weight loss (*P*=.057)

There was no difference between the groups when the LoHS was evaluated (*P*=.147)(Table 3). The median LoHS was 12 (6-41) days in patients with weight loss. Patients with weight loss and SNS had the longest LoHS with 19.5 (7-40) days, but it was not significant (*P*=.072). When the groups were compared pairwise, it was observed that those who did not receive NS had longer LoHS than the SNS and IN groups, and this difference was statistically

Table 3. Surgical Site Infection and Length of Hospitalization in the Groups					
	Total	**NNS (n=31)**	**SNS (n=34)**	**IN (n=49)**	***P***
SSI**	37	15 (48.4%)	6 (17.6%)	16 (32.7%)	***.030***
Superficial SSI	5	1 (20.1%)	2 (40.0%)	2 (40.0%)	*.288*
Deep SSI	12	9 (75.0%)	1 (8.3%)	2 (16.7%)	***.014***
Organ cavity infection	20	5 (25.0%)	3 (15.0%)	12 (60.0%)	*.070*
LoHS (days)*		15 (6-40)	9 (6-41)	12 (6-75)	*.147*
>10% without weight loss	11 (6-75)	10.5 (6-30)	8 (6-40)	14 (6-75)	.271
>10% weight loss	12 (6-41)	19.5 (7-40)	11.5 (6-41)	11.5 (6-37)	.072

*Median (minimum-maximum).
**n (%).
Statistical significance in the comparison of the three groups.

significant ($P=.028$, $P=.045$, respectively). On the other hand, no difference was found between SNS and IN ($P=.372$). In those without weight loss, the median LoHS was 11 (6-75) days, and there was no difference in LoHS between the groups ($P=.271$).

In the correlation analysis, no correlation was found between albumin ($P=.320$), prealbumin ($P=.268$), and NRS ($P=.245$) and postoperative LoHS, while a significant negative correlation was observed between albumin and NRS ($r=-0.312$, $P<.001$).

DISCUSSION

The prognostic importance of weight loss in major surgery has been recognized since the 1930s.[20] Weight loss (due to anorexia, malabsorption, and increased caloric requirements) has been reported in more than 80% of pancreatic cancer patients at diagnosis, and more than two-thirds of these patients LoHS more than 10% of their initial body weight. Although body mass index (BMI) is an important indicator in determining malnutrition, it can be misleading in obese individuals. Therefore, obese patients may be more malnourished than those with low body mass index. In addition to the patient's weight loss and BMI, sarcopenia and sarcopenic obesity should also be considered. These patients have an NRS-2002 score of ≥3 and require further nutritional assessment.[21,22] In our study, although mean BMI and albumin values were within normal limits, 57% of the patients had weight loss. The NRS-2002 score was also high in proportion to weight loss.

In particular, malnourished patients and patients at risk of malnutrition are associated with a higher rate of postoperative complications and longer lengths of hospitalization than well-nourished patients.[23] Therefore, the 2017 ESPEN guidelines found oral/supplement, enteral, or parenteral feeding regimens aiming to achieve standard nutritional status before a major operation such as hepatopancreatobiliary surgery.[24] However, preoperative NS in pancreatic surgery has not been proven to reduce complication rates or accelerate recovery. Level A evidence (prospective randomized controlled trials showing the benefits of meaningful clinical outcomes are few and mostly dated, and none of the different screening methods for malnutrition have been shown to have any prognostic significance for patients undergoing pancreatic surgery.[25] On the other hand, although preoperative NS in patients with moderate to severe malnutrition is recommended by the 2017 ESPEN guideline, none of the 35 controlled studies that make up the database date after 2004. Therefore, preoperative NS is a controversial issue. The use of a nasogastric tube, NJ tube, or needle-catheter jejunostomy recommended by ESPEN guidelines for the postoperative period is not recommended by ERAS guidelines. Early initiation of oral feeding, available in the ERAS program, also varies between cases. Therefore, both ESPEN and ERAS recommendations can be combined to provide an additional benefit to the patient, and the use of artificial NS may be useful in patients at high risk of postoperative complications.[17,24,26] To optimize patient outcomes, it is generally accepted to delay surgery and initiate aggressive NS in patients with albumin < 2.5 mg/dL or weight loss > 10% or BMI:18.5 kg/m^2 and to give preoperative NS to patients with albumin < 3 mg/dL or weight loss between 5% and 10%.[27]

Proinflammatory cytokine levels are also high in PAT, especially in pancreatic cancer patients.[28] In light of all this theoretical information, it is thought that using specific agents such as IN products that both modulate the immune system and have trophic effects on the intestinal mucosa may have positive effects in the postoperative period. The ESPEN guidelines also recommend using IN (glutamine and arginine, ω-3 fatty acids, and nucleotides) in major abdominal surgery to prevent infectious complications.[24] Conflicting results have been reported in the literature. Some studies have reported no difference between IN and standard oral supplements regarding postoperative complications.[11,29] A meta-analysis published in 2014 provides similar data.[30] In a recent meta-analysis, the use of IN was not shown to affect overall postoperative complications, non-infectious complications, and mortality after PD, but it was reported to reduce infectious complications and shorten the LoHS.[31-33] The main problem is that most studies on this issue are severely biased, and these benefits are LoHS when industry-sponsored studies are excluded.[25] In addition, factors such as the malnutrition status of patients and differences between diagnoses may affect homogenization and cause heterogeneity of groups, leading to conflicting results in the data obtained from studies. The ERAS guidelines for pancreatic surgery recommend artificial NS only in patients with severe malnutrition and do not recommend using IN in any patient.[17]

In our study, SSI was most common in the group with weight loss and NNS, and there was no difference between whether the selected NS was SNS or IN support. No effect of NS or IN support could be demonstrated in patients without weight loss. However, borderline significant results were obtained between the groups in patients with weight loss regarding LoHS; the longest hospitalization period was seen in the patient group without NS. In short, the lack of NS in patients with weight loss can be considered an important risk factor for LoHS and SSI.

Considering the effect of factors such as biliary drainage and BMI on SSI, the similar distribution of these

parameters in all groups equalizes the negative effect of these parameters on SSI in all groups in our study.

In our study, the highest rate of SSI was observed in the NNS group, and while there was a significant difference between the NNS and SNS groups, there was no difference between the IN and NNS groups in terms of SSI. This may be explained by the fact that three-quarters of SSI in the IN group were organ cavity infections. After PD, organ cavity infection usually develops due to postoperative pancreatic fistula. In the IN group, 75% (9 cases) of the patients with organ cavity infection had Grade B pancreatic fistula, and 8.3% (1 case) had chylous leakage, leading to intra-abdominal collection in 83.3% of the cases. This rate was 100% in patients receiving SNS and 80% in the NNS group. Pancreatic fistula is associated with pancreatic fistula score, including parameters such as pancreatic nature, duct diameter, and preoperative blood transfusion. Therefore, we think that organ cavity infection in this group may be due to reasons other than nutritional status and supportive treatment. The effect of NS on the pancreatic fistula has not been demonstrated in the literature.[11,33,34] When organ cavity infection is excluded, incisional SSI is significantly more common in the NNS group than in the SNS and IN groups. This difference is due to the much higher incidence of deep SSI, especially in the NNS group. Incisional SSI was found to be 32.3% in 31 patients in the NNS group and 8.4% in 83 patients on NS. However, no difference was found between the types of NS.

The limitations of our study are that it is retrospective, the number of patients is limited, and some of the comorbid pathologies that may be effective on SSI are not included in the parameters of the study.

In conclusion, weight loss is a significant symptomatology for patients at risk of malnutrition. Providing NS in malnourished and malnourished patients at risk of malnutrition reduces postoperative infectious complications, whereas NS in well-nourished patients and customized NS were not effective on SSI and LoHS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Bursa Uludag (Date: January 11, 2023, number: 2023-1/45).

Informed Consent: Written informed consent was obtained from each patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Design – P.T.; Supervision – S.K.; Materials – S.K.; Data Collection and/or Processing – P.T.; Analysis and/or Interpretation – S.K; Literature Search – S.K., P.T.; Writing Manuscript – S.K., P.T.; Critical Review – S.K.

Acknowledgments: We would like to thank for statistical evaluation Dr. Deniz Sigirli for their contributions.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: There was no financial support or sponsorship provided for this study.

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CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.23060

Protein Energy Intake in Hospitalized Cancer Patients: Point Prevalence Research

Arif Timuroğlu[1], Sadet Menteş[1], Selda Muslu[1], Süheyla Ünver[1], Serda Meral Çelebi[2], Kadriye Uzunoğlu[3]

[1]Department of Anesthesiology and Reanimation, University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
[2]Department of Nutrition and Dietary, University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
[3]Department of Nursing, University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

Cite this article as: Timuroğlu A, Menteş S, Muslu S, Ünver S, Çelebi SM, Uzunoğlu NK. Protein energy intake in hospitalized cancer patients: point prevalence research. *Clin Sci Nutr.* 2023;5(2):70-75.

ABSTRACT

Objective: Malnutrition is a common complication in cancer patients that can adversely affect treatment outcomes and quality of life. The aim of this study was to assess the prevalence of malnutrition in inpatient cancer patients and evaluate the impact of nutritional support on their dietary intake.
Methods: A cross-sectional study was conducted on 71 inpatient cancer patients. Nutritional status was assessed using the Subjective Global Assessment tool. Patients were divided into 2 groups based on whether or not they received nutritional support during their hospital stay. Dietary intake was assessed using a 24-hour dietary recall.
Results: The prevalence of malnutrition in our study population was 78.9%. Patients who did not receive nutritional support had a significantly lower intake of both protein and energy compared to those who did receive nutritional support ($P < .001$). The SGA score was significantly correlated with protein intake ($r=0.342$, $P < .001$) and energy intake ($r=0.283$, $P < .001$).
Conclusion: Our study highlights the high incidence of malnutrition in inpatient cancer patients, with almost 80% of patients experiencing malnutrition. Nutritional support was found to have a significant impact on dietary intake, with patients who received nutritional support having a higher intake of protein and energy. These findings emphasize the importance of nutritional screening and support for cancer patients, particularly those at higher risk of malnutrition. Further research is needed to determine the most effective strategies for providing nutritional support to cancer patients and improving their nutritional outcomes.

Keywords: Cancer, malnutrition, nutritional assessment

INTRODUCTION

Cancer patients are at a significantly higher risk of malnutrition, as the disease itself and the treatments utilized can worsen the nutritional status of patients. Malnutrition among cancer inpatients can lead to numerous negative outcomes, such as prolonged hospitalization, decreased tolerance and response to treatment, increased complications, and, ultimately, a decrease in overall survival and quality of life.[1] Thus, addressing the issue of malnutrition in cancer patients is of critical importance for optimizing treatment outcomes and improving patient well-being.

Recognizing and addressing malnutrition in cancer patients is paramount for improving their nutritional status and, ultimately, treatment outcomes. Malnutrition can arise from a variety of factors, including disease-related metabolic disorders, insufficient food intake, nausea and vomiting, mucositis, and diarrhea.[2,3] In fact, malnutrition can even manifest at the time of cancer diagnosis and may worsen as the disease progresses and cytotoxic treatments are administered.[4]

Preventive measures aimed at improving the nutritional status of cancer patients should be prioritized in clinical practice. These measures may include early screening and identification of malnutrition, implementing individualized nutritional support strategies, and actively managing symptoms such as nausea, vomiting, and mucositis to promote adequate food intake. By addressing malnutrition in cancer patients, healthcare providers can improve

[1]Preliminary data for this study were presented as a poster presentation at the Turkish Society of Clinical Enteral & Parenteral Nutrition Congress, May 2019

Corresponding author: Arif Timuroğlu, E-mail: ariftimuroglu@yahoo.com

Received: April 26, 2023 Accepted: May 22, 2023
Publication Date: June 12, 2023

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3$ μL^{-1}	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg dL^{-1} (μmol L^{-1})	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[a]
Central Nervous System (CNS)					
Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg dL^{-1} (μmol L^{-1})	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL per day				<500	<200

FIO_2: fraction of inspired oxygen; MAP: mean arterial pressure; PaO_2: partial pressure of oxygen.
[a]Catecholamine doses are given as $\mu g kg^{-1} min^{-1}$ for at least 1 h.
[b]Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.

Figure 1. Sequential Organ Failure Assessment (SOFA) score.

treatment efficacy, decrease hospitalization time, and enhance patient quality of life.

It has been observed that a significant proportion of cancer patients fail to meet the recommended protein intake of 1.2-1.5 g/kg/day.[5] Recent guidelines suggest a higher protein intake to improve protein balance and maintain muscle mass, especially in cancer patients.[6] Therefore, it is essential to evaluate the nutritional status of cancer patients undergoing in-hospital treatment and determine the rate at which they achieve the recommended protein and energy targets.

The current research aims to address this important issue by examining the protein and energy intake of cancer patients receiving in-hospital treatment and assessing their nutritional status. This information is critical for developing effective nutritional interventions to improve treatment outcomes and patient quality of life. By understanding the factors that contribute to poor nutritional status in cancer patients, healthcare providers can better tailor interventions to meet the individualized needs of patients and promote optimal nutritional support.

Main Points

- Cancer patients are at risk of malnutrition due to the disease and its treatments, which can lead to negative outcomes such as longer hospital stays, decreased response to treatment, increased complications, and reduced overall survival and quality of life.
- Malnutrition in cancer patients can be caused by various factors such as disease-related metabolic disturbances, inadequate food intake, nausea and vomiting, mucositis, and diarrhea. Malnutrition can occur even at the time of cancer diagnosis and can worsen with disease progression and cytotoxic treatments.
- Preventive measures should be taken to ensure adequate nutrition in cancer patients, such as early screening and diagnosis of malnutrition, implementation of personalized nutrition support strategies, and active management of symptoms such as nausea, vomiting, and mucositis.
- This study aims to provide critical information for developing effective nutrition interventions by examining the protein and energy intake and nutrition status of cancer patients during hospitalization.
- The research findings show that cancer patients do not meet their daily calorie and protein requirements. However, patients receiving nutrition support had higher calorie and protein intake compared to those who did not receive support.

METHODS

To ensure ethical standards were met, the study received approval from the local ethics committee (-). The study included all cancer patients over the age of 18 who received treatment in the internal medicine department and consented to participate. The research team recorded demographic data, anthropometric measurements (height, weight, and arm diameter), and biochemical parameters of patients on the day of the study. The diagnosis of patients, total calories and protein intake in the last 24 hours, additional diseases, and Sequential Organ Failure Assessment (SOFA) values were also documented; the components of the SOFA score are shown in Figure 1.[7] In this study, the Glasgow coma scale (GCS) score was used to evaluate patients' neurological status and to assess whether they had any restrictions on oral intake due to altered consciousness. The team also recorded calorie and protein levels in patients receiving nutritional support, included enteral, parenteral, and both. Nutritional risk was assessed using the Nutritional Risk Screening (NRS)-2002 tool, and malnutrition was

diagnosed using the Subjective Global Assessment (SGA) method, with patients classified as malnourished if admitted as SGA-B and SGA-C.[8,9] The amount of basal calories patients required was calculated using the Schofield equation, and total energy requirements were estimated by multiplying the activity rate with basal energy expenditure.[10,11]

Statistical Analysis

The IBM Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) 24.0 program was used for statistical analysis, which included frequency analysis of patient distribution and demographic data using descriptive statistics. Mann–Whitney *U* test and chi-square test were utilized to analyze the data, and statistically significant results were determined by a *P* value below .05.

RESULTS

In total, 71 cancer patients over the age of 18 were included from various departments. Demographic data and the diagnoses of the patients are presented in Tables 1 and 2. According to SGA values, 78.9% of the patients were diagnosed with malnutrition (SGA-B and SGA-C). Furthermore, 70.4% of the patients had an NRS score of 3 or above, and 71.8% of patients experienced weight loss in the last 6 months. Of the total group, 38% of patients experienced weight loss of 10% or more in the last 6 months. Among the patients, 65.8% received sufficient calories. The average daily amount of protein received by patients per kilogram was 0.76 grams (Table 3). In total, 22.5% of patients received nutritional support, and these patients received a higher amount of protein per kilogram compared to those without nutritional support.

Patients receiving nutritional support had a lower body mass index (BMI), whereas SOFA and GCS values were independent of nutritional support. Patients with NRS-3 or above received more nutritional support. However, co-morbid diseases, the type of tumor (solid vs. hematologic), and metastasis involvement did not have an effect on the rate of receiving nutritional support (Table 4).

Table 1. Demographic Data of Patients

	Mean (SD)
Age (years)	**54.1 (15.5)**
Female	53.5 (17.1)
Male	54.6 (14.5)
Weight (kg)	**70.1 (13.6)**
Female	67.4 (14.6)
Male	72.9 (12.5)
Height (cm)	**166.5 (9.5)**
Female	157.9 (6.5)
Male	172.1 (6.4)
BMI (kg/m²)	**25.6 (5.1)**
Female	27.0 (5.6)
Male	24.6 (4.6)

Female, n=28; male, n=43.
BMI, body mass index.

Table 2. Diagnose of Patients

Type of Malignancy	Frequency, n	%
Lung	8	11.1
Acute lymphoblastic leukemia	2	2.8
Acute myeloid leukemia	13	18.1
Rhabdomyosarcoma	1	1.4
Brain	2	2.8
Hypopharynx cancer	1	1.4
Hodgkin lymphoma	1	1.4
Liver	1	1.4
Colon	1	1.4
Larynx	1	1.4
Myelodysplastic syndrome	1	1.4
Breast	6	8.3
Bladder	1	1.4
Stomach	2	2.8
Multiple myeloma	1	1.4
Nasopharynx	2	2.8
Non-Hodgkin lymphoma	8	11.1
Oropharynx	1	1.4
Osteosarcoma	2	2.8
Esophagus	1	1.4
Pancreas	5	6.9
Parotid	1	1.4
Prostate	1	1.4
Rectum	5	6.9
Gall bladder	2	2.8
Cervical	1	1.4
Testis	1	1.4

Table 3. Daily Protein and Energy Intake Values	
	Mean (SD)
Daily calorie needs (kcal)	**2278 (350)**
Female	2031 (230)
Male	2439 (321)
Total calories taken (kcal)	**1476 (559)**
Female	1354 (522)
Male	1555 (574)
Goal to reach calories (%)	**65.8**
Female	66.9
Male	65.2
Total protein taken (g)	**51.3 (24.0)**
Female	46.7 (20.1)
Male	54.3 (25.6)
Protein/weight (g/kg)	**0.76 (0.41)**
Female	0.74 (0.44)
Male	0.77 (0.40)
Female, n=28; male, n=43.	

DISCUSSION

Our study revealed that inpatient cancer patients are not meeting their daily calorie and protein requirements. However, patients who received nutritional support had higher calorie and protein intake compared to those who did not receive nutritional support.

The incidence of malnutrition in cancer patients varies widely depending on several factors such as age, cancer type, and stage of cancer, with rates reported between 20% and 90% in the literature.[12–14] In our study, we found that 70.4% of the patients had experienced weight loss in the last 6 months and that 78.9% of the patients were malnourished based on the SGA values for malnutrition (Figure 2). This malnutrition rate is consistent with previous reports in the literature.

Indirect calorimetry is the recommended method for calculating the total energy needs of cancer patients who are at risk for malnutrition.[15] However, if indirect calorimetry is not available, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines suggest that other methods can be used.[6,16] In our study, we used the Schofield equation and activity rates to calculate the daily energy requirement of the patients, which was 2278 kcal.

Table 4. Nutritional Support for Patients			
	Nutritional Support		***P***
	Yes (n=16)	**No (n=55)**	
BMI (kg/m^2)	22.6 (4.1)	26.4 (5.1)	.008
Weight loss in the last 6 months (%)	10.8 (6.1)	8.2 (9.3)	.29
Total protein (gram)	75.4 (26.8)	44.3 (18.0)	<.001
Protein/weight (gr/kg)	1.24 (0.51)	0.61 (0.24)	<.001
Goal to reach calories (%)	76.7 (26.8)	62.7 (24.5)	.17
SOFA	0.44 (0.81)	0.18 (0.48)	.25
GCS	15	15	1.0
NRS < 3 (%)	4.8	95.2	.027
NRS ≥ 3 (%)	30.0	70.0	
Patient with comorbidity (%)	22.6	77.4	1.0
Patient without comorbidity (%)	22.5	77.5	
Patient with solid tumor/ without hematologic cancer (%)	28.9	71.1	.164
Patient without solid tumor/patient with hematologic cancer (%)	11.5	88.5	
Patient with metastasis (%)	27.8	72.2	.531
Patient without metastasis (%)	20.8	79.2	
Values are mean results. BMI, body mass index; GCS, Glasgow Coma Scale; NRS, Nutritional Risk Screening; SOFA, Sequential Organ Failure Assessment.			

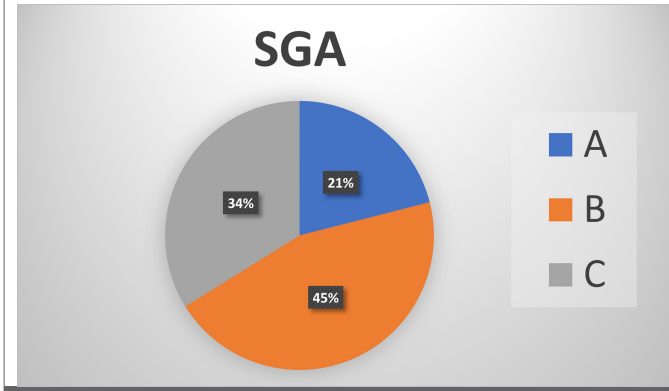

Figure 2. Distribution of patients' SGA values. SGA, Subjective Global Assessment.

However, the patients only consumed 1476 kcal, resulting in a rate of reaching the targeted calories of 65.8%. Patients who received nutritional support had a higher success rate of achieving the target calorie intake, with a rate above 75%.

There is no clear consensus on the optimal amount of protein that cancer patients should consume. However, the general recommendation is to consume at least 1 g/kg/day of protein, with a targeted protein intake of 1.2-2 g/kg/day.[17] In our study, we found that the average protein intake of the patients was only 0.76 g/kg/day. However, when patients received nutritional support, their protein intake increased to 1.24 g/kg/day. It is important to note that insufficient protein intake not only leads to loss of skeletal muscle but also affects metabolism. A study by Stobaus et al[18] demonstrated that cancer patients who consumed less than 1 g/kg/day of protein had 3.3 times higher 6-month mortality rate. The study also emphasized the importance of providing nutritional support to patients receiving chemotherapy.

According to our study, we observed that patients who received nutritional support had a lower BMI compared to those who did not receive nutritional support (22.6-26.4). We hypothesized that patients with a higher BMI may not have been diagnosed with malnutrition as they may not have experienced significant weight loss. This may have led to these patients being overlooked for nutritional support. Furthermore, research conducted by Pressoir et al[19] has shown that obese patients have an increased risk of malnutrition. Similarly, Prado et al[20] found that sarcopenia, a condition characterized by loss of muscle mass and strength, may also be associated with obesity. Therefore, we believe that nutritional support should not be ignored in patients with a relatively high BMI.

In conclusion, our study highlights a high incidence of malnutrition, with 78.9% of inpatient cancer patients experiencing malnutrition. We found that patients who did not receive nutritional support had a lower intake of both protein and energy compared to those who did receive nutritional support. Our findings suggest that providing nutritional support may be crucial in helping patients achieve their targeted nutritional values.

These results are consistent with previous research on the importance of nutritional support for cancer patients. Given the high prevalence of malnutrition in this population, it is important for healthcare providers to prioritize nutritional screening and support for cancer patients, particularly those at higher risk. Future studies may explore the most effective strategies for providing nutritional support to cancer patients and improving their nutritional outcomes.

By conducting a comprehensive evaluation of the nutritional status of cancer patients receiving in-hospital treatment, this study provides valuable insights into the factors that contribute to malnutrition in this population. The detailed measurements and assessments performed in this study enable a more individualized and tailored approach to nutritional interventions, ultimately leading to improved treatment outcomes and enhanced patient well-being.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Date: January 7, 2019, number: 189).

Informed Consent: Written informed consent was obtained from each patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.T., S.M.; Design – A.T., S.M.; Supervision – S.Ü.; Resources – A.T., S.M., S.M.; Materials – A.T., S.M., S.M.; Data Collection and/or Processing – S.M.Ç., K.U.; Analysis and/or Interpretation – A.T.; Literature Search – A.T.; Writing Manuscript – A.T.; Critical Review – S.Ü., S.M.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: There was no financial support or sponsorship provided for this study.

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CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.23064

Psoas Muscle Loss During Treatment is a Negative Predictive Factor in Gastric Cancer Patients

Hüseyin Furkan Öztürk, Süheyla Aytaç Arslan, Gonca Altınışık İnan, İpek Pınar Aral, Yılmaz Tezcan

Department of Radiation Oncology, Yıldırım Beyazıt University; Ankara Bilkent City Hospital, Ankara, Turkey

Cite this article as: Öztürk HF, Aytaç Arslan S, Altınışık İnan G, Aral İP, Tezcan Y. Psoas muscle loss during treatment is a negative predictive factor in gastric cancer patients. *Clin Sci Nutr.* 2023;5(2):76-84.

ABSTRACT

Objective: Our aim in this study is to examine the changes in the psoas muscle during the gastric cancer treatment process and to evaluate the effects on prognosis.

Methods: Twenty-eight gastric cancer patients underwent curative surgery, and chemoradiotherapy were analyzed. Changes were noted by calculating the psoas muscle areas before and after the cancer treatment. Patients were classified as high delta and low delta according to median change. The effect of muscle loss on progression-free and overall survival was examined using the logistic regression model.

Results: Psoas muscle loss was observed in all patients during the treatment. While the median psoas muscle area before treatment was 14.5 cm^2, it was calculated to be 11.8 cm^2 after treatment ($P=.0$).

In the high-delta group with excessive muscle loss, 3-year progression-free survival was 38%, compared with 80% in the low delta group ($P=.07$). The 3-year overall survival was found to be 42% in the high-delta group, while it was 84% in the group with less muscle loss ($P=.05$).

Conclusion: Muscle loss is a negative predictive factor in gastric cancer patients undergoing surgery and chemoradiotherapy. Dynamic psoas muscle area changes during treatment may play a role in survival.

Keywords: Adjuvant radiochemotherapy, concurrent radiochemotherapy, gastric cancer, nutrition therapy, sarcopenia

INTRODUCTION

Gastric cancer is the sixth most common cancer and the second cause of cancer death in 2018 Worldwide.[1] In Western reports, 5-year overall survival has been found 10%-30% in regional disease.[2,3] While sole locoregional failure is observed in 16% patients, this rate can increase to 36% in metastatic condition.[4] Surgery is the mainstay of gastric cancer treatment and adjuvant therapies are needed due to the local and distant recurrences. Today, total/subtotal gastrectomy and lymph node dissection with neoadjuvant and/or adjuvant chemotherapy or adjuvant chemoradiotherapy (CRT) is the standard care of therapy in locally advanced gastric cancer patients. While all these treatments like surgery, chemotherapy, and radiotherapy are improving oncological outcomes, they may also cause gastrointestinal toxicities and complications, resulting in loss of weight, lean body mass loss, and malnutrition.

Altered body composition in malnutrition usually manifests with a decrease in muscle mass, and this may lead to sarcopenia, a syndrome defined as progressive and generalized skeletal muscle loss, related to increased adverse outcomes.[5-7] Dual-energy x-ray absorptiometry, computed tomography scanning (CT), magnetic resonance imaging (MRI), and bioelectrical impedance (BIE) are validated methods used to measure skeletal muscle loss.[8] Several studies have shown that the psoas muscle area (PMA) in a single abdominal section can estimate the overall muscle mass in the whole body.[9,10] In studies with surgical or chronic patients, the sum of the right and left PMA has been shown to be an independent risk factor for adverse outcomes.[11-14]

The purpose of this study is to calculate the PMA loss during gastric cancer treatment as an indicator of sarcopenia and to examine the effect of this change on progression-free and overall survival.

This study was presented as an oral presentation at 11th International Gastrointestinal Cancers Conference in December 2011.

Corresponding author: Hüseyin Furkan Öztürk, e-mail: furkanozt@gmail.com

Received: March 08, 2023 Accepted: June 03, 2023
Publication Date: July 14, 2023

METHODS

Patients and Data Collection

Patients who received adjuvant chemo radiotherapy (CRT) after surgery for local gastric cancer were reviewed in a single institution, and a total of 28 patients, whose computerized tomography (CT) images could be obtained and allowed evaluation just before surgery and after the end of CRT, were recruited into this study. Clinically or pathologically proven stage 4 patients were excluded from the study. Age, sex, pathological staging, and survival data were collected for the entire cohort. Data on the chemotherapy regimens, treatment breaks, histopathological features, and type of surgery were also documented. The American Joint Cancer Committee on Cancer (AJCC) criteria (8th edition) was used for staging. The patients were followed up every 3 months for 2 years and every 6 months thereafter. This study was approved by the local ethics committee of Yıldırım Beyazıt University Medical School (Date: December 24, 2020, No: 26379996/136). Locoregional recurrence was defined as recurrence at the anastomosis and regional lymph nodes. Any radiological or pathologic verified metastases outside of the radiation portal or solid organs like liver, lung, brain, or malign ascites were defined as distant recurrences. Intergroup 0116 study CRT protocol was used for the majority of the patients.[15] Patient demographics, pathological reviews, radiotherapy and chemotherapy data, surgical information, and CT images and reports were collected from the hospital registry and patient files, retrospectively. Overall survival was calculated from the date of surgery to death, and progression-free survival was determined from the date of surgery to local or distant progression.

Assessment of Psoas Muscle Area

Psoas muscles were delineated at the third lumbar vertebrae level where both pedicles of this vertebrae are completely visible in 2 different CT sets as before and after on axial images for each patient (Figure 1). These CT images were obtained from the local hospital registry database. ExtremePacs Teleradiology (ExtremePacs, Ankara, 2017) software program was used for measurements with the region of interest (ROI) tool in square centimeter.

Main Points

- Psoas muscle changes during gastric cancer treatment may play a role in treatment success.
- Dynamic measurement of psoas muscle mass over the course of treatment may better predict nutritional status than cross-sectional measurement.
- Psoas muscle loss during gastric cancer treatment adversely affects progression-free and overall survival.

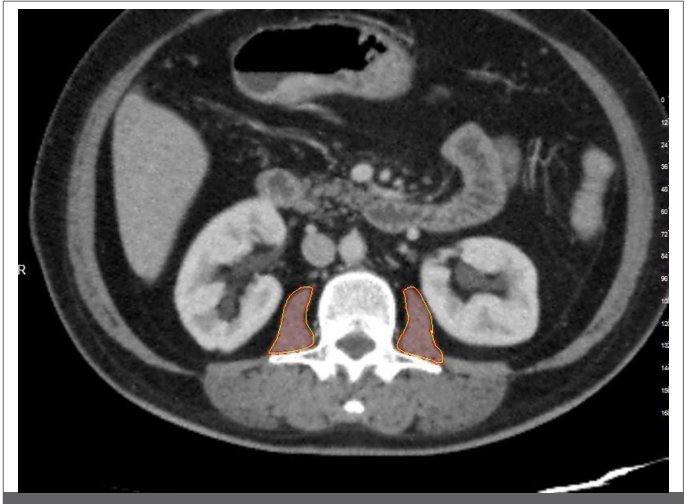

Figure 1. Delineation and measurement of psoas muscle area (PMA).

Predetermined Hounsfield units −30 and +400 were used to separate the psoas muscle from other abdominal structures.[16] Total PMA was defined with a sum of the area of the right and left psoas muscles as an indicator of muscle loss in both preoperative and post-adjuvant therapy CT scans. The changes were recorded as delta PMA (Δ PMA), using [(PMA (cm^2) after CRT-PMA (cm^2) before CRT)/PMA (cm^2) after CRT] × 100 formula. Median proportional PMA changes were calculated. These data were dichotomized due to this median change as high- or low-Δ PMA groups.

Statistical Analysis

Categorical data are presented in count and proportion. The median and minimum-maximum values were used for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. The variables were compared with the Student's *t*-test, Fisher's exact test, and Wilcoxon rank-sum test between groups. Kaplan–Meier test for survival estimation and log-rank test for survival comparisons were performed. The proportional PMA changes were dichotomized as ≥20% or <20% according to the median proportional change 20%. Statistical significance was considered at a P value ≤ .05.

RESULTS

Patient Characteristics

Gastric cancer patients treated in a single institution radiation oncology department were reviewed. Metastatic patients at the time of diagnosis and the patients whose images were not found in the hospital's local image database were excluded. Patient characteristics and demographics are listed in Table 1. Patient characteristics were quite well balanced. Totally, 28 patient data and 56 CT images were analyzed. The median age was found as 58 (range: 30, 78). The majority of patients were male (21,

Table 1. Patient Demographics and Clinical Data				
	Overall	**High-Δ PMA Group**	**Low-Δ PMA group**	***P***
Sex, n (%)				
Female	7 (25)	3 (23.1)	4 (26.7)	1
Male	21 (75)	10 (76.9)	11 (73.3)	
Age, median (minimum–maximum)	58 (30-78)	56 (45-74)	66 (30-78)	.78
≥65 (n)	13	5 (38.5)	8 (53.3)	.54
<65 (n)	15	8 (61.5)	7 (46.7)	
Stage				
I and II	10	3 (23.1)	7 (46.7)	.25
III	18	10 (76.9)	8 (53.3)	
Tumor location, n (%)				
Cardia	7 (25)	5 (38.5)	2 (13.3)	.13
Fundus	2 (7.1)	1 (7.7)	1 (6.7)	
Corpus	6 (21.4)	4 (30.8)	2 (13.3)	
Antrum and pylorus	13 (46.4)	3 (23.1)	10 (66.7)	
Surgery, n (%)				
Total gastrectomy	13 (46.4)	9 (69.2)	4 (26.7)	.024*
Subtotal gastrectomy	15 (53.6)	4 (30.8)	11 (73.3)	
Dissected LN (median)	27 (4-68)	36 (17-68)	21 (4-51)	.14
RT technic, n (%)				
Conformal	24	11 (84.6)	13 (86.7)	1
IMRT	4	2 (15.4)	2 (13.3)	
RT dose (median)	45 Gy	45 Gy (41.4-50.4)	45 Gy (36-45)	
Concomitant CT, n (%)				
Yes	25 (89.3)	11 (84.6)	14 (93.3)	.58
No	3 (10.7)	2 (15.4)	1 (6.7)	
CT protocol, n (%)				
FUFA	18 (64.3)	7 (53.8)	11 (73.3)	.65
Xelox	7 (25)	4 (30.8)	3 (93.3)	
Unknown	3 (10.7)	2 (15.4)	1 (6.7)	

CT, chemotherapy; FUFA, 5-FU and folinic acid; IMRT, intensity-modulated radiotherapy; LN, lymph nodes; PMA, psoas muscle area: high-delta PMA ≥20, low-delta PMA group <20; RT, radiotherapy; Xelox, capecitabine and oxaliplatin; *, statistically significant.

75%) and total/subtotal gastrectomy was performed without any surgical positivity except for 2 patients. No patient received neoadjuvant chemotherapy. One patient was staged as 1, and 9 and 18 patients were staged 2 and 3, respectively. Three patients were not able to complete adjuvant CRT because of gastrointestinal toxicity. These 3 patients received 3600 cGy, 3780 cGy, and 4140 cGy. One patient received 5040 cGy because of the margin positivity. For all remaining patients, 4500 cGy RT concurrent with chemotherapy were administered.

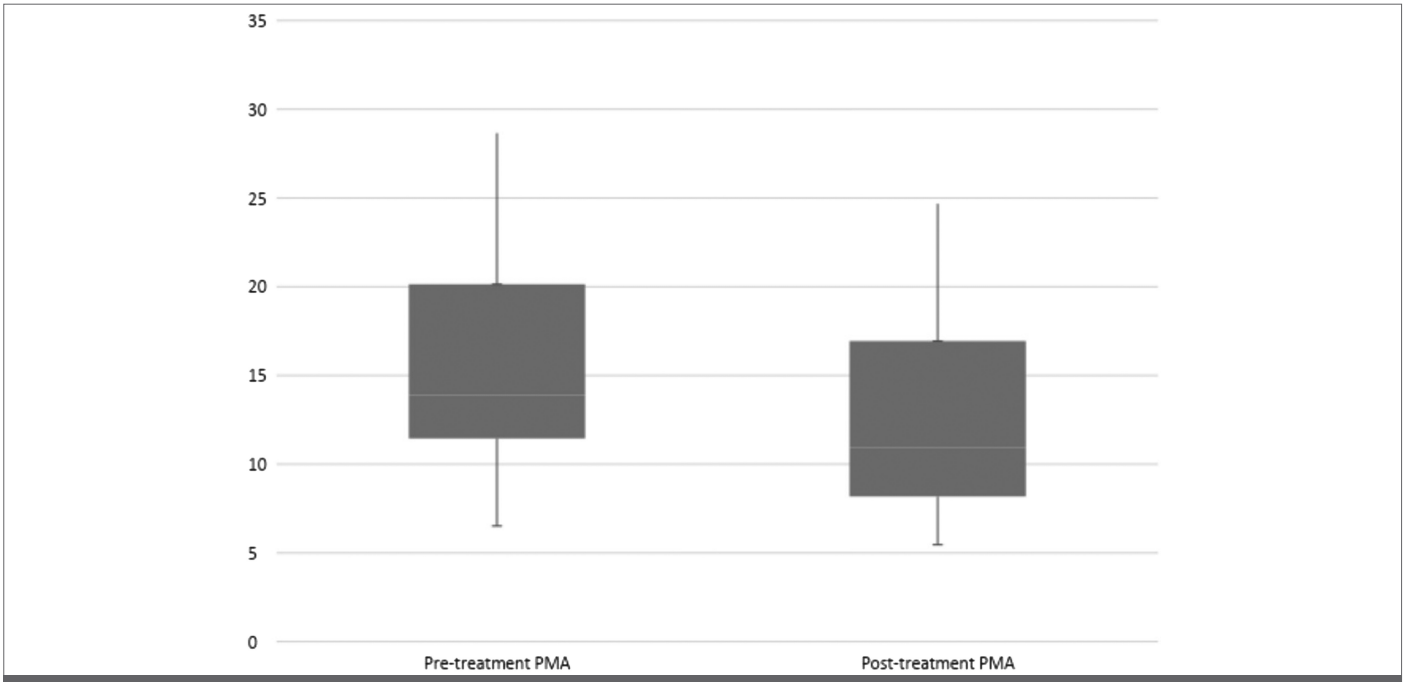

Figure 2. Pre-treatment and post-treatment psoas muscle area changes (cm^2, $P < .001$).

Psoas Muscle Changes and Survival

Median preoperative PMA was calculated as 14.5 cm^2 and was found as 11.8 cm^2 after completion of surgery and adjuvant CRT. This change in PMA was statistically significant ($P = .0$) (Figure 2). All the patients showed a psoas muscle decrease, and the median proportional change

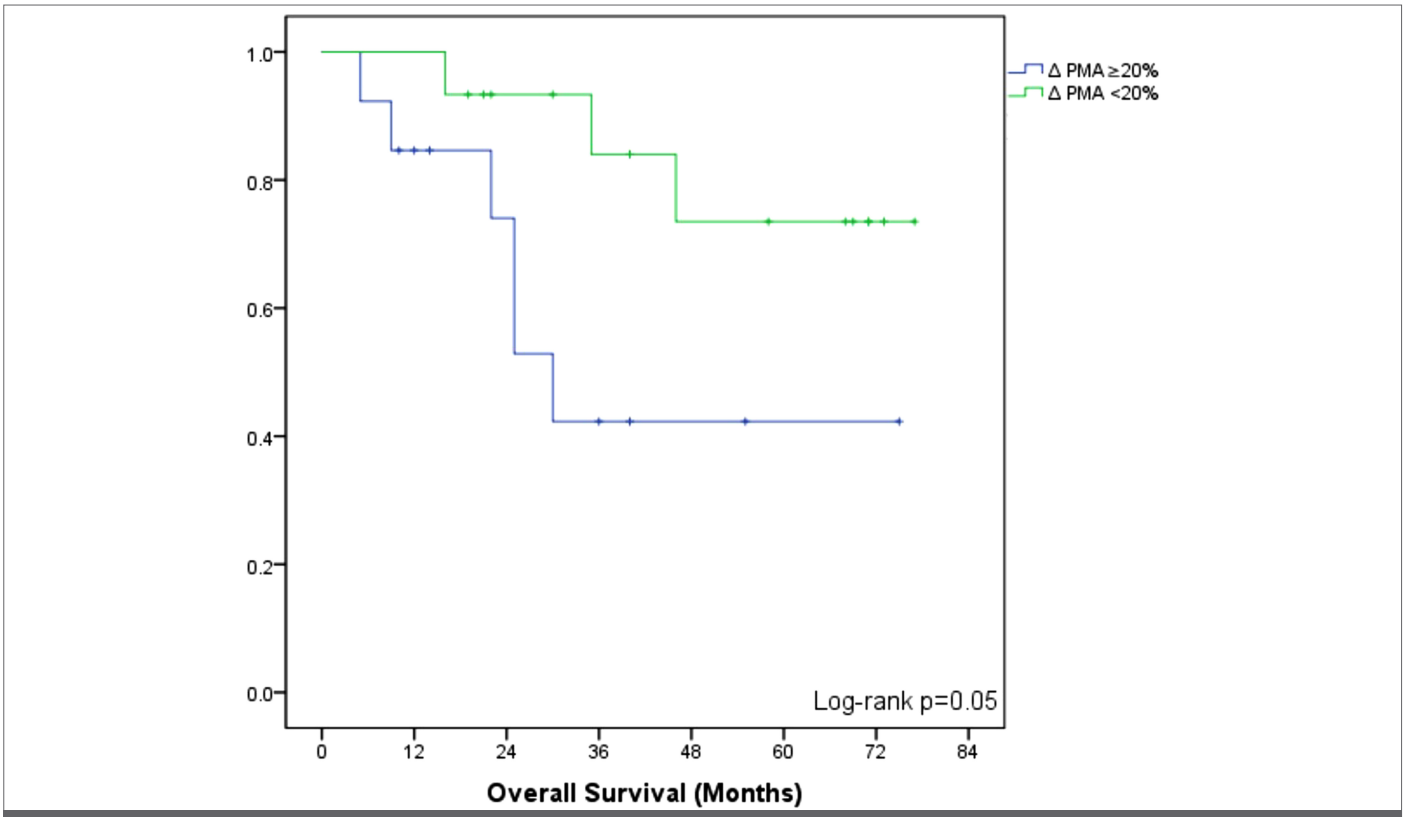

Figure 3. Kaplan–Meier survival curves for overall survival for high- and low-Δ psoas muscle area (PMA) groups. The 3-year overall survival rates were 42% and 84% in the high- and low-Δ group, respectively ($P = .05$).

was found as 20%. In 13 patients, this change was equal to or higher than the median change. After dichotomization regarding the median proportional change of 20%, the patients were classified into 2 groups as low- and high-Δ PMA.

Three-year overall survival was found to be 65%, and the median survival has not been reached at the time of analysis. Three-year progression-free survival was calculated as 62% for the entire cohort. Univariate analysis revealed that high-Δ groups are related to worse survival. Three-year overall survival rates were found to be 42% and 84% in the low- and high-Δ group, respectively ($P=.05$) (Figure 3). Three-year progression-free survival rates were also found lower in the high-Δ PMA group as 80% vs. 38% ($P=.07$) (Figure 4)

In our cohort, 10 patients were at stages 1 and 2, 18 patients were at stage 3. Three-year overall survival rates were found to be 90% and 50% between early- and late-stage groups, respectively ($P=.06$). We also examined the effect of age on survival, and no difference was found in survival between the patients older than 65 and the others ($P=.74$).

DISCUSSION

This current study showed that psoas muscle loss during treatment affects survival negatively in non-metastatic gastric cancer patients.

Despite the emerging new strategies, historically locally advanced gastric cancer treatment includes surgery +/− CRT or perioperative chemotherapy plus surgery. During all these treatments, oral intake can be deteriorated due to the disease itself, surgical morbidity, and toxicities. In the cornerstone, Intergroup 0116 trial, 33% grade 3 gastrointestinal toxicity was observed during adjuvant CRT,[15] which brings a malnutrition risk and weight loss, especially in this patient group.

Malnutrition is one of the most important prognostic factors in cancer patients. Some studies showed an adverse relationship between malnutrition and survival.[17,18] This syndrome is not only related to poor oncological outcomes but also associated with deterioration of the immune system, delayed wound healing, higher infection rate, and longer hospital stay.[19-22] All these negative factors may also diminish the patient's compliance with the

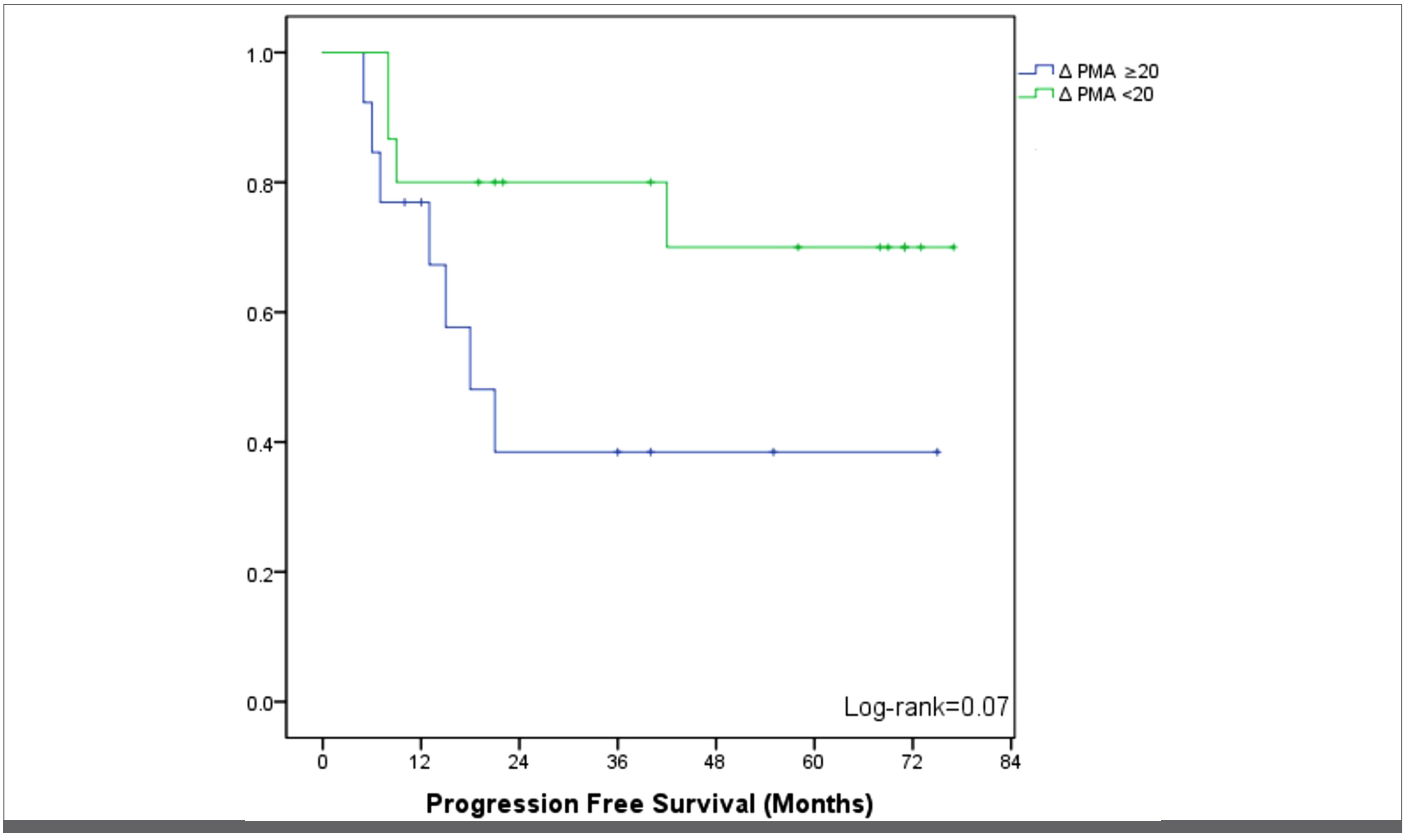

Figure 4. Kaplan–Meier survival curves for progression-free survival for high- and low-Δ psoas muscle area (PMA) groups. The 3-year progression-free survival rates were 38% and 80% in the high- and low-Δ PMA group, respectively ($P=.07$).

treatment. In the recent GLIM consensus, reduced muscle loss was accepted as one of the strongest phenotypic criteria of malnutrition. Chronic inflammation and reduced food intake lead cancer patients to altered metabolism and body composition that manifests with a decrease in any marker of muscle mass like fat-free mass, muscle mass index, or body cell mass.[23]

There are several techniques to measure lean body mass and detect muscle loss. Magnetic resonance imaging (MRI) and CT are the best methods to quantify the skeletal muscle mass (SMM) highly correlated with cadaveric measurements.[24,25] Despite the high accuracy and reproducibility, these techniques are not easy to perform for each patient and have a high cost of instrumentation. Bioelectric impedance is also used for this purpose. This noninvasive technique measures the body composition indirectly using electric signals.[26] This method is faster and easier than whole-body MRI and CT, but this also needs extra effort and cost. The psoas muscle is one of the most important muscle groups for the perpendicular system. This muscle group can be evaluated on CT images for staging and follow-up periods, without an extra process and that can bring an easier evaluation of muscle mass status instead of the whole-body muscle mass evaluation. So, calculating the PMA for detecting reduced muscle mass on CT images in cancer patients seems to be reasonable. In recent trials, measuring PMA on CT images was found as a non-invasive tool to predict SMM.[16,28]

In the cross-sectional analysis of healthy donors with a mean age of 32.5 before liver transplantation, the cutoff values for PMA in the Turkish patient population were found to be 16 cm^2 for the male patient group and 9 cm^2 for the female population.[28]

Some studies showed that perioperative nutritional support for gastrointestinal malignancies reduces the number and severity of postoperative complications even if they do not have any sign of malnutrition.[29,30] In a study of 100 patients undergoing surgery for colorectal cancer, the number of patients with grade 3 or higher perioperative complications was found to be significantly higher in the sarcopenic group with 8to5 patients compared to the non-sarcopenic group.[11] In a recently published meta-analysis of 81 studies, mostly consisting of gastrointestinal system (GIS) cancers and investigating the relationship between muscle mass loss and mortality, hazard ratio (HR) for mortality was 1.41 (95% CI, 1.24-1.59) in all cancer patients, while this rate was found to be 1.56 (1.36 to 1.78) in patients with GIS cancer.[31] These studies also underlie the important role of nutritional support on morbidity and mortality, especially in gastrointestinal cancers. In this study, we hypothesized that psoas muscle loss as a sign of SMM loss, sarcopenia, and malnutrition during the treatment is a negative prognostic factor on survival.

Cheng-Le Zhuang et al[32] retrospectively reviewed the gastric cancer patients who had undergone curative surgery, and they found that low skeletal muscle index, calculated with PMA and patient height, was related to postoperative severe complications as an independent risk factor. They also found sarcopenia as an independent risk for overall and disease-free survival especially in stage 2 and 3 patients, as well. They found the 3-year overall survival to be 53.8% vs. 73.6% ($P < .001$) and 3-year disease-free survival to be 54.7% vs. 73.5% ($P < .001$) in favor of patients without sarcopenia. A similar study was held in bladder cancer patients and sarcopenia was also found as related to a longer hospital stay, higher rate of perioperative complications, and worse overall survival.[33] Park et al[16] also found preoperative low PMA as a negative risk factor for overall survival in surgically treated esophageal cancer patients. They found 3-year overall survival 64.9% in the high-PMA group vs. 37.1% in the low-PMA group ($P=.002$). The results were similar in patients with upper urinary tract urothelial carcinoma among preoperative cases[34] and rectal cancer patients before neoadjuvant CRT.[35] A systematic review of 13 studies and meta-analysis also denote that sarcopenia is significantly related to all-cause mortality in hepatocellular cancer patients.[36]

These trials in different types of cancer patients showed that muscle loss is related to poorer outcomes, but all these trials were based on only a single measurement of the PMA before surgery or CRT. In this trial, we aimed to assess the change in the PMA before and after the whole cancer treatment modalities, including surgery, chemotherapy, and radiation therapy, and to investigate the effects of the change on survival as well. All these treatments have serious surgical complications and gastrointestinal side effects like nausea, vomiting, and diarrhea, and these treatment-related factors may let the patients get deteriorated; so, we tried to evaluate the impact of all treatment procedures on SMM and we found a 2.7 cm^2 PMA decrease during gastric cancer treatment and an inverse relationship between PMA loss and overall survival was found (42% vs. 84%, $P=.05$).

Two studies from the United States and South Korea examined the change of psoas muscle volume (PMV) and area and its effects on patients treated with chemotherapy and radical cystectomy for muscle-invasive bladder cancer and surgically treated esophageal cancer patients, respectively. Zargar et al[37] from the United States measured all psoas volumes and calculated the change during

the neoadjuvant chemotherapy undergoing radical cystectomy in bladder cancer. In this study, median 5% PMV and higher loss are associated with decreased but not statistically significant complete and partial pathological complete response rates and overall survival. Park et al[16] also focused on the prognostic effect of the PMA change in esophageal cancer patients after 1 year who underwent surgery, and they found that psoas muscle loss of more than 10% was a significant risk factor for overall survival. In the low-Δ PMA group, they found a 3-year overall survival rate of 58.2% and 18.9% in the high-Δ PMA group (P=.049). Three-year disease-free survival rates were 47.3% and 18.8% in favor of low-Δ PMA group. We have found 3-year overall and progression-free survival rates as 84% vs. 42% (P=.05) and 80% vs. 38% (P=.07) in favor of low-Δ PMA group. In our small cohort, we also examined the effects of age and stage on overall and disease-free survival. There was a trend for early-stage and younger ages, but we could not find a statistical difference. The small number of cohorts should be the possible explanation, and studies with a larger number of age groups may help to clarify the relationship between age and psoas muscle loss on survival.

The limitations of our study are primarily its retrospective design and possible selection bias. Although patients who were treated in a single center and whose full data could be accessed were included in this study, our findings should be confirmed by prospective studies. Second, although our study includes a homogeneous patient group, the relatively small number of patients is another weakness of our study. The strength of our study is that it evaluates muscle loss over a treatment period rather than a cross-sectional evaluation at a single moment and reveals the effect of this change on treatment more clearly. Lastly, sarcopenia is an age-related syndrome characterized by a loss of muscle mass and strength, and the onset of sarcopenia often begins in middle age due to an unbalanced diet in association with a lack of physical activity. Therefore, age-related muscle wasting may co-exist with treatment-related muscle wasting. In order to make this distinction, in studies with a larger number of young patients, the amount of muscle loss due to treatment and its effect on treatment can be shown more clearly.

Despite the uncertainties in measuring methods, accessibility, and cutoff values of reduced muscle mass, there is strong evidence to use it as a single phenotypic criterion in the diagnosis of malnutrition.[6] In the current study, we have tried to evaluate the dynamic changes, not a sectional evaluation because our patient population is different from the other chronic diseases and older adults. These gastric cancer patients generally have more acute/subacute reversible changes due to the treatments and treatment-related toxicities, and so dynamic measurements should be better than sectional measurement to estimate survival or morbidity.

This study examines dynamic PMA changes and their impact on survival in gastric cancer patients. These outcomes highlight the importance of muscle loss changes on survival and nutritional assessment and support in locally advanced gastric cancer patients during all treatment steps. On behalf of emerging data, muscle loss cutoff values and methods should be validated in a prospective randomized trial as a predictive factor, and this may lead us to give further attention to nutritional status as a cause and/or effect in cancer patients. Further prospective trials are needed to prove these retrospective small cohort data.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University (Date: December 24, 2020, Number: 26379996/136).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.F.Ö.; Design – H.F.Ö.; Supervision – S.A.A., Y.T.; Resources – i.P.A., G.A.İ.; Materials – H.F.Ö.; Data Collection and Processing – H.F.Ö., G.A.İ., İ.P.A.; Analysis and Interpretation – H.F.Ö., İ.P.A.; Literature Search – H.F.Ö., G.A.İ.; Writing Manuscript – H.F.Ö.; Critical Review – S.A.A.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

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CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.22048

Nutrition Support Team Can Reduce Nutritional Product Expense: An Implementation in a Neurology Intensive Care Unit

Zeynep Parlak Özer[1], Tuba Ustaoğlu[2]

[1]Department of Gastronomy and Culinary Arts, Hasan Kalyoncu University, Faculty of Fine Arts and Architecture, Gaziantep, Turkey
[2]Department of Nutrition and Dietetics, Sanko University, Faculty of Health Sciences, Gaziantep, Turkey

Cite this article as: Parlak Özer Z, Ustaoğlu T. Nutrition support team can reduce nutritional product expense: an implementation in a neurology intensive care unit. *Clin Sci Nutr.* 2023;5(2):85-90.

ABSTRACT

Objective: "Quality and Accreditation for Qualified and Effective Health Services" of the Health Transformation Program of Turkey mandated the establishment of nutrition support team in hospitals in 2016.
Methods: Nutrition support team was set up for the Neurology Intensive Care Unit of Gaziantep 25 Aralık State Hospital at the end of 2016 to manage the complex nutritional needs of the patients. Pre-nutrition support teams' nutritional requirements were defined by the patients' doctors, whereas after 2016 nutritional therapy and interventions were defined by doctors, dieticians, and nurses of nutrition support team.
Results: This study evaluates the effectiveness of nutrition support team on the hospital cost and improvement of the treatment. The parenteral nutrition products in energy decreased from 75.98% to 39.02% and the enteral products in total energy increased from 24.02% to 60.98% after nutrition support team. The total product expenses decreased from 80 029.53 ₺ to 75 550.00 ₺.
Conclusion: The Hospital Quality Standards require the establishment of the nutrition support team which helps to decrease nutrition product expenses and increase energy supply via enteral nutrition products instead of parenteral nutrition products.

Keywords: Nutritional product expense, enteral, parenteral nutrition, nutrition support team, hospital cost

INTRODUCTION

Nutrition support team (NST) is a multidisciplinary, inter multidisciplinary, transdisciplinary team consisting of doctors, dieticians, nurses, and pharmacists.[1] The main purpose of the NST is to advise the healthcare professionals responsible for the nutritional needs of patients.[2] Nutrition support team reports to the hospital management on cost savings and quality.[3]

Research studies are conducted to evaluate the effectiveness of the NST on the incidence of infection, mortality, and morbidity caused by diseases related to malnutrition, length of hospital stay, and nutritional deficiencies.[4,5] Furthermore, the effects of NST on the direct cost of the products and the cost of secondary complications caused by infections and metabolic complications are investigated.[6-8]

"Quality and Accreditation for Quality and Effective Health Services" is included in the Health Transformation Program in Turkey, and in this connection "Regulation on the Development and evaluation of Quality in Healthcare" was published in the official gazette 29399 dated 27.06.2015.[9] "Quality Standards in Health Hospital-Version 5" prepared by the Department of Quality and Accreditation in Health Care Services stipulates "making arrangements for the nutritional support needs of patients by establishing NST".[10]

The pre-NST patient's needs for enteral nutrition and parenteral nutrition and monitoring the therapeutic effects and side effects of nutrition therapy were physician-centered, whereas post-NST services are provided by multidisciplinary team members.[11]

The evaluation of the effectiveness of NST in Turkey is important for the development of new policies and practices.

The objective of the study is to compare the total enteral parenteral nutrition energies and the costs between the periods: 2 years before and 2 years after the establishment of NST in which the team actively worked in the Neurology Intensive Care Unit (ICU).

Corresponding author: Zeynep Parlak Özer, e-mail: zeynep.parlakozer@hku.edu.tr

Received: October 24, 2022 Accepted: February 21, 2023
Publication Date: March 30, 2023

METHODS

The research was approved by the Gaziantep University Clinical Research Ethics Committee on May 27, 2020 (Decision number 2020/121).

This study was planned as a retrospective study. The change in the nutritional product usage and expense of the Neurology ICU of 25 Aralık State Hospital which accepts neurological diseases such as acute stroke and Parkinson, with a bed capacity of 10 patients, over the years (2015-2018) have been evaluated.

The nutritional requirements of the patients were defined by the doctors of the Neurology ICU before NST. After 2016, nutritional requirements were defined by multidisciplinary NST, whose members consist of a doctor, a dietician, and a nurse.

The monthly consumption and the cost data of the enteral and parenteral nutrition products were obtained for pre-NST and post-NST periods from the automation system in Excel format. The annual budget and the budget allocated for the purchase of medical drugs were obtained from the chief physician of the hospital.

Ready-to-use nutritional products were included in the enteral product cost as well as ready-to-use 3-chamber bag systems containing amino acid, glucose, and fat emulsions. The expense of manpower and disposable medical supplies were not taken into account.

Calculation of Product Energies, Protein, Product Expenses, Percentage of Expenditure in Hospital Budget and, in the Pharmaceutical Budget

The total energy contents of the products were calculated by multiplying the energy content in the packaging by the amount of product used.

Main Points

- This study is a single study examining the effect of nutrition support team on the hospital expences and the product use.
- The NST increased the total energy supplies to the patients and the energy supplied from the enteral nutrition product instead of the parenteral nutrition products.
- The NST reduced the total product cost and proportions of the product cost in drug budget and hospital budget.
- The necessity of the Hospital Quality Standards of NST helped to save costs in the hospital.

The total protein of enteral products was calculated by multiplying the protein content in the packaging by the amount of enteral nutrition product used.

The product cost is calculated separately for each item by multiplying the price of the product by the amount of product used.

$$\text{The percentage cost in the hospital budget}(\%) = \frac{\text{Total monthly product cost}}{\text{Hospital budget}} \times 100$$

$$\text{The percentage cost in the drug budget}(\%) = \frac{\text{Total monthly expenses}}{\text{The drug budget}} \times 100$$

RESULTS

The energy, protein content, and costs of the enteral and parental products before and after NST, the percentage of the expenses in the drug budget, and the percentage of the expenses in the hospital budget are given in Table 1.

Energy

The total energy provided by the enteral and parenteral products in pre-NST was 3 013 793 kcal. The enteral nutrition products and parental nutrition solutions provided 24.02% and 75.98%, respectively (Figure 1A).

In post-NST, 60.98% of 3 424 303 kcal energy was provided by enteral nutrition products; 39.02% was provided by parenteral nutrition products (Figure 1B).

Protein

Proteins obtained from enteral products before and after NST are 37 385.2 g and 97 972.3, respectively.

Product cost

The costs of the enteral and parenteral nutrition products before NST were 5461.00 ₺, and 74 267.00 ₺, respectively. The costs of the enteral and parenteral nutrition products after NST were 15 163 ₺, and; 60 387.75 ₺, respectively.

The total cost of the products decreased from 80 029.53 ₺, to 75 550.00 ₺,.

While the enteral product cost was 7.30% of the total product cost before the NST, post-NST it increased to 20.07%. The cost of parenteral nutrition products decreased from 92.7% of the total cost to 79.03% (Figure 1C).

Table 1. Enteral and Parenteral Nutrition Products Energy, Protein, Cost, Percentage of Products Cost in Drug Budget, and Percentage of Product Cost in Hospital Budget

	2015-2016			2017-2018		
	Enteral Nutrition Products	Parenteral Nutrition Products	Total	Enteral Nutrition Products	Parenteral Nutrition Products	Total
Energy (kcal)	724 143	2 289 650	3 013 793	2 089 783	1 337 520	3 424 303
Energy (%)	24.02	75.98		60.98	39.02	
Protein (g)	37 385.2			97 972.3		
Cost (₺)	5761.00	74 267.00	80 029.53	15 163	60 387.75	75 550.00
Cost (%)	7.30	92.7		20.07	79.03	
Percentage of product cost in drug budget (%)	0.16	2.02	2.18	0.06	1.54	1.61
Percentage of product cost in hospital budget (%)	0.007	0.091	0.09	0.008	0.06	0.036

Percentage of product cost in drug budget

Pre-NST costs of the enteral and parenteral nutrition products in the drug budget were 0.16% and 2.02%, respectively.

Post-NST costs of the enteral and parental nutrition products in the drug budget were 0.06% and 1.54%.

The total cost of the enteral and parenteral nutrition products in the pharmaceutical budget decreased from 2.18% to 1.61%.

Percentage of product costs in the hospital budget

The pre-NST costs of the enteral and parenteral nutrition products in the hospital budget were 0.007% and 0.09%, respectively.

The post-NST costs of the enteral and parenteral nutrition products in the hospital budget were calculated as 0.008% and 0.06%, respectively.

The total cost in the hospital budget decreased from 0.1% to 0.04%.

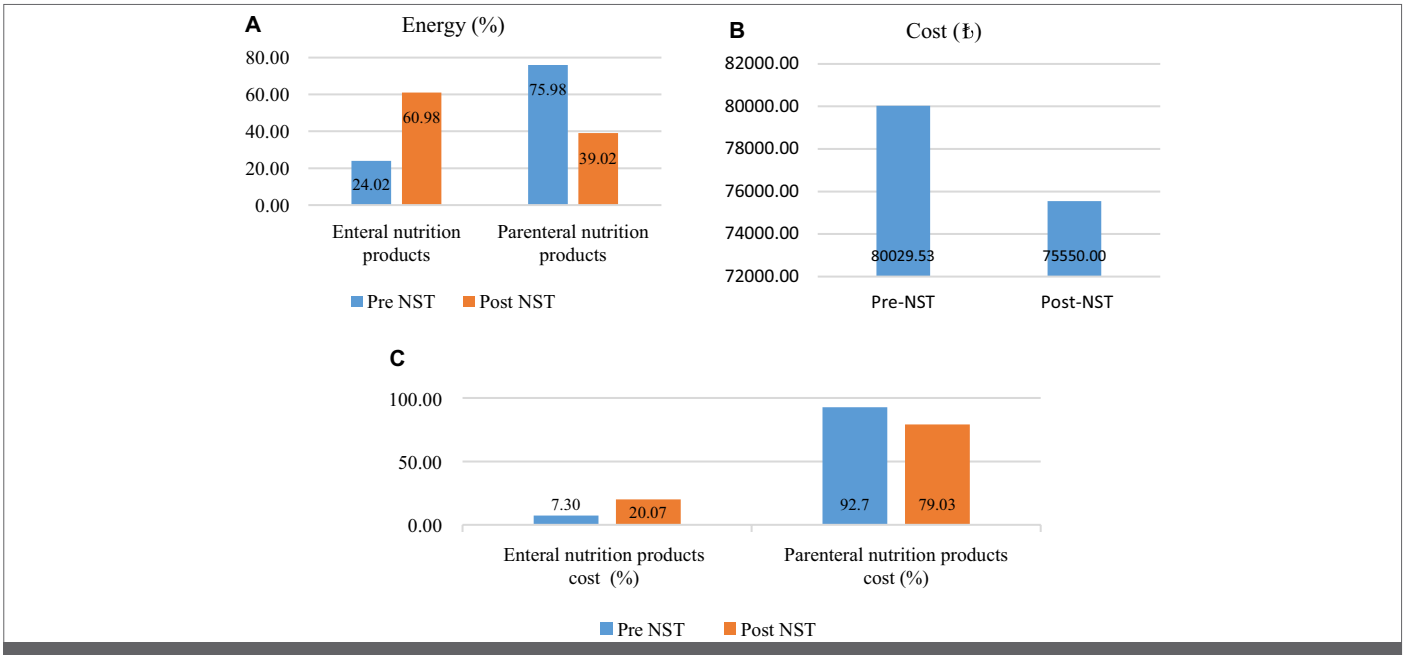

Figure 1. (A) Energy (%), (B) total cost w, and (C) enteral, parenteral nutrition products cost (%).

DISCUSSION

Malnutrition increases healthcare spending.[12] Prevention of diseases related to malnutrition also contributes to cost savings.[4] Nutrition support has positive effects on malnutrition, morbidity, mortality, length of hospital stay, and reduction of recovery time.[7]

The prevalence of malnutrition is 23.9% in hospitalized neurology patients and 52% in ICU.[13] In a study by Hafsteinsdóttir et al.[14], it was determined that 34% of the patients were at risk of malnutrition, 7% were malnourished, and 59% were well-nourished according to Mini Nutritional Assessment (MNA) on the first day of hospitalization in the Neurology ICU. However, 10 days after hospitalization, 57% of the patients were found to be at risk of malnutrition, 22% were undernourished, and 21% were well fed. It has been determined that the risk of malnutrition in the Neurology ICU increases with the length of hospital stay.[14]

In our study, it was determined that the intervention of NST increased the total energy and protein obtained from enteral nutrition solutions. It was found that the total energy obtained from the products also increased. It has been reported in the literature that NSTs provide more energy and protein.[15,16]

In addition to the increase in the total energies provided, the presence of NST has been found to shorten the time to start feeding and to achieve higher percentages of the energy and protein intakes.[11] Our study does not take into consideration the number of patients; we considered only retrospectively the total product use and cost. Since the volume and energy differences of the enteral and parenteral nutrition solutions used are taken into consideration, the energy provided for each product used was calculated and comparisons were made on this basis.

During the periods when the NST worked actively, the total energy provided was higher than the pre-NST.

Gönderen et al. reported that the use of parenteral nutrition of the nutritional support supplement decreased by 30%, the number of patients using enteral nutrition products increased by 42%, and this reduced the total nutritional cost.[17] Total Parenteral Nutrition (TPN) increases the cost of hospitalization.[18] Multidisciplinary decision-making on the use of parenteral nutrition products reduces hospital costs.[19] It has been reported that the nutritional support team reduced the use of inappropriate parenteral products from 16.5% to 8.9%. In a study examining retrospective nutrition records, it was reported that 14 of 176 people who received TPN within 12 months used inappropriate total parenteral nutrition for a total of 87 days, and if they received enteral nutrition solution support with the recommendation of the NST, the expense would be $2430. It has been found that stopping it prevents $45 186 additional hospital expenses.[20]

It has been determined that NST can prevent the use of inappropriate parenteral nutrition products.[21] In another study, the effect of the nutritional support team on the use and cost of the product was evaluated, and it was found that the use of parenteral nutrition products was reduced and the cost per patient decreased from £100 to £55.[6] In our study, direct product cost was studied, but in the light of the literature, it is known that in addition to the direct cost of parenteral nutrition, the complications associated with parenteral nutrition and developing complications also incur additional costs.[20]

The energy provided by the nutritional products after NST increased and the product cost decreased. This was due to the use of enteral nutrition products with lower cost isocaloric or hypercaloric options instead of ready-to-use parenteral nutrition bags. Since the enteral nutrition products are more affordable than the parenteral nutrition, reducing the use of high-priced parenteral nutrition solutions results in a reduction in NST medical expenses.[22] While more energy can be provided with the right product selection and rational use, product expense can be reduced.

The NST has the potential to positively impact enteral nutrition management in ICU, by continuing education and nutrition management protocols.[23]

Cost-effectiveness studies show that money can be saved, but nutritional intervention does more than saving money, such as improving disease-related malnutrition, improving quality of life, and preventing secondary complications.

Kennedy and Nightingale evaluated the tangible cost impact of the nutritional support team, use of the parenteral nutrition, and reduction of parenteral nutrition-associated sepsis resulting in a gain of £50.715. In this study, tangible costs, medical equipment, examinations, and medication costs are included.[3] In our study, only the cost of the products was calculated, and the equipment used was not added to the expense. In our study, since the energy components of nutritional support products are not standard, the number of products used was not compared, the energy provided with the products was compared and the direct effect of the NST on the product expense was investigated.

Cost-benefit analysis revealed a $4.20 benefit for every $1 invested in NST management.[23]

The duties of health professionals in the NST in hospitals may differ.[1] Following the hospitalization of a patient, the nutritional status is evaluated by the responsible nurse, and an electronic health record is created for the nutritional status evaluation. Nutrition support team interviews the patient after the review of the health record. Physician in the NST determines the route of nutrition of the patient with nutritional indicators. The dietitian determines the nutritional needs, makes the product selection, and consults the doctor about the dose of the product. The physician, dietitian, and nutrition nurse follow-up together on the complications related to nutrition. In addition to keeping electronic nutrition records of each patient, the nutrition nurse gives approval electronically for the product to be released from the hospital pharmacy after the request of the patient's doctor. The products released from the pharmacy are checked by the nurse. In cases of the wrong type and dose, the nurse rejects the delivery of the product from the pharmacy and can send a message to the relevant physician and pharmacy with the reason for the rejection. This ensures that the wrong product use, excess and unavailable product requests are prevented. It is reported in the literature that the use of electronic medical records can reduce nutritional costs.[8]

The NST evaluates the patient's nutritional status, calculates the patient's needs, determines the route of nutrition and product selection, and gives approval when the recommended product is released from the hospital pharmacy. The electronic nutrition management record and electronic nutrition administration record within the electronic medical record system used in the hospital are very important in terms of confirming the accuracy of the product delivery from the pharmacy and following the implementation of the recommendations of the NST.

The use of nutrition products in the neurology ICU, whose number of beds did not change for 4 years, was evaluated in the study. In the NST, the dietitian and nurse carry out the daily patient evaluation together with the responsible physician of the ICU. The pharmacist is not in the NST, but in the nutrition committee to purchase the hospital nutrition products. With the active work of the NST, the use of parenteral nutrition products decreased; it was found that the use of enteral nutrition products increased and the total energy given was increased. It has been shown that with the rational use of products, the cost can be reduced and the benefit increased.

It has been determined that while providing more energy, the product's expenses are decreased. This is due to the use of enteral nutrition solutions with lower unit prices instead of the use of parenteral products with a high unit price. On the other hand, it is considered that feeding by parenteral nutrition products consists only of macronutrients and needs to be supplemented by vitamins and minerals into products pocket, which leads to other tangible costs.

The total energy given before the NST is 3 013 793 kcal, and the energy given after the NST is 3 424 303. Total product costs before and after the NST are 80 029.54 ₺, and 75 550.00 ₺, respectively. It has been shown that with the rational use of products, the cost can be reduced and the benefit increased. The necessity of the Hospital Quality Standards of NST helped to save costs in the hospital. This study has limitations. One of them is that is single-center. There is a need for multi-center studies investigate the effect of nutritional support teams on hospital expences in Turkey. In addition, the other limitation is that the medical supplies, examinations, medications and, man power were not evaluated while examining the effect of the NST on hospital expence. It is recommended to consider the limitations for planning future studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (Date: May 27, 2020, Number: 2020/121).

Informed Consent: Since patient data were not used in this study, written informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Acknowledgment: Thanks to the members of the Gaziantep State Hospital Nutrition Support Team; Doctor Aslı Gün Yıldırım and Nurse Ruşen Özdemir for their support.

Author Contributions: Concept – Z.P.Ö.; Design – Z.P.Ö.; Supervision - Z.P.Ö., T.U.; Resources – Z.P.Ö.; Materials – Z.P.Ö., T.U.; Data Collection and/or Processing – Z.P.Ö.; Analysis and/or Interpretation – T.U.; Literature Search – Z.P.Ö.; Writing Manuscript – Z.P.Ö.; Critical Review – Z.P.Ö., T.U.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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