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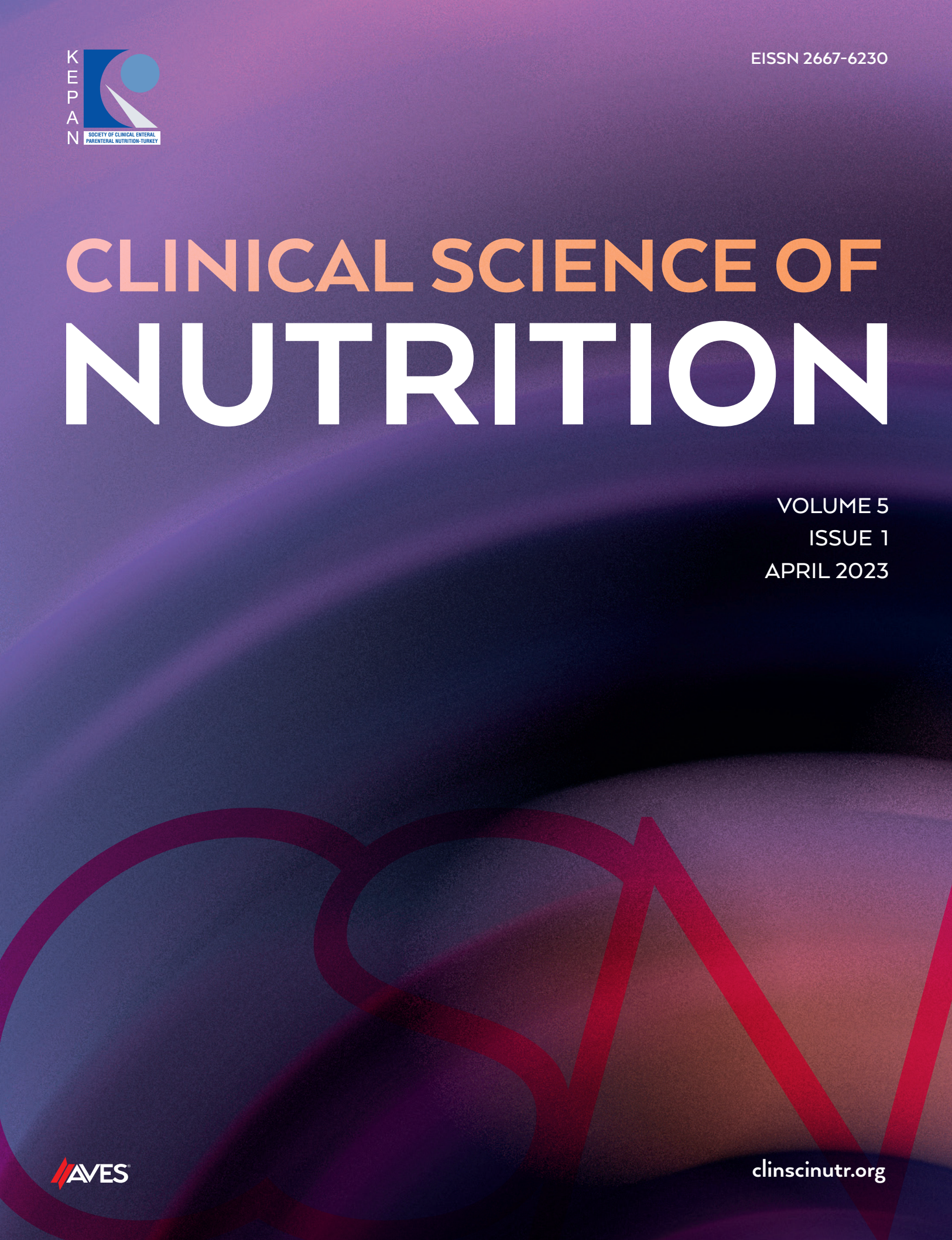

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AIMS AND SCOPE

Clinical Science of Nutrition (Clin Sci Nutr) is a scientific, open Access periodical published in accordance with independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Society of Clinical Enteral Parenteral Nutrition – Turkey, and it is published tri-annually in April, August, and December. The publication language of the journal is English.

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

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

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

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

Clinical Science of Nutrition currently indexed in EBSCO, Gale, and China National Knowledge Infrastructure (CNKI).

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME),Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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CONTENTS

CLINICAL SCIENCE OF NUTRITION

Original Article

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Enteral Nutrition Challenge in Patients Requiring Vasoactive Agents: A National Survey

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ABSTRACT

Objective: In this study, it was aimed to determine the approaches of physicians with intensive care unit experience to enteral nutrition therapy in patients requiring vasoactive drugs.
Methods: A 14-question electronic questionnaire was applied to physicians practicing in intensive care units.
Results: A total of 244 physicians (54.5% women) with a mean (SD) age of 39.76 (8.45) years participated in the study. The specialties of the participants were intensive care (35.2%), anesthesiology and reanimation (30.7%), and general surgery (16.4%). Interestingly, 39.3% of the study participants were not using any screening tool for the nutrition of critical patients. Although most of the physicians encountered enteral nutrition intolerance and gastrointestinal system complications as the most common reasons for enteral feeding interruption in patients receiving vasoactive drugs, it is demonstrated that the rate of vasoactive drug dose threshold use, routine assessment of organ failure, and follow-up organ perfusion was low.
Conclusion: Based on the results of this study, it is seen that there are differences among physicians in terms of nutritional approach to critically ill patients. It is obvious that these differences are more pronounced in doctors of different titles and institutions. In order to provide a standard treatment, especially in this critically ill patient population, it will be beneficial to increase the importance given to "nutrition therapy" in both specialist training and in-service training. In addition, it is thought that standardization will be achieved in patient care by including "nutrition therapy" in treatment protocols, considering the recommendations made by current guidelines.

Keywords: Enteral nutrition, critical illness, shock, vasoactive drugs, enteral nutrition intolerance

INTRODUCTION

Critical illness progresses with catabolic pathophysiological changes. Mucosal integrity is impaired and enterocytes become hyperpermeable. Enteral nutrition (EN) has been shown to alleviate the catabolic state by increasing the blood flow to the gastrointestinal system (GIS). Enteral nutrition preserves the structural integrity and barrier function of the gut, promotes symbiosis, maintains normal immune function, and prevents GIS complications.[1-7] Some of the critically ill patients with hemodynamic instability need to receive intensive treatments such as vasoactive drugs. Vasoconstriction at the splanchnic circulation and peripheral tissues maintains vital organ perfusion with redistribution of blood flow in the case of vasoactive treatment. Vasoconstriction and redistribution may lead to impaired oxygen supply/demand ratio and intestinal ischemia.[8] Thus, potential benefits of early EN should be balanced with the risks.

In the first 24 to 48 hours of intensive care unit (ICU) admission, EN is recommended.[9-11] For patients with shock, firstly providing the hemodynamic and tissue perfusion goals with fluid resuscitation/vasopressor/inotrope after low-dose EN is recommended. The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends initiation/continuation of EN to patients who receive a stable vasoactive drug dose and who progress with a decrease in lactate level with sufficient perfusion pressure; European Society of Intensive Care Med suggests initiating low-dose EN if the patient has fluid response shock or hemodynamic stability is achieved with vasopressor

The study was presented as an oral presentation in KEPAN 2021, Antalya, Turkey.

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support at a fixed or decreasing dose and if there is no increase in the level of lactate during the follow-up.[12,13]

In the NUTRIREA trial and some of the observational studies, it is suggested that the frequency of intestinal ischemia was higher in patients who are receiving vasopressors if early EN is started.[14-16] During this period, remaining vigilant for the signs of bowel ischemia is also recommended.

In this study, we aimed to examine the approaches of physicians with ICU experience to nutritional therapy of critically ill patients receiving vasoactive drugs.

METHODS

Cukurova University Faculty of Medicine Non-interventional Clinical Research Institutional Ethics Committee approved the study protocol (date: 2021, decision no. 2021/109-51).

Study Participants

This crosssectional survey study was performed between February 2 and 9, 2021, via an electronic questionnaire among physicians currently practicing in Turkey with ICU experience. Pediatricians were not included in the study.

Survey Development and Distribution

A questionnaire consisting of 19 questions was prepared to evaluate physicians' approach to nutritional therapy in patients requiring vasoactive drugs. After a comprehensive literature review, survey questions were developed by the researchers specifically for this study. The survey was created on Google® Forms online survey platform. The questionnaire was piloted with the researchers' colleagues (medical residents) before the initialization. The total time to completely answer these 19 questions was approximately 10 minutes. The questionnaire consisted of 2 parts; the first part includes 6 questions regarding the participants' demographic information (age, gender, medical specialty, employing healthcare facility, duration of professional experience, and title) and the second part includes 13 multiple-choice questions regarding the participants' approaches and experiences on EN of patients who require a vasoactive agent. While 11 of those questions have only 1 answer option, 2 of them (3rd and 11th questions) have more than 1 answer option. Answers were evaluated groups that are composed according to demographic information.

The participants of the survey were physicians with ICU experience who were individually invited to participate in the survey via professional email groups. Participation in the survey was on a voluntary basis, and reminder emails were sent only once. Participants who voluntarily participated in the study first approved the informed consent form via the survey link and then answered the questions online. Only entirely completed surveys were included in the study analysis.

Statistical Analysis

IBM Statistical Package for Social Sciences 20.0 (IBM SPSS Corp., Armonk, NY, USA) software program was used for statistical analysis. Mean (±SD) or median (minimum-maximum) values were given for numerical variables as descriptive statistics, and number (percentage) values were given for categorical variables. The *t*-test, Mann–Whitney *U*-test, and post-hoc analysis were used to compare quantitative data. In terms of normal distribution, the Kolmogorov–Smirnov test was used. The chi-square and Fischer's exact tests were used to compare categorical variables. For all the tests, $P < .05$ was considered statistically significant.

According to power analysis, a total of 240 participants were required for a 0.20 effect size with 95% power and 5% error margin (G* Power 3.0.10 software).

RESULTS

The number of participants was 244 (55% female). The mean ± SD age was 39.76 ± 8.45 years. Participants' demographic data (medical specialty, title, employing healthcare facility, and duration of professional experience) are given in Table 1.

Thirteen multiple-choice questions in order to evaluate the physicians' approaches and answers to these questions are summarized in Tables 2 and 3.

Participants were grouped according to their age, gender, medical specialty, employing healthcare facility, duration of professional experience, and title. The answers of the 13 multiple-choice questions evaluated according to these groups. The results are stated below.

Nutritional Screening

With regard to the specialty, pulmonologists were not using screening tools ($P < .001$); intensive care specialists were using the Nutric score and nutritional risk screening (NRS) 2002 scales ($P < .001$); associate professors, professors, and intensivists were using NRS 2002 ($P < .001$), while the others were not using a screening scale ($P < .001$). With regard to the experience, those with more than 20 years of professional experience were using the NRS 2002 scale ($P < .05$). According to the institution, physicians practicing in secondary-level public and private hospitals were not tending to use a screening scale ($P < .05$).

Table 1. Demographic Information of the Participants	
	n (%)
Specialties	
Intensive care	86 (35.2)
Anesthesiology and reanimation	75 (30.7)
General surgery	40 (16.5)
Internal medicine	26 (10.6)
Pulmonology	12 (4.9)
Neurology	5 (2.1)
Title	
Specialist doctor	95 (38.9)
Intensivist	60 (24.6)
Research assistant	55 (22.6)
Professor	19 (7.8)
Associate professor	15 (6.1)
Duration of professional experience	
<5 years	45 (18.4)
5-10 years	76 (31.1)
10-15 years	52 (21.3)
15-20 years	27 (11.1)
>20years	44 (18.1)
Employing healthcare facility	
University and Training and Research Hospitals	135 (55.4)
State Hospital	64 (26.2)
Private and Foundation Hospitals	45 18.4)

Table 2. Approaches of Physicians to EN Therapy in Patients Requiring Vasoactive Drugs—Questions
1. What is your preferred nutritional screening score?
2. When do you start EN in hemodynamically stable shock patient?
3. When do you interrupt/stop EN?
4. What is the lactate level to interrupt EN?
5. Which is true for shock patients?
6. While planning to start EN therapy in shock patients, would you also consider organ failure?
7. What would be your preference of nutrition treatment for patients requiring vasoactive drugs until hemodynamic stability is achieved?
8. What is the maximum dose range of norepinephrine in patients receiving EN treatment?
9. What is the maximum dose range of dopamine in patients receiving EN treatment?
10. Have you experienced any EN intolerance during vasoactive drug therapy?
11. If the answer is yes, which complications did you notice during EN intolerance due to vasoactive drug therapy?
12. Would you do GRV control in hemodynamically stable patients receiving vasopressor and EN?
13. Would you consider starting PN in patients whose EN could not reach the target?
EN, enteral nutrition; GRV, gastric residual volume; PN, parenteral nutrition.

Time to Initiate Enteral Nutrition

Time to initiate EN to hemodynamically stable shock patients was questioned, and most of the participants (55.7%, n = 136) declared that they initiate immediately. There was no difference detected between the groups ($P > .05$).

Reasons of Enteral Nutrition Interruption

More than 1 answer option is provided to the question of "In which cases do you interrupt/stop your patient's EN therapy while in the presence of vasoactive agents." The top 3 answers given by the physicians to this question were abdominal distension (n = 208, 85.2%), vomiting (n = 196, 80.3%), and excess gastric residual volume (GRV) (n = 187, 76.6%).

Organ Failure Assessment

Lactate threshold to interrupt EN questioned 54.9% of the participants answered as above 4 mmol/L while 35.2% of them were not considering the lactate level. There was no significant difference detected between the groups ($P > .05$).

Routine assessment of organ failure was evaluated with the question "While planning to start EN therapy in shock patients, would you also consider organ failure?" About 9.8% of the participants were not considering organ failure, 31.6% were evaluating with "sequential organ failure assessment" score, and 57.8% declared that they were evaluating on a patient basis. There was no significant difference detected between the groups ($P > .05$).

Nutrition of Vasoactive Agent Requiring Patient

There were significant differences with regard to the specialty of the physicians to the question "What would

Table 3. Approaches of Physicians to EN Therapy in Patients Requiring Vasoactive Drugs—Top 3 Answers (%)		
1. I don't use any screening tool (39.3)	NRS 2002 (34.4)	Nutric score (21.7)
2. Immediately (55.7)	Within the first 72 hours (37.3)	Within 3-7 days (4.9)
3. Abdominal distention (85.2)	Vomiting (80.3)	GRV excess (76.6)
4. >4 mmol/L (54.9)	I do not consider lactate level (35.2)	>2 mmol/L (9.8)
5. Nutrition is not a priority (79.5)	Nutrition is priority (20.5)	—
6. I evaluate on a patient basis (57.8)	I consider SOFA's ≥2-point increase (23.4)	I do not consider the presence of organ failure (9.8)
7. Trophic EN (36.9)	Intravenous dextrose (30.7)	PN (13.5)
8. I do not use a dose threshold (41.4)	0.3-0.5 μg/kg/min (18.0)	0.05-0.1 μg/kg/min (14.8)
9. I do not use a dose threshold (44.7)	5-10 μg/kg/min (24.6)	10-20 μg/kg/min (15.6)
10. Yes (74.2)	No (25.8)	—
11. GRV excess (79.9)	Abdominal distention (72.4)	Vomiting (69.8)
12. I do it on selected patients (34.4)	I do it every day in all patients (32.0)	I don't (12.3)
13. Yes (70.9)	No (29.1)	—

EN, enteral nutrition; GRV, gastric residual volume; NRS, nutritional risk screening; PN, parenteral nutrition; SOFA, sequential organ failure assessment.

be your preference of nutrition treatment for patients requiring vasoactive agent until hemodynamic stability is achieved?" While 53.8% of internists and 47.4% of general surgeons stated that they preferred intravenous dextrose, 53.5% of intensive care specialists and 40% of anesthesiology and reanimation specialists stated that they prefer trophic nutrition ($P < .05$). The rate of trophic nutrition was higher in female physicians than male ($P < .05$).

It was determined that 41.4% (n = 101) and 44.7% (n = 109) of the physicians did not use a threshold dose value for norepinephrine and dopamine while managing EN treatment, and there were no significant differences detected between the groups. In addition, 74.2% of the physicians stated that they had previously experienced EN intolerance in patients receiving vasoactive drugs and mostly noticed this with abdominal distention, excess GRV, and vomiting.

Measurement of Gastric Residual Volume

Gastric residual volume practices of participants were evaluated with the question "Would you do GRV control in hemodynamically stable patients receiving vasopressor and EN?" There was no significant difference detected between the groups ($P > .05$).

Supplemental Parenteral Nutrition

Supplemental parenteral nutrition (PN) support was questioned for vasoactive agent receiving patients whose energy target could not be reached with EN, nearly one-third of the participants declared that they were not considering supplemental PN.

DISCUSSION

To our knowledge, this is the first study evaluating the approach of physicians to the nutrition therapy of patients requiring vasoactive drugs, and we determined that physicians with ICU experience had varied approaches to EN in patients requiring vasoactive agents. The main results of our study could be specified as follows.

Nutritional Screening

Screening of nutrition with a scale is questioned. It has been detected that 39.3% of the participants declared that they did not tend to use a nutrition scale, although screening of all critical patients' nutritional status is recommended by the guidelines.[17,18] The rate of nutrition screening with a scale was found to be statistically significantly low in pulmonology and neurology specialists and secondary level hospital employees ($P < .05$). Use of the nutrition screening scale was evaluated according to the title, associate professors, professors, and intensivists were using nutrition screening tools more than the others ($P < .05$).

Time to Initiate Enteral Nutrition

Most of the participants stated that they initiate EN in the first 72 hours of ICU admission. This finding was

found to be in line with the recommendation of nutrition guidelines;[9,10,15] however, there are contrary studies demonstrating EN latency in the literature.[19-21]

Organ Dysfunction Assessment

Critically ill patients with hemodynamic instability need to receive intensive treatments such as fluid replacement and vasoactive drugs. Approach to EN may be a determinant factor for outcome of patients with hemodynamic instability and should be individualized. Organ failure scoring systems are used to predict the degree of organ dysfunction, course of the disease serially over time, and decrease in complications.[22,23,29-31] However, a significant number of the study participants declared that they do not tend to use determinants of tissue perfusion such as organ failure scoring systems, threshold value for vasopressor therapy, or a threshold value for the lactate level.

Reasons for Enteral Nutrition Interruption

Reasons for EN interruption were questioned, and GIS symptoms such as excess GRV, abdominal distention, and vomiting were stated as the common causes. We demonstrated that the declared frequency of GIS symptoms was higher than the literature.[12,19,24] We think that the lack of attention to tissue perfusion and organ failure may have resulted with increased GIS complications.

Measurement of Gastric Residual Volume

Routine measurement of GRV as evidence of digestive system dysfunction is not recommended in the recent guidelines because of the difficulties and infectious risks such as SARS-CoV-2.[17,18,25] Nearly a third of the participants declared that they routinely measure GRV. Gastrointestinal system symptoms are reported as the most common cause of EN latency,[17,21,26,27] and similarly EN complications are suggested as the most common cause of failure to achieve nutritional targets;[27] in this situation, supplemental PN is suggested.[28,29]

Supplemental Parenteral Nutrition

Nearly one-third of the participants declared that they were not considering supplemental PN, although it is recommended in the randomized controlled trials and guidelines.[13,30] A higher ratio of supplemental PN could be expected because of the high ratio of EN complications.

Considering all the answers, the nutritional status screening is not sufficient at ICU admission, the timing of EN initiation is compatible with the guidelines, and tissue perfusion and organ failure follow-up is not enough as expected in patients receiving vasoactive agents. Despite the high rate of GIS complications declared by the participants, the rate of supplemental PN considering participants was low.

Study Limitations

The survey was designed online. Only completed forms could be included in the study. The number of dropout/nonresponsive surveys could not be calculated.

In conclusion, based on the results of this study, it is seen that there are differences among physicians in terms of nutritional approach to critically ill patients. It is obvious that these differences are more pronounced in doctors of different titles and institutions. In order to provide a standard treatment, especially in this critically ill patient population, it will be beneficial to increase the importance given to "nutrition therapy" in both specialist training and in-service training. In addition, it is thought that standardization will be achieved in patient care by including "nutrition therapy" in treatment protocols, considering the recommendations made by current guidelines. The main points that are emphasizing the results of the study are listed below:

- The rate of participants' nutrition screening during the ICU admission was low.
- Time to EN initiation was compatible with the guidelines, but there were issues that need attention during the follow-up period.
- The ratio of using threshold dose for vasoactive agents, also follow up for tissue perfusion with lactate level organ failure assessment scales and the ratio of supplemental PN was found to be low. The rate of GIS complications declared by the participants was high.
- Qualification of the hospital (secondary/tertiary-level hospitals), specialty of the physician, professional experience period, and titles of physicians were the main determinants for approach to EN therapy in patients requiring vasoactive drugs.

Ethics Committee Approval: The study protocol was approved by the Cukurova University Ethics Committee (Date: February 2, 2021, decision no. 2021/109-51).

Informed Consent: Participants who voluntarily participated in the study first approved the informed consent form via the survey link and then answered the questions online.

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Cachexia and Pre-Cachexia in Cancer Patients

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ABSTRACT

Objective: This study aimed to determine the stages of cachexia and existence of pre-cachexia in cancer patients using the parameters of the cachexia score.
Methods: The study included 333 cancer patients (males, 61.3%; mean age, 59.0 ± 13.2 years) who were followed at our clinic and received radiotherapy. The cachexia score of the patients was calculated, and their cachexia stages and pre-cachexia status were evaluated using the parameters of cachexia scoring system.
Results: According to the cachexia score of the patients, 30.9% had severe cachexia and 5.7% had terminal cachexia. The frequency of severe+terminal cachexia was the highest in gastric cancer (92.9%), followed by pancreas (57.1%) and lung (51.2%) cancers. Moreover, the frequency of severe+terminal cachexia was also the highest in the patients who received chemothera py+radiotherapy+surgery (44.2%).
Conclusion: Assessing cachexia in the early period and planning nutritional support as a part of treatment is essential. Patients with gastrointestinal or lung cancer need to be monitored for cachexia more closely.

Keywords: Cancer cachexia, cancer, cachexia scoring system, pre-cachexia

INTRODUCTION

Cachexia is a multifactorial condition frequently encountered in cancer patients and has an impact on treatment, prognosis, quality of life, and survival. Cancer cachexia is characterized by muscle wasting (with or without loss of fat mass) and causes progressive dysfunction.[1]

Although cancer cachexia is a common condition in clinical practice, there are difficulties in its early diagnosis. One of the reasons for this includes the differences among diagnostic criteria.[2] Definitions of cachexia focus only on weight loss; conventionally, it is defined as a certain weight loss within a certain period of time such as "weight loss by ≥5% in the last 6 month." Studies on more comprehensive definitions taking body composition, physical functioning, and molecular biomarkers into account are ongoing; however, these definitions have not been included in clinical practice yet.[1,2] In addition to the need for clear and objective diagnostic criteria, one of the essential requirements for both clinical trials and patient treatment is a staging system that enables cancer patients to be classified according to the severity of cachectic syndrome. A staging system assessing the severity of cachexia will also be beneficial while deciding the type of treatment.[3]

The cachexia score (CASCO) is a scoring system used for the staging of cachectic cancer patients.[4] The scoring system takes the following 5 factors into account: body weight and lean body mass; inflammatory, immunological, and metabolic disturbances; physical performance; anorexia; and quality of life.[4] The present study aimed to determine the stages of cachexia in cancer patients using the parameters of the scoring system.

METHODS

Patients

Adult patients (> 18 years old) who received radiotherapy for cancer and were planned to receive nutrition therapy were enrolled in the study. Cachexia scoring was performed for the patients prior to radiotherapy. This study was approved by the Clinical Research Ethics Committee (24.12.2015/ E-15-714) and has been performed in accordance with the ethical standards as laid down in the

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1964 Declaration of Helsinki and informed consent was obtained from all individual participants included in the study.

Cachexia Score

The cachexia scoring system includes a number of comprehensive measurements. Physical or biochemical tests are used together with related questionnaires completed by the patient him/herself.[4] In the present study, CASCO was calculated by the formula: cachexia score = BWC (0-40) + IMD (0-20) + PHP (0-15) + ANO (0-15) + QOL (0-10); where BWC indicates body weight loss and composition, IMD indicates inflammation/metabolic disturbances/immunosuppression, PHP indicates physical performance, ANO indicates anorexia, and QOL indicates quality of life. The CASCO ranges between 0 and 100 and classifies cachexia as mild cachexia (a score of 0-25), moderate cachexia (a score of 26-50), severe cachexia (a score of 51-75), and terminal cachexia (a score of 76-100).

Parameters Used for Scoring and the Questionnaires

Parameters used for the evaluation of cachexia and their scores are presented in Table 1 (BWC, IMD, PHP, ANO, anorexia, QOL, C-reactive protein (CRP), hemoglobin (Hb), Simplified Nutritional Appetite Questionnaire (SNAQ).

The questionnaire used for the evaluation of physical performance is presented in Table 2.

The SNAQ was used to evaluate anorexia (Table 3).

Main Points

- Clinicians should give importance to the nutrition of the patient as much as they give to the treatment of cancer. Our study revealed that the frequency of severe+terminal cachexia was the highest in the group that received chemotherapy+radiotherapy+surgery. The idea of only "curing cancer" is not acceptable because the patient with malnutrition may also have to interrupt or postpone cancer treatment.
- Early recognition of cachexia and management before it progresses is almost essential, as treatment would be much more challenging in advanced cases like refractory cachexia. According to the cachexia score of the patients, 30.9% were classified as severe cachexia and 5.7% were classified as terminal cachexia.
- Cachexia is not just a "weight loss." In addition to weight loss, as we used in that study, lean body mass; inflammatory, immunological, metabolic changes; physical performance; anorexia; and quality of life are also important. A scoring system that takes all these into account may help with early diagnosis and prompt initiation of treatment.

The questionnaire used for evaluating the quality of life is presented in Table 4.

Evaluation of Pre-Cachexia

Cachexia-related conditions such as inflammation and decreased physical activity might have already occurred in subjects having no significant weight loss yet (≤5% in the last 12 months) and usually having an underlying disease associated with cachexia. This is called pre-cachexia. However, despite many recommendations, there is yet no consensus on how pre-cachectic patients would be classified. If the sum of different parameters, excluding particularly the weight loss and body composition, in the patient is at least 35, this means there is pre-cachexia (4). In the present study, pre-cachexia was calculated using the formula: (BWC = 0, (IMD + PHP + QOL + ANO) > 35). As was mentioned before, the absence of significant weight loss is required for the diagnosis of pre-cachexia.

Statistical Analysis

The Predictive Analytics Software Statistics 18.0 for Windows (SPSS Inc., Chicago, Ill, USA) was used for statistical analyses. Descriptive statistics were expressed as number and percentage for categorical variables and as mean and standard deviation for numerical variables. Normality of data was analyzed using the visual (histogram and probability graphics) and analytic (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. The Mann–Whitney *U*-test was used for 2 group comparisons for nonnormally distributed numerical variables. Two-group and multiple-group comparisons for categorical variables were performed using the chi-square test or, if chi-square condition was not provided, by Fisher's exact test. The level of statistical significance was accepted as $P < .05$.

RESULTS

The study included 333 cancer patients with a mean age of 59.0 ± 13.2 years, of whom 61.3% were males. The general characteristics of the patients are demonstrated in Table 5.

According to the CASCO of the patients, 30.9% were classified as severe cachexia and 5.7% were classified as terminal cachexia (Table 6).

Comparison of the patients with mild+moderate cachexia and those with severe+terminal cachexia in terms of characteristics other than those included in the staging system revealed no difference regarding age, gender, smoking status, alcohol consumption, and presence of comorbidity. Vitamin D level was found to be significantly lower in the patients with severe+terminal cachexia (Table 7).

Table 1. Parameters Used for Evaluation of Cachexia and Their Scores*

	Contribution to the Score (%)	Measurement	Score	Total Score
BWC	40	Weight loss		32
		<5%		
		≥5%, mild		
		≥10%, moderate		
		≥15%, severe		
		≥20%, terminal		
		Lean body mass		8
		Unchanged lean body mass		
		Loss of lean body mass		
IMD	20	Inflammation,		8
		Plasma CRP, mg/L		
		≤ 10		
		> 10 to ≤ 20		
		>20		
		Metabolic disorders		8
		Plasma albumin < 3.2 g/dL		
		Plasma pre-albumin < 16 mg/dL		
		Plasma lactate > 2.2 mM		
		Plasma triglycerides > 200 mg/dL		
		Anemia, Hb < 12 g/dL		
		Plasma urea > 50 mg/dL		
		Immunosuppression		4
		Peripheral lymphocytes: assessment of proliferation or positive skin hypersensitivity reaction		
PHP	15	Physical performance, questionnaire, or monitoring		15
		Total activity		
		Handgrip strength		
		Stair climbing		
		6-minute walk distance		
ANO	15	SNAQ		15
QoL	10	Quality of life questionnaire		10
		Mild		
		Moderate		
		Severe		

*It was benefited from the CASCO (4) scoring system.
ANO, anorexia; IMD, inflammation/metabolic disturbances/immunosuppression; PHP, physical performance; QoL, quality of life; SNAQ, Simplified Nutritional Appetite Questionnaire.

When the distribution of cachexia status among cancer types was evaluated, the high rate of severe+terminal cachexia (92.9%) in the patients with gastric cancer was striking (Table 8).

Evaluation of cachexia stage according to the treatment revealed that the frequency of severe+terminal cachexia was the highest in the group that received chemothera py+radiotherapy+surgery (44.2%; Table 9).

DISCUSSION

Nutritional intervention in addition to treatment has been demonstrated to have favorable effects on prognosis and/or QoL in various types of cancer.[5,6] Early diagnosis of malnutrition or cachexia in cancer patients helps with the decision of providing nutritional support or pharmacological treatment when necessary.[7] It has been reported that assessment of baseline nutritional status of cancer patients should be a part of routine clinical practice and that nutritional intervention might be required in pre-cachexia period.[8]

In addition to the currently available scoring systems used to assess nutritional status and to determine cachexia in cancer patients, there are new scoring systems recommended by various study groups.[9-16] Nevertheless, a generally accepted objective definition or classification system is still lacking. It has been reported that evaluations performed using different criteria yield different outcomes related to nutritional status and hence the prevalence of cachexia ranges widely based on the criteria used.[17,18] This makes comparison between the studies performed using different scoring systems difficult. The present study used a CASCO including the following parameters: body weight and lean body mass; inflammatory, immunological, and metabolic disturbances; PHP; ANO; and QoL.

Weight loss in cancer patients results from the imbalance between energy intake and energy consumption. In a study performed on adult cancer outpatients presenting for diagnosis or therapy or follow-up, 1000 patients from 17 centers were evaluated in terms of nutritional status and a significant weight loss (≥10%) was observed in 39.7% of these patients.[19] It has been reported that the rate of weight loss is higher in advanced ages[20] and in certain types of cancer (lung, gastrointestinal).[21] Weight loss in the early period is associated with poor prognosis.[22] In the scoring system used in the present study, a weight loss of ≥5% and loss of lean body mass were taken into account.

Table 2. Assessment of Physical Performance*

Questionnaire During the past week: Have you noticed any particular decrease in your routine daily physical activities (i.e., at work, at home, at leisure, etc.)? Have you had any problems doing strenuous activities, like carrying a heavy shopping bag or suitcase? Have you noticed any loss of handgrip force? Did you have to put more effort on climbing stairs?? Have you felt tired after walking approximately half a kilometer?
Monitoring** Total physical activity Grip force Stair-climb 6-minute walk distance
*It was benefited from the CASCO (4) scoring system. **The results of the measurements performed concurrently with the questionnaire were evaluated.

Table 3. Simplified Nutritional Appetite Questionnaire

My appetite is
a. Very poor b. Poor c. Average d. Good e. Very good
When I eat
a. I feel full just after eating only a few mouthfuls b. I feel full after eating about a third of a meal c: I feel full after eating over half a meal d. I feel full after eating most of the meal e. I hardly ever feel full.
Foods tastes
a. Very bad b. Bad c. Moderate d. Good e. Very good
Normally I eat
a. Less than one meal a day b. One meal a day c. Two meals a day d. Three meals a day e. More than three meals a day
*It was benefited from the CASCO (4) scoring system. a=1, b=2, c=3, d=4, e=5.

Table 4. Quality of Life Questionnaire
During the past week
Did you need to stay in bed or a chair all day long?
Did you need help while eating, dressing, washing yourself, or using the toilet?
Were you limited in doing either your work or other daily activities?
Were you limited in pursuing your hobbies or other leisure time activities?
Were you short of breath?
Have you had pain?
Did you need to rest?
Have you had trouble sleeping?
Have you felt weak?
Have you felt nauseated?
Have you vomited?
Have you been constipated?
Have you had diarrhea?
Did pain interfere with your daily activities?
Have you had difficulty in concentrating on things like reading a newspaper or watching television?
Did you feel tense?
Did you worry?
Did you feel irritable?
Did you feel depressed?
Have you had difficulty remembering things?
Has your physical condition or medical treatment interfered with your family life?
Has your physical condition or medical treatment interfered with your social activities?
How would you rate your overall health status during the past week?
How would you rate your overall quality of life during the past week?
**It was benefited from the CASCO (4) scoring system. For the first 22 questions: not at all: 1, a little: 2, quite a bit: 3, very much: 4; last 2 questions: excellent: 1, good: 2, poor: 3, very poor: 4.

Chronic systemic inflammatory response has been suggested as one of the underlying mechanisms of cancer cachexia. Various clinical studies have demonstrated the relationship between cachexia and inflammatory biomarkers (acute phase proteins such as CRP and albumin and cytokines such as interleukin-6) in various types of cancer and these biomarkers are used in cachexia scoring systems.[12,21,23-28] As a convenient, sensitive, and specific test available in routine laboratory analyses, CRP is one of the parameters most frequently used in assessing inflammatory response. It is known that survival is poorer in cancer patients with high CRP levels.[21] Evaluation of high CRP level (> 10 mg/L) together with low albumin level (< 35 g/L) has been reported to have prognostic value in cancer patients.[21,25,29,30] In the scoring system used in the present study, CRP and albumin levels were also taken into account.

Table 5. General Characteristics of Cancer Patients	
Characteristics	
Age, year	59.01 ± 13.2
Gender	
Male	204 (61.3)
Female	129 (38.7)
Body mass index, kg/m^2	26.4 ± 5.17
Diagnosis	
Breast cancer	69 (20.7)
Lung cancer	43 (12.9)
Head and neck cancer	42 (12.6)
Prostate cancer	34 (10.2)
Rectum cancer	34 (10.2)
Gastric cancer	28 (8.4)
Brain tumors	23 (6.9)
Pancreas cancer	14 (4.2)
Bladder cancer	11 (3.3)
Lymphoma	8 (2.4)
Metastasis	6 (1.8)
Multiple myeloma	4 (1.2)
Other	17 (5.1)
Data are presented as mean ± standard deviation or number (%), where appropriate.	

Performance status is one of the parameters used in the definition and classification of cachexia. The tools frequently used for this purpose by the researchers include the Eastern Cooperative Oncology Group performance status.[11,13,14] In the present study, in addition to the

Table 6. Distribution of Cancer Patients Among Cachexia Stages and Their Pre-cachexia Status	
Cachexia Stage	**n (%)**
Mild	30 (9.0)
Moderate	181 (54.4)
Severe	103 (30.9)
Terminal	19 (5.7)
Pre-cachexia	118 (35.4)

Table 7. Characteristics of the Patients According to the Cachexia Stage

	Patients with Mild + Moderate Cachexia n = 211	Patients with Severe + Terminal Cachexia n = 122	*P*
Gender			
Male	124 (58.8)	80 (65.6)	.219
Female	87 (41.2)	42 (34.4)	
Age, year	58.66 ± 13.4	59.61 ± 12.87	.382
Vitamin D level, ng/mL	15.02 ± 12.05	13.61 ± 12.51	**.033**
Alcohol consumer	7 (3.3)	3 (2.5)	.751
Smoker	30 (14.2)	14 (11.5)	.476
Presence of comorbidity	90 (42.7)	46 (37.7)	.376

Data are presented as mean ± standard deviation or number (%), where appropriate.

questionnaire adapted from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30,[4] grip strength, stair climbing, and 6-minute walk tests were used to assess the performance status.

Anorexia is a common characteristic symptom of cancer patients and is a parameter found in various scoring systems used for the evaluation of cachexia.[11,13] In the present study, SNAQ was used in assessing anorexia.

Cancer cachexia is closely associated with poorer quality of life. The EORTC QLQ-C30 is one of the scoring systems used frequently for assessing the quality of life.[13,18] Quality of life is poor also in patients with cancer cachexia.[13,14] In the present study, quality of life was assessed using the questionnaire adapted from the EORTC QLQ-C30.[4]

In the present study, of 333 cancer patients, 30.9% were determined to have severe cachexia and 5.7% were determined to have terminal cachexia using the scoring system composed of aforementioned parameters.

Cachexia is also associated with the type of cancer. It has been reported that weight loss is higher and weight loss and decreased performance appear in the early stages in patients with gastrointestinal cancer and lung cancer.[19,21,31]

Table 8. Distribution of Cachexia Status Among Cancer Types

	n	Mild + Moderate Cachexia n (%)	Severe + Terminal Cachexia n (%)
Breast cancer	69	56 (81.2)	13 (18.8)
Lung cancer	43	21 (48.8)	22 (51.2)
Head and neck cancer	42	31 (73.8)	11 (26.2)
Prostate cancer	34	26 (76.5)	8 (23.5)
Rectum cancer	34	26 (76.5)	8 (23.5)
Gastric cancer	28	2 (7.1)	**26 (92.9)**
Brain tumors	23	13 (56.5)	10 (43.5)
Pancreas cancer	14	6 (42.9)	8 (57.1)
Bladder cancer	11	8 (72.7)	3 (27.3)
Lymphoma	8	4 (50.0)	4 (50.0)
Metastasis	6	3 (50.0)	3 (50.0)
Multiple myeloma	4	4 (100.0)	0 (0.0)
Other	17	11 (64.7)	6 (35.3)

The significant bold values are represented as majority of the patients.

Additionally, it has been reported that the prevalence of malnutrition is over 80% in elderly patients (≥ 65 years) receiving chemotherapy for cancer and malnutrition is more prevalent in those with digestive cancer than in those with nondigestive cancer.[20] In the present study, the frequency of severe+terminal cachexia was the highest in gastric cancer (92.9%), followed by pancreas (57.1%) and lung (51.2%) cancers.

Assessing cachexia, which is prevalent in cancer patients, in the early period and planning nutritional support as a part of treatment is essential because they are not fed enough. Patients with gastrointestinal or lung cancer need to be monitored for cachexia more closely. A scoring system based on more objective and comprehensive criteria and allowing also staging should be preferred.

Table 9. Cachexia Stage According to the Treatment			
	n	Mild + Moderate Cachexia n (%)	Severe + Terminal Cachexia n (%)
Chemotherapy + radiotherapy + surgery	156	87 (55.8)	**69 (44.2)**
Chemotherapy + radiotherapy	98	63 (64.3)	35 (35.7)
Radiotherapy + surgery	39	33 (84.6)	6 (15.4)
Radiotherapy	38	26 (68.4)	12 (31.6)
Chemotherapy + surgery	2	2 (100.0)	0 (0.0)
The significant bold values are represented as majority of the patients.			

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital Clinical Research Ethics Committee. (Date: December 24, 2015, Decision no: E-15-714).

Informed Consent: Written informed consent was obtained from all individual participants who participated in this study.

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Nutritional Characteristics of the Patients Followed by the Nutrition Support Team and the Relationship Between the Nutritional Therapy Applied and the Results

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ABSTRACT

Objective: The aim of this study was to investigate the general characteristics, management strategies for malnutrition, and clinical outcomes in hospitals according to age groups and examine the relationships between mortality and nutritional way of the patients followed by our nutrition support team.
Methods: Totally, 411 patients were enrolled in this retrospective study. Demographic characteristics, reasons for hospitalization, comorbidities, wards the patients were staying, first day Nutritional Risk Screening 2002 scores, length of hospital stay, and clinical outcomes of the patients were recorded. Clinical parameters were compared between young patients and elders.
Results: The median age was 75 years (18-96) [54.3% male, median length of hospital stay 23 days (0-261), in-hospital mortality rate 43.6%]. The median survival was lower in elders compared to young patients (42 vs. 76 days, $P = .002$). The median survival was higher in patients with oral feeding compared to those without oral feeding (63 vs. 41 days, $P < .001$). The median survival was lower in patients with parenteral than oral and/or enteral feeding (14 vs. 48 days, $P < .001$). Age (hazard ratio: 1.028, 95% CI: 1.010-1.046), sepsis (hazard ratio 4.365, 95% CI: 1.810-10.528), malnutrition in the first day of admission (hazard ratio: 2.223, 95% CI: 1.198-4.126), parenteral nutrition (hazard ratio: 2.458, 95% CI: 1.432-4.220), oral nutrition (hazard ratio: 0.090, 95% CI: 0.045-0.182), tube feeding (hazard ratio: 1.915, 95% CI: 1.015-3.614), and feeding by gastrostomy/jejunostomy (hazard ratio: 0.113, 95% CI: 0.057-0.224) were found to be independently associated factors for hospital mortality (all parameters had $P < .05$).
Conclusion: It was shown that the study population had high hospital mortality rate, and age, malnutrition, severe infection, and nutritional ways were independently correlated factors for hospital mortality.

Keywords: Hospitalized patients, malnutrition, mortality, older adults

INTRODUCTION

Nutrition is the basic element for health in every period of life. Malnutrition can also indirectly or directly cause many diseases. Therefore, recognizing and treating malnutrition is vital, especially for improvements in clinical care. Malnutrition is a nutritional disorder that occurs with impaired physical and mental functions that lead to altered body composition (decreased lean mass) and decreased body cell mass, as well as the presence of starvation, disease, or aging, alone or in combination, accompanied by impaired clinical outcomes.[1] More than 30% of inpatients are at risk of malnutrition, which is closely related to increased mortality and morbidity, functional decline, prolonged hospital stays, and increased healthcare costs.[2,3]

By evaluating the nutritional status of each patient within the first 24 hours of hospitalization with a reliable and simple screening method, rapid identification of patients with malnutrition and malnutrition risk and arranging individualized medical nutrition therapy can improve the patient's clinical outcomes and reduce healthcare costs and mortality.[4-6]

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In this study, it was aimed to examine the general nutritional clinical characteristics of the patients who were consulted with our Nutrition Support Team while they were hospitalized and the effects of the applied nutritional treatments on the clinical outcomes. As a secondary outcome, it was also aimed to compare the data by age groups.

METHODS

A total of 411 patients, who were hospitalized at Konya Education and Research Hospital, consulted with our nutritional support team and evaluated daily, and provided with enteral and parenteral nutrition support, were included in this retrospective and observational study.

Among the general characteristics of the patients, age, gender, and underlying chronic diseases were scanned from the hospital information management system and recorded. Patients aged 65 years and over were considered to be elderly. The reasons for hospitalization were determined by examining the hospital registry system and patient files. The weight (kg) of each patient consulted to our nutrition support team was recorded by weighing with scales if possible or according to the statement of the patient or family. The height of the patients was measured, if possible, or recorded according to the statements of the patient or family. According to the recorded weight and height values, the body mass indexes of the patients were calculated in kg/m². The scores of the "Nutritional Risk Screening 2002" (NRS 2002) applied by the service nurse to determine the nutritional status of each inpatient at the time of admission were recorded, and patients with a score of 3 and above were categorized as nutritionally risky (malnutrition risk).[7] Each patient consulted to our nutrition support unit is screened for malnutrition risk, oral food consumption records are reviewed, and a treatment plan is recommended in line with European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations for patients who are found to be malnourished. The dates of consultation of the patients to our nutritional support unit, the units consulted, and the wards they were hospitalized were recorded. Medical nutrition therapy plans applied to patients were recorded daily in the hospital automation system by the dietitians working in our nutrition support team. The latest status in the hospital (death, discharge, referral, and continuing hospitalization) along with their dates was recorded in the hospital information management system. Approval for this study was obtained from the Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine, Non-Pharmaceutical and Medical Device Research (decision number: 2019/1689, date: February 8, 2019). Due to the retrospective design of the study, informed consent was not taken.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, and whether the numerical parameters were normally distributed or not was evaluated using the histogram (Kolmogorov–Smirnov tests). Normally distributed numerical parameters are expressed as mean ± SD, and non-normally distributed numerical parameters are expressed as median (minimum–maximum). The Student's *t*-test was used to compare the mean between the 2 groups, the Mann–Whitney *U*-test was used to compare the median, and the chi-square or Fisher's exact test were used to compare categorical variables. The correlation between the length of hospital stay (LOS) and other numerical parameters was analyzed by the Spearman's test. Parameters related to the length of hospitalization were evaluated with the linear regression analysis model. A *P* value of <.05 was accepted as statistical significance.

RESULTS

Of the 411 patients included in the study, 54.3% were male. The median age of the patients was 75 (minimum–maximum 18-96) years. Seventy-three percent of the patients were elderly (65 years and older). The most common reasons for hospitalization were neurological (55%), pulmonary (42.6%), and cardiological (23.1%) problems. About 49.1% of the patients had at least 1 chronic disease. The most common chronic diseases were hypertension (28.5%), diabetes (20.7%), and chronic obstructive pulmonary disease (17.8%), respectively. The units that consulted our nutrition support unit included intensive care units (57%), internal medicine clinics (35%), and surgical clinics (8%), respectively. The general characteristics of the patients are summarized in Table 1.

The proportion of patients who were found to be at risk of malnutrition on the first day of hospitalization was 68.4%. During the hospitalization, it was observed that the patients were most frequently provided with nutritional support with a nutrition tube (60.1%). Although parenteral nutrition support was applied to 40.4% of the patients, only 1.7% of the patients received parenteral nutrition therapy alone. Patients who received only parenteral nutrition (n = 7) had a shorter median hospital survival than those who received oral–enteral nutrition support (n = 404) (14 vs. 48 days; $P < .001$). Patients who were able to receive oral nutrition at any time during the follow-up period (n = 155) and patients who could

Table 1. General Characteristics, Comorbidities, and Other Clinical Properties of the Patients

Properties	
Age, years, median (minimum–maximum)	75 (18-96)
BMI, kg/m^2, median (minimum–maximum)	25 (14.7-50.78)
Gender, male, n (%)	223 (54.3)
Reason for hospitalization, n *(%)*	
Neurologic disorders	185 (55.0)
Pulmonary disorders	175 (42.6)
Cardiovascular disorders	95 (23.1)
İnfections	89 (21.7)
Endocrinological disorders	50 (12.2)
Malignancies	50 (12.2)
NRS 2002 score, median (minimum–maximum)	3 (0-7)
Length of hospital stay, days, median (minimum–maximum)	23 (0-451)
Wards the patients were staying, n *(%)*	
Intensive care unit	235 (57)
Medical wards	143 (35)
Surgery wards	33 (8)
Last status of the patients, n *(%)*	
Dead	179 (43.6)
Discharged	165 (40.1)
Still in hospital	36 (8.8)
Referred to another hospital	31 (7.5)
Nutritional support strategies, n *(%)*	
Nasogastric feeding	247 (60.1)
Total parenteral nutrition	166 (40.4)
Nutrition via percutaneous endoscopic gastrostomy	120 (29.2)
Oral nutrition support	155 (37.7)

The patients taking oral nutrition support refer to the patients supported by both oral nutritional supplements and oral nutritional regimes.
BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002.

not receive any oral nutrition during the follow-up period (n=256) (patients who were fed enterally and/or parenterally and did not receive any oral nutritional support) were compared in terms of hospital survival time. The median hospital survival time was longer in patients who could be provided with oral nutritional support (63 vs. 41 days; $P < .001$). It was observed that there was no difference between young (<65 years) and elderly (65 years and older) patients in terms of the choice of administration route of nutritional therapy ($P > .05$). It was observed that percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy (PEJ) was applied to 120 patients, and PEJ was applied to 3 of these patients. In addition to patients who were never interrupted and who continued enteral nutrition, which was recommended to 98.3% of patients, the longest break was 31 days, with a median value of 0. The reasons for interrupting enteral nutrition are presented in Table 2.

Table 2. Reasons for Interruption of Enteral Nutrition

Reasons for interruption of enteral nutrition, n (%)	
Problems related to percutaneous endoscopic gastrostomy	50 (12.2)
Gastrointestinal system intolerance	39 (9.5)
Invasive procedures	29 (7.1)
Septic shock	14 (3.4)
Patient rejection	1 (0.2)

On the day of hospitalization, the rate of having pressure ulcers during follow-up in the hospital in patients with malnutrition risk (n=161/281; 56.9%) was higher than in those without malnutrition risk (n=44/130; 33.8%) ($P < .001$).

For the patients included in the study, the median LOS was 23 days (minimum–maximum: 0-451) and the mortality rate was 43.6%. The median hospital survival was shorter in elderly patients (42 vs. 76 days; $P=.002$). At least 1 pressure ulcer was detected in 49.6% of the patients during their hospitalization. Pressure ulcers were more common in elderly patients (55.3% vs. 34.2%, $P < .001$). When the dead patients were compared with the surviving patients, it was detected that the median age, female sex ratio, pulmonary and renal problems, pressure ulcer and sepsis rates, NRS 2002 score, and parenteral and nasogastric tube nutrition rates were found to be higher in patients who died. Detailed information is presented in Table 3. Age [hazard ratio (HR): 1.028], sepsis (HR: 4.365), risk of malnutrition on the day of hospitalization (HR: 2.223), parenteral nutrition (HR: 2.458), oral nutrition (HR: 0.090), nutritional tube feeding (HR: 1.915), and feeding with gastrostomy/jejunostomy (HR: 0.13) were found to be independent parameters associated with hospital mortality ($P < .05$ for all parameters) (Table 4).

Table 3. Comparison of Clinical Parameters According to the Hospital Mortality in the Study Population			
Parameters	**Dead Patients (n=179)**	**Alive patients (n=232)**	***P***
Age, years	78 (19-96)	70 (18-95)	**<.001**
Gender, female	83 (46.4)	105 (45.3)	.823
Reasons for hospitalization			
Neurological disorders	101 (56.4)	125 (53.9)	.607
Orthopedic problems	10 (5.6)	15 (6.5)	.712
Intoxication	2 (1.1)	3 (1.3)	1.000
Malignancy	21 (11.7)	29 (12.5)	.813
Hematological problems	5 (2.8)	5 (2.2)	.753
Infections	44 (24.6)	45 (19.4)	.206
Cardiovascular problems	44 (24.6)	51 (22.0)	.536
Pulmonary problems	90 (50.3)	85 (36.6)	**.006**
Endocrinological problems	22 (12.3)	28 (12.1)	.946
Gastrointestinal problems	14 (7.8)	24 (10.3)	.381
Renal disorders	23 (12.8)	16 (6.9)	**.041**
Comorbidities			
Coronary artery disease	7 (3.9)	12 (5.2)	.546
Asthma	6 (3.4)	7 (3.0)	.848
Chronic obstructive pulmonary disease	33 (18.4)	40 (17.2)	.753
Hypertension	50 (27.9)	67 (28.9)	.833
Chronic kidney disease	19 (10.6)	15 (6.5)	.130
Diabetes mellitus	38 (21.2)	47 (20.3)	.810
Having at least 1 comorbidity	86 (48.0)	116 (50.0)	.694
Pressure ulcer	103 (57.5)	101 (43.5)	**.005**
Sepsis	32 (17.9)	14 (6.0)	**<.001**
Wards the patients were admitted			
Surgical clinics	2 (1.1)	12 (5.2)	**<.001**
Non-surgical clinics	11 (6.1)	4.4)	
Intensive care unit	166 (92.7)	117 (50.4)	
BMI, kg/m^2	25.7 (14.7-46.3)	24.7 (14.9-50.8)	.081
Number of comorbidities	0 (0-4)	0.5 (0-4)	.974
Length of hospital stay, day	28 (1-261)	21 (0-451)	.063
NRS 2022 score	4 (0-7)	3 (0-7)	**<.001**
Malnutrition risk at the time of admission	151 (84.4)	130 (56.0)	**<.001**
Nutritional interventions			
Parenteral	96 (53.6)	70 (30.2)	**<.001**
Oral feeding	27 (15.1)	128 (55.2)	**<.001**
Nasogastric tube feeding	149 (83.2)	98 (42.2)	**<.001**
PEG/PEJ	35 (19.6)	85 (36.6)	**<.001**

BMI, body mass index; NRS 2002, Nutritional Risk Screening 2002; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

Table 4. Regression Analysis Results Showing Associated Factors with Hospital Mortality

Parameters	Hazard ratio	95% CI	*P*
Sepsis	4.365	1.810-10.528	**.001**
Malnutrition risk	2.223	1.198-4.126	**.011**
Parenteral nutrition	2.458	1.432-4.220	**.001**
Oral nutrition	0.090	0.045-0.182	**<.001**
Enteral nutrition (via feeding tube)	1.915	1.015-3.614	**.045**
PEG/PEJ	0.113	0.057-0.224	**<.001**
Age	1.028	1.010-1.046	**.002**

The parameters which were significantly associated with hospital mortality according to the univariate analyses including pulmonary, neurological problems, pressure ulcer, sepsis, malnutrition risk, parenteral (n = 166), oral, enteral feeding and using PEG/PEJ, and age were included in multivariate logistic regression analysis model. Backward stepwise method was used. The last step (step 7) is shown in the table. Omnibus test fort his model had *P* value <.05 and Hosmer–Lemeshow test had *P* = .235.
PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

DISCUSSION

In this retrospective and observational study, age, malnutrition risk, severe infections, and parenteral nutrition were shown to be independently associated parameters with increased hospital mortality. On the other hand, it was determined that hospital mortality was lower in patients who could be fed orally and enterally.

In general, it has been reported that the frequency of disease-induced malnutrition is 30%-60% in hospitalized patients.[8,9] In our study, according to NRS 2002, the risk of malnutrition in the first days of hospitalization was 68.4%. The risk of malnutrition detected in this study has a higher prevalence than in the study recently conducted by Sanson et al.[10] Again, in the study of Chen et al.[11] the rate of patients who were found to be at risk of malnutrition according to NRS 2002 during admission to the hospital was lower than our result. The reason for this may be that the patients under the follow-up of the nutrition team, not the general hospital population, were included in the study; these patients were mostly hospitalized in intensive care units, and NRS 2002 was applied to a group with a higher mean age compared to the study by Chen et al.[11]

While 49.6% of the patients had at least 1 pressure ulcer during their hospitalization, pressure ulcers developed more frequently in elderly patients. In the study conducted by Lyder et al[12] in 2012, the prevalence of pressure ulcers during hospitalization was 5.8%, while pressure ulcers developing during hospitalization were found to be 16.7%. Again in this study, the mean age of patients with pressure ulcers was found to be between 75 and 84 years. According to the study conducted by Shahin et al[13] in hospitals and nursing homes in 2010, the risk of developing pressure ulcers is higher in elderly patients. The prevalence of pressure ulcers is high in patients who are elderly, have high risk of malnutrition, and long hospital stay, and who are polymorbid and immobile patients.[14-16] Since we included elderly patients having various comorbidities, malnutrition risk, and long-term hospitalization in our study, we can say that the results are similar to the literature.

While the mortality rate of the patients included in the study was 43.6%, when the patients who died and those who survived were compared, the median age, female sex ratio, pulmonary and renal problems, pressure ulcer and sepsis rates, NRS 2002 score, and parenteral and nasogastric tube feeding rates were found to be higher in patients who died. In the study of Zhang et al.[17] the NRS 2002 score was found to be an independent risk factor affecting the mortality of hospitalized geriatric patients. On the other hand, it was determined that hospital mortality was lower in patients who could be fed orally and enterally. In a study conducted by Kaegi-Braun et al in 2021,[18] the survival rate was found to be higher in patients who were fed orally alone. As a result, mortality rates are high in hospitalized patients with nutritional risk, and providing nutritional support may benefit these patients. On the other hand, in our study, it was determined that the rate of gastrostomy/jejunostomy insertion in dead patients was lower than in surviving patients. This may support the knowledge that gastrostomy or jejunostomy may not be preferred in patients with severe clinical course and low life expectancy. On the other hand, the low rate of patients who underwent gastrostomy/jejunostomy in the dead patient group may be due to the low life expectancy in this patient group.

One of the most important limitations of our study is that it was retrospective and single centered. On the other hand, it can be said as a limitation that we presented the data of a population with high mortality and critical illness and generally could not reflect the data of patients who were hospitalized and at risk of malnutrition. In this study, the data (available) of all patients who were followed in both intensive care units and inpatient services and who were in our follow-up are included. Prospectively designed studies with specific patient groups will be able to provide more detailed information on this subject.

It was observed that the patients we followed up generally consisted of a population with high hospital mortality. Age, malnutrition, severe infection, and parenteral nutrition have been shown to be parameters independently related to increased hospital mortality. It was determined that hospital mortality was lower especially in patients fed orally and with gastrostomy/jejunostomy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University (Date: February 8, 2019, Number: 2019/1689).

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

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CLINICAL SCIENCE OF NUTRITION

Original Article

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Evaluation of the Nutritional Status of Inpatients by Using Different Malnutrition Screening Methods in a Palliative Care Center: A Cross-Sectional Study

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ABSTRACT

Objective: Patients receiving treatment and care in a palliative care center are at high risk of malnutrition. This study aimed to determine the malnutrition status of patients hospitalized in a palliative care center using different scales and to compare them with the results of the Global Leadership Initiative on Malnutrition criteria.
Methods: The geriatric nutritional risk index, prognostic nutritional index, Mini-nutritional Assessment—Short Form, Nutritional Risk Screening-2002, and Global Leadership Initiative on Malnutrition criteria were used for the evaluations of nutritional status. A questionnaire to recognize the sociodemographic characteristics of the participants and the modified Charlson comorbidity index was administered to the patients.
Results: A total of 120 patients were included in the study. The mean age of the participants was 69.9 ± 15.9 years; 47.5% were women and 60.8% were married. According to the Global Leadership Initiative on Malnutrition criteria, 83.3% of the participants had malnutrition. There was no statistically significant relationship between malnutrition and gender, marital status, and having a caregiver (formal or informal) ($P = .462$, $P = .358$, and $P = .098$, respectively). Patients with malnutrition were older and had higher modified Charlson comorbidity index scores ($P = .010$ and $P = .001$, respectively). Geriatric nutritional risk index, prognostic nutritional index, Mini-nutritional Assessment—Short Form, and Nutritional Risk Screening-2002 tests showed malnutrition risk in 72.5%, 95%, 98.3%, and 84.2% of the participants, respectively. In the receiver operating characteristic curve analysis performed using the Global Leadership Initiative on Malnutrition criteria, the area under the curve values for geriatric nutritional risk index, prognostic nutritional index, Mini-nutritional Assessment—Short Form, and Nutritional Risk Screening-2002 were 0.797, 0.749, 0.927, and 0.781, respectively. The cutoff value of Mini-nutritional Assessment—Short Form tool to indicate malnutrition risk was ≤5 points, with 85% sensitivity, 90% specificity, and 54.5% negative predictive and 97.7 positive predictive values.
Conclusion: Although each screening test showed a high agreement with the Global Leadership Initiative on Malnutrition criteria, a Mini-nutritional Assessment—Short Form score of ≤5 points had the highest sensitivity and specificity to diagnose malnutrition risk in palliative care ward.

Keywords: Diagnosis, inpatient, malnutrition, palliative care

INTRODUCTION

According to the definition of the World Health Organization, palliative care aims to relieve the physical, psychosocial, and spiritual symptoms of patients through a comprehensive assessment and treatment as well as to support caregivers and alleviate their suffering.[1] Patients receiving treatment and care in a palliative care center are at high risk of developing malnutrition (MN). Studies have shown that patients with appropriate nutrition support have shorter hospital length of stay and decreased nosocomial infections and complications.[2] Regular nutritional risk screening during hospitalization will provide awareness, early diagnosis, and effective treatment. A nutritional assessment tool should be cost-effective, reliable, easily applicable, and reproducible and should have high sensitivity and specificity rates to diagnose MN. Early detection of MN and providing appropriate treatment will increase the quality of life.[3]

There are many screening tools that can be used to determine nutritional risk in patients receiving palliative care. However, although it is not known which test is the most accurate, the appropriate screening tool should be used in

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line with the recommendations of evidence-based sources. Accordingly, nutrition treatment is given correctly, and the patient's well-being is sustainable.[4] Among the MN screening tools, the most frequently used are Mini-nutritional Assessment—Short Form (MNA-SF), Nutritional Risk Screening-2002 (NRS-2002), and malnutrition universal screening tool. On the other hand, some formulas used for MN screening are available in the literature such as geriatric nutritional risk index (GNRI) and prognostic nutritional index (PNI), and new studies are emerging every day. The Global Leadership Initiative on Malnutrition (GLIM) criteria on MN, created by the nutrition committees in the recent past, are seen as a global MN diagnosis and screening tool. While the previous criteria aimed to screen for MN and identify patients at risk, a consensus has now been reached to diagnose MN with these GLIM criteria.[5]

Although there are some studies on screening for MN in patients hospitalized in palliative care units, those designed with GLIM criteria are few. On the other hand, studies examining the compatibility of different MN assessment tools with each other in this patient group are also limited. To the best of our knowledge, there is no study that compared the GLIM criteria with the other MN screening tools in the palliative care unit. Therefore, our study aimed to determine the nutritional status of patients hospitalized in a palliative care center using the GNRI, PNI, MNA-SF, and NRS-2002 tests and to compare these results with the GLIM criteria.

METHODS

This study was a descriptive and cross-sectional design and was carried out in the Palliative Care Center of Konya City Hospital.

Ethical Statements

Patients were informed about the procedures, and they signed written consent forms. The approval of the ethics committee was obtained before initiation of the study (Health Sciences University, Hamidiye Scientific Research Ethics Committee, meeting date: March 11, 2022, decision number: 22/120). All procedures involving human participants were in accordance with the ethical standards specified by the institutional and national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. Verbal and written informed consents were obtained from the patient or his/her relatives before including them in the study.

Main Points

- Patients in palliative care center are at high risk of malnutrition.
- Palliative care patients should be screened at regular intervals using malnutrition screening tests.
- The malnutrition screening tools evaluated in this study were in good consistency with the GLIM criteria.
- MNA-SF is the most compatible screening test with GLIM criteria.

Sample Size and Study Population

The sample size was calculated with the OpenEpi v3.01 program. Based on the number of beds in the palliative care center (15 beds) and the time period determined for data collection (3 months), the sample size should include at least 73 patients at 5% significance level, 95% CI, and 95% power. A total of 120 patients were included in the study.

The GNRI, PNI, MNA-SF, NRS-2002 tests, and GLIM criteria were evaluated. In addition, a questionnaire form was used to recognize the sociodemographic characteristics of the individuals. Patients who did not want to participate in our study for any reason and whose anthropometric measurements could not be performed (because of amputation or wounds) were excluded from the study.

Anthropometric Measurements

Middle upper arm circumference

In a standing upright position, the arm was bent 90° from the elbow, the midpoint between the acromial process on the shoulder and the olecranon process on the elbow was marked, and the circumference was measured with a tape measure. Patients who could not stand were measured in a sitting or lying position. The cutoff points were taken as 23.95 cm in men and 23.9 cm in women.[6]

Calf circumference

Calf circumference (CC) was measured with a tape measure from the widest part of the calf in sitting position. In bedridden patients who could not sit, it was measured with a tape measure from the widest part of the calf while lying down. The cutoff points were taken as 30.75 cm in men and 29.45 cm in women.[6]

Assessment Tools

Sociodemographic form

It was a questionnaire in which individual variables such as age, gender, occupation, income status, educational status, marital status, disease history, where and with whom the patient lives, and the status (formal or informal) of caregiver were asked.

Nutritional evaluation scales

1. Global Leadership Initiative on Malnutrition criteria: First, risky patients are identified using one of the

validated screening tests. Then, the second step is done to diagnose MN. The second step included involuntary weight loss, low body mass index (BMI), and low muscle mass in the phenotypic criteria, and decreased food intake and severity of the underlying disease that is associated with the MN as the etiological criteria. Among these criteria, percentage of weight loss, low BMI, and decreased muscle mass are accepted as phenotypic criteria, while decreased food intake or digestion and severity of disease/inflammation status are accepted as etiological criteria. According to GLIM, at least 1 phenotypic criterion and 1 etiological criterion are required for the diagnosis of MN. It has also been accepted by European Society of Clinical Nutrition and Metabolism (ESPEN) and American Society for Parenteral and Enteral Nutrition (ASPEN) that the GLIM criteria can be used in screening patients with MN.[5]
Patients who could stand up were weighed with standard scales and those who could not were weighed with patient beds with weighing feature. Height was measured with a standard tape measure. Body mass index was expressed as kg/m^2 in weight/height^2. Middle upper arm circumference (MUAC) and CC were measured to determine decreased muscle mass. Less than expected values for at least one of these measurements were considered low muscle mass. Measurements were made primarily on the right limbs (left limbs in amputation, etc.) with a standard 1.5-m tape measure. Inflammation, within the GLIM criteria, was evaluated according to the C-reactive protein value (evaluated according to laboratory reference values) or according to the presence of acute disease/injury or chronic diseases (conditions accompanied by inflammation such as rheumatic disease, malignancy, and COPD).

2. Geriatric nutritional risk index: The GNRI is used to assess the nutritional status of elderly bedridden care patients. Geriatric nutritional risk index is calculated using the height, weight, and serum albumin values of the patients: GNRI = [1.489 × albumin (g/L)] + [41.7 × (body weight/ideal body weight)]. The GNRI falls into 4 categories. A GNRI score <82 indicated severe MN risk, between 82 and 92 indicated moderate MN risk, between 92 and 98 indicated mild MN risk, and over 98 indicated normal nutritional status.[7]
3. Prognostic nutritional index: The PNI is calculated according to the following formula:
[10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3)]
According to this formula, a score ≥50 was considered as normal, between 45 and 49.9 was considered as mild MN risk, between 40 and 44.9 was considered moderate MN risk, and <40 was considered severe MN risk.[8,9]
4. Mini-Nutritional Assessment—Short Form: The MNA-SF consists of 6 questions including anthropometric measurements of individuals (BMI), food intake, weight loss, mobility, psychological stress, and neuropsychological problems. According to MNA-SF, 12-14 points are defined as normal nutritional status and <11 points are defined as MN risk.[10]
5. Nutrition Risk Screening-2002: The scoring system consists of 2 parameters as "nutritional status" and "disease severity" and provides scoring as "no problem," "mild," "moderate," and "severe" MN risk. Scoring is made between 0 and 3 for each section. For patients over 70 years of age, 1 more point is added to the score due to age. Those with a total score of ≥3 was MN risk.[11]

Parameters related to hospitalization in the palliative care unit

The comorbidities of the patients, the reasons for hospitalization in the palliative care unit, and the number of drugs used were also noted. Comorbidities were scored according to the Modified Charlson comorbidity (MCC) index.[12]

Statistical Analysis

Statistical Package for Social Sciences (IBM SPSS Corp., Armonk, NY, USA) 26.0 program was used for statistical analysis. Frequency (n), percentage (%), mean ± SD, minimum–maximum, and median values from descriptives were used for statistical evaluation. The normal distribution of the data was evaluated with the Kolmogorov–Smirnov test. For the median comparison in 2 independent groups, the Mann–Whitney *U*-test was used, and Kruskal–Wallis tests were used in more than 2 groups. Interdata correlation analysis was performed with Spearman correlation test. Categorical data were expressed as numbers and percentage. The chi-square test was used to compare categorical data. Receiver operating characteristic (ROC) curve analyses were performed by using the MedCalc software program to screen tools according to the GLIM criteria, and the strengths of those MN screening tools were compared. A *P*-value <.05 was accepted as statistical significance.

RESULTS

A total of 120 patients, 57 females (47.5%) and 63 males (52.5%), were included in the study. The mean age of the participants was 69.9 ± 15.9 years. Table 1 shows the sociodemographic characteristics of the participants.

According to the GLIM criteria, 83.3% of the participants had MN. The GNRI, PNI, MNA-SF, and NRS-2022 tests showed MN risk in 72.5%, 95%, 98.3%, 84.2% of the participants, respectively (Table 2).

Table 1. Sociodemographic Characteristics of the Participants

Parameters	Number	%
Gender		
Female	57	47.5
Male	63	52.5
Marital status		
Married	73	60.8
Single	47	39.2
Chronic disease		
Present	114	95.0
Absent	6	5.0
	Median	(Minimum–maximum)
Age, years	74	19-95
Height, cm	165.0	150-185
Weight, kg	65.5	40-105
BMI, kg/m^2	23	15.0-38.0
Albumin	29	16-44
Charlson comorbidity index	10	3-16

BMI, body mass index.

Table 2. Evaluation of the Nutritional Status by Different Scales

According to	n (%)
GLIM criteria	
Normal nutritional status	20 (16.7)
Malnutrition	100 (83.3)
MNA-SF	
Normal nutritional status	2 (1.7)
MN risk	118 (98.3)
GNRI	
Normal nutritional status	33 (27.5)
Mild MN risk	45 (37.5)
Moderate MN risk	12 (10.0)
Severe MN risk	30 (25.0)
PNI	
Normal nutritional status	6 (5.0)
Mild MN risk	13 (10.8)
Moderate MN risk	23 (19.2)
Severe MN risk	78 (65.0)
NRS-2002	
Normal nutritional status	19 (15.8)
Malnutrition risk	101 (84.2)

GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; MN, malnutrition; MNA-SF, Mini-nutritional Assessment—Short Form; NRS-2002, Nutritional Risk Screening-2002; PNI, prognostic nutritional index.

There was no statistically significant relationship between MN and gender, marital status, education level, presence of chronic disease, and closeness of the caregiver ($P=.462$, $P=.358$, $P=.909$, and $P=.261$, $P=.098$, respectively). Patients with MN were older and had higher MCC index scores ($P=.010$ and $P=.001$, respectively). The comparison of sociodemographic characteristics according to nutritional status is shown in Table 3.

In the ROC analysis performed using the GLIM criteria, the area under the curve (AUC) values for GNRI, PNI, MNA-SF, and NRS-2002 were 0.797, 0.749, 0.927, and 0.781, respectively (Table 4). Accordingly, the cutoff value of score 5 for MNA-SF had 85% sensitivity, 90% specificity, 54.5% negative predictive value, and 97.7% positive predictive value in predicting the MN risk.

DISCUSSION

In this study which compared different nutritional screening scales with the GLIM criteria, MNA-SF was the most appropriate screening test in palliative care setting with the highest sensitivity and specificity (85% and 90%, respectively). Other screening tools were also well compatible with the GLIM criteria at the specified cutoff values. In this study population, the frequency of MN was 83.3% according to the GLIM criteria.

The need for palliative care centers is increasing due to aging and higher prevalence of cancer and other chronic diseases in the population. Early diagnosis and the treatment of MN and effective fight against MN can increase the quality of life of patients and their relatives in need of palliative care, reduce the formation of pressure sores, and provide positive effects in terms of prognosis.[13] In a study conducted with patients who received palliative care services by using inpatient and home care services, the MN risk rate with MNA-SF was 57.4%.[14] In our study, 98.3% of the participants had MN risk according to MNA-SF. This may be due to the fact that patients with MN need more inpatient palliative care.

Table 3. Comparison of Sociodemographical Characteristics by Malnutrition Status

	Malnutrition		Normal nutritional status		
	Number	%	Number	%	*P*
Gender					
Female	46	80.7	11	19.3	.462
Male	54	85.7	9	14.3	
Marital status					
Married	59	80.8	14	19.2	.358
Single	41	87.2	6	12.8	
Chronic disease					
Present	96	84.2	18	15.8	.261
Absent	4	66.7	2	33.3	
	Median	Minimum–maximum	Median	Minimum–maximum	
Age, years	76	20-95	64.5	19-81	.001
BMI, kg/m^2	22	15.0-38.0	26	21.0-33.0	.001
Charlson comorbidity index	10	3-16	6.5	3-12	.001

BMI, body mass index.

The musculoskeletal system, immune system, respiratory system, cardiovascular system, and nervous system are adversely affected in patients with MN.[15] In a study, it was reported that sarcopenia, tendency to infections, pressure sores, acute renal failure, and increased mortality were observed more frequently in malnourished patients.[16] In our study, no significant relationship was found between the presence of chronic diseases and MN. This may be due to the fact that palliative care patients mostly have multimorbidity and at least one chronic disease.

Table 4. ROC Analysis Results for Nutritional Assessment Scales

Parameters	AUC	Cutoff	*P*	Sensitivity	Specificity	NPV	PPV
GNRI	0.797	≤94	<.001	76	75	38.5	93.8
MNA-SF	0.927	≤5	<.001	85	90	54.5	97.7
PNI	0.749	≤38.2	<.001	62	80	29.6	93.9
NRS-2002	0.781	>3	<.001	65	80	31.4	94.2
GNRI vs. MNA-SF			.027				
GNRI vs.NRS-2002			.827				
GNRI vs. PNI			.452				
MNA-SF vs. NRS-2002			.004				
MNA-SF vs. PNI			.003				
NRS-2002 vs. PNI			.697				

AUC, area under the curve; GNRI, geriatric nutritional risk index; MNA-SF, Mini-nutritional Assessment—Short Form; NPV, negative predictive value; NRS-2002, Nutritional Risk Screening-2002; PNI, prognostic nutritional index; PPV, positive predictive value; ROC, receiver operating characteristic.

There are many different nutritional screening scales in the literature; however, there is no consensus on their effectiveness in the studies.[17] Nutritional Risk Screening-2002 has been validated in case–control studies in hospitalized patients, and it is shown among the tests that can be used by ESPEN to screen inpatients and to select patients who can benefit from nutritional support in line with the data obtained.[11] In a study comparing the scales used for nutritional assessment in hospitalized patients, it was found that GLIM and NRS-2002 and GLIM and Subjective Global Assessment showed good agreement (κ=0.784 and κ=0.804, respectively).[18] In another study, the NRS-2002 and Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT) scales were compared with GLIM, and it was found that the RFH-NPT showed better compliance (k=0.64; AUC=0.823).[19] In a study evaluating the nutritional status of patients with liver cirrhosis, MNA-SF was the most compatible scale with the GLIM criteria (sensitivity 88% and specificity 97%).[20] In our study, similar to this finding, MNA-SF was the most compatible test with GLIM, with 85% sensitivity and 90% specificity. A study evaluating the nutritional status of geriatric patients and comparing GLIM with MNA-LF and MNA-SF showed the AUCs as 0.92 and 0.90, respectively, and it was concluded that the short form can also be used for ease of administration.[21]

Malnutrition was evaluated in hospitalized elderly patients using the MNA-SF and GLIM criteria. According to MNA-SF, 34% of the patients were found to be at risk of MN and 18% were malnourished. Afterward, these patients were also evaluated with the GLIM criteria, and 33% of them had MN.[22] In a study conducted with geriatric oncology patients, the GLIM criteria and MNA-SF were compared, and the AUC for MN risk was 0.75 and the cutoff value was 11. The cutoff values for MNA-SF and MNA-LF were above the original cutoff values of the scales. This difference may point out that MNA-LF and MNA-SF are more rigorous than the GLIM criteria in indicating MN risk.[23] In our study, on the contrary, the cutoff value for MNA-SF was found to be 5, and it was below the original cutoff value of 7. This difference may be due to the fact that the other study was conducted on oncological patients.

Our research has some limitations. It was conducted in a single center, and since it was conducted in a palliative care center, the number of patients with normal nutritional status was low, which may have caused the results to be insignificant in statistical comparisons with the sociodemographic data. Multicenter studies with larger case series are needed. In addition, the fact that we used MUAC and CC values for the evaluation of muscle mass within the scope of GLIM criteria is a limitation, considering that the study population is palliative care patients. Because this patient group often have poor nutritional status and peripheral edema. If muscle mass measurements were made with ultrasonography, computed tomography, or magnetic resonance imaging methods, it could be evaluated with more objective data. In laboratory evaluation, albumin, which is a negative acute-phase reactant, may not be sufficient because most of these patients have inflammation and concomitant infections.

As a result, the AUC value in predicting MN diagnosis of each scale was at the desired level when compared to the GLIM criteria in the ROC analysis performed in our study. Accordingly, MNA-SF has a significantly higher AUC value than other scales. In addition, each evaluated scale shows high compliance with the cutoff values specified with the GLIM criteria, which can be used for nutritional assessment in suitable patients.

Ethics Committee Approval: Ethics committee approval was received for this study from Hamidiye Scientific Research ethics committee of Health Sciences University (Date: March 11, 2022, Number: 22/120).

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

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CLINICAL SCIENCE OF NUTRITION

Review Article

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Methods Used in Confirmation of the Position of Nasogastric Feeding Tubes: Advantages and Limitations

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ABSTRACT

Confirmation of the placement of the nasogastric tube is essential to ensure safe feeding without the risk of aspiration, pneumonia, and pneumothorax that may occur due to incorrect placement of the nasogastric tube. The risk of incorrect placement of the nasogastric tube may increase in the high-risk patient group, especially with some factors such as decreased consciousness, weak gag reflex, intubation, mechanical ventilation, and sedation. In addition to the problems that may occur during the initial placement of the nasogastric tube, displacement of the nasogastric tube may occur during the enteral feeding process. For this reason, tube placement should be checked regularly in order to minimize the complications of enteral nutrition. Although there are some advantages and limitations of the methods used to determine the location of the nasogastric tube, it is seen that there is no standard practice on this subject in clinics. The aim of this review is to summarize the commonly used methods for the initial placement of the nasogastric tube and the confirmation of the tube position during the feeding process and to summarize the advantages and limitations of these methods.

Keywords: Enteral nutrition, nasogastric tube, nursing, evidence-based practice

INTRODUCTION

Today, nasogastric (NG) tube placement in intensive care patients and clinics has become one of the most invasive procedures performed by physicians and nurses, together with the developments in technology, prolongation of life expectancy in patients, and increasing importance of nutritional support.[1-6] Nurses providing enteral nutrition (EN) support have serious difficulties in placing the NG tube correctly and verifying its placement.[7-10] Although it seems to be a simple and safe procedure, the misplacement of the NG tube is frequently reported in both pediatric and adult patients. Generally, risks for patients arise from incorrect placement of the NG tube. The incidence of NG tube placement outside the gastrointestinal system has been reported as 1.3%-2.4% in >2000 procedures.[11-14] In addition to the lack of a complete reporting system on the subject, the 2017 Pennsylvania Patient Safety Authority reported 166 cases of NG tube misplacement between 2011 and 2016. In this report, 10.2% of misplacements occurred in pediatric patients.[15] In the report of the UK national health center, misplacement of the NG tube was reported in 95 people between 2011 and 2016.[16] Incorrect placement of the NG tube can cause serious fatal complications in the patient. Important complications that may occur with the placement of the tube in the lungs are aspiration, pneumonia, pneumothorax, hemothorax, atelectasis, emphysema, and esophageal perforation.[14-17]

In a report by the US Food and Drug Administration, 51 cases of pneumothorax associated with the misplacement of the NG tube were reported between 2012 and 2017. Most cases have a history of emergency intervention such as decompression and chest tube placement, with some cases resulting in cardiopulmonary arrest and death.[17] In another study, 95 cases in which the NG tube was accidentally placed in the lungs over a 5-year period were detected and this resulted in the death of 32 patients. The risk of misplacement of the NG tube may increase in the high-risk patient group, especially with some factors such as decreased consciousness, weak gag reflex, intubation, mechanical ventilation, and sedation.[18] In addition to the problems that may occur during the

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initial placement of the NG tube, displacement of the NG tube may occur during the enteral feeding process.

For this reason, in order to minimize the complications associated with the placement of the tube during the EF support process, especially pulmonary aspiration secondary to the placement of the tube in the respiratory tract and gastroesophageal reflux, tube placement should be checked before each feeding in intermittent feeding, at least twice a day on continuous feeding, and more frequently if the patient has vomiting, retching, or respiratory problems such as coughing spasms.[19]

Evaluation of NG tube position is an important issue in maximizing the functionality of the NG tube, minimizing tube- and feeding-related complications, and ensuring optimal patient safety. Methods used in clinics to determine the location of the NG tube include radiological examination, pH measurement of gastric aspirate, observation of color of gastric aspirate, auscultation, enzyme tests, and measurement of the length of the NG tube.[20] In light of this information, this review aims to provide information about reliable and practical verification methods in confirming the placement of the NG tube, as well as to reduce the complications that may occur with the use of the most reliable and accurate method in clinics in our country, to present the results of studies with a high level of evidence for the use of common reliable methods, and to shed light on new studies to be done. Table 1 presents the advantages and limitations of the methods used to place the NG tube. Below are the methods used to determine the location of the NG tube and information about the studies performed with these methods.

Radiological Examination

The placement of feeding tubes should be checked regularly. Especially in patients with high risk and endotracheal tubes, it is recommended to control the tube location with the radiological method in the first placement of the NG tube.[21] The most reliable and valid evaluation method for checking the location of the NG feeding tube is properly obtained and interpreted radiography. Radiological examination is accepted as the gold standard method for distinguishing the placement of the tube in the stomach and lungs.[11,19,21-28] Guidelines published on the subject have reported that radiography is the gold standard testing method.[29]

While radiological verification is accepted as the gold standard in tube placement, this method is not a mandatory policy in institutions. It is difficult to say that it is used routinely in every hospital because it has some disadvantages such as the cost of the procedure, the difficulty of interpretation by health personnel due to radio-opacity or insufficient radio-opacity in some tubes, and poor x-ray quality, continuous exposure to radiation, and the need to constantly go to the hospital for patients who continue to be treated at home.[22,23,27,29] In children's hospitals, the radiological examination method is not used as the first choice, especially to reduce radiation exposure.[30] In addition, it is very important that the radiological examination is carried out by experts and that the result is interpreted correctly. In a report by the National Patient Safety Agency, the radiological examinations of 45 patients with NG tubes were misinterpreted, resulting in the death of 12 patients.[22,23,31]

In recent years, ultrasonography and sonography techniques are among the other radiological examination methods recommended to confirm the location of the NG tube, since it is a non-invasive and radiation-free imaging method and it is a faster application compared to x-ray. In addition, studies have reported that it is a suitable method for emergency intervention in unconscious patients.[19,32-34] In a study conducted in the pediatric intensive care unit, it was reported that confirming the location of the NG tube by a radiologist with bedside ultrasonography and sonography was 100% sensitive.[33] In a study conducted in the adult intensive care unit, the ultrasound method correctly determined the location of the NG tube in 34 of 35 patients; however, studies with larger groups were recommended due to the limited sample size in studies on this method.[35]

In a study conducted by community health nurses, the confirmation of the NG tube location of 68 adult patients was compared with ultrasound and pH measurement by nurses, and the sensitivity and specificity of ultrasound were determined as 95.45% and 100%, respectively. It was emphasized that ultrasound could be used in cases where the x-ray device could not be used.[36] A systematic review and meta-analysis examining studies on 420 patients with NG tubes reported that the diagnostic performance of ultrasound was useful for confirming

Main Points

- Nasogastric (NG) tube placement in intensive care patients and clinics is one of the most invasive procedures performed by physicians and nurses.
- Misplacement of the NG tube and/or failure to evaluate the tube position after placement may lead to serious fatal complications in the patient.
- Control of the placement/location of the NG tube should be ensured with practices with a high level of evidence supporting patient safety, and adequate training and competence of health personnel on the subject should be supported.

Table 1. Advantages and Limitations of Methods Used to Confirm Nasogastric Tube Position		
Method	**Advantages**	**Limitations**
Radiological examination	There is no need to aspirate gastric contents from the tube	It causes radiation exposure It has relatively high cost Bedside application and interpretation by every healthcare professional is difficult.
pH test	It is easy to apply It is cost-effective It can distinguish the stomach, intestine, and lung location	There is a need to aspirate stomach contents from the tube Last feeding time, continuous infusion feeding, and some medications such as proton pump inhibitors may affect gastric pH and alter the outcome. pH value is limited in detecting esophageal localization
Auscultation method	There is no need to aspirate gastric contents from the tube It is cost-effective	Regardless of whether the nasogastric tube is in the stomach, duodenum, or proximal jejunum, inflated air sounds can be heard from the upper abdominal wall.
Biochemical markers	The use of biochemical markers increases the accuracy of the pH result. pH and bilirubin levels detect gastric location highly and accurately in all respiratory tract locations	The gastric contents need to be aspirated. There are limited studies on the method There is no pepsin and trypsin test that can be done on the bedside, so it is difficult and costly to apply. Similar to the pH method, the last feeding time, continuous infusion feeding, and some drugs such as proton pump inhibitors can affect the gastric pH and change the result.
Capnography/calorimetric capnometry	There is no need to aspirate gastric contents from the tube It can detect tracheal localization with very high accuracy.	Contact of gastric reflux with capnometry may cause false-positive results. Fizzy drinks and medications containing sodium bicarbonate can potentially cause carbon dioxide in the stomach
Ultrasound	It defines the placement of the tube in the stomach and esophagus	It is difficult for intubated patients to determine that the nasogastric tube is in the trachea. Its cost can be high Additional training is required for users and evaluators

NG tube placement, but not optimal for detecting incorrect NG tube position.[37] On the other hand, the fact that radiological examination methods will be constantly performed and evaluated by a radiologist creates a limitation for nurses and other health personnel to verify the location of the bedside tube. It has also been emphasized that this may delay the start of feeding and interrupt the feeding process.[38] Tsujimoto et al.,[35] on the other hand, reported that the ultrasound method should not be applied alone to confirm the location of the NG tube, but it could help in determining the location of the NG tube in cases where the x-ray device could not be used. It is emphasized that more studies are needed with a larger sample group on the subject.[1]

pH Test

Testing gastric pH by aspirating a small amount of liquid from the tube is considered an alternative method for confirming the location of the NG tube. Measuring the acidity of stomach contents is accepted as an evidence-based method used to confirm the location of the NG tube. Studies have shown that the pH value of 5.5 and below for the aspirate obtained from the NG tube indicates that the tube is properly placed in the stomach. In the studies performed, the value with the highest sensitivity and specificity in determining the location of the NG tube was determined as pH $\leq$ 5.5.[39-41]

A working group was formed in 2012 by the American Society for Parenteral and Enteral Nutrition (ASPEN) in order to eliminate the disadvantages of radiography, which is accepted as the gold standard, and to identify a practical and applicable method with the highest level of evidence for radiography. This working group constituted of the American Association for Critical Care Nurses, Society of Pediatric Nurses, National Association of Neonatal Nurses, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Children's Healthcare Association Patient Safety Organization, and ASPEN and it is known as the New Opportunities for Verification of Enteral Tube Location (NOVEL) project.[19] The NOVEL project's recommendation to confirm the placement of the NG tube is to measure gastric pH, especially in children. As an indication of gastric location,

gastric pH ≤ 5.5 is accepted as an indication that the tube is in place. In cases where gastric contents cannot be obtained, radiological examination is recommended. Moreover, the working group prepared a chart on how to measure pH from the NG tube (Figure 1).

As a standard practice by the UK National Patient Safety Center and the American Association of Intensive Care Nurses, pH measurement is performed to confirm the location of the NG tube, and a pH value between 1 and 5.5 is accepted as an accurate indicator for the placement of the tube in the stomach.[15] Although it is an easy, practical, and cost-effective method that can be applied at the bedside, the method has some limitations. The pH measurement is helpful in distinguishing gastric location from pleural or intestinal location (usually pH ≥ 6), but it is difficult to say that it is completely reliable in confirming the location in the esophagus. Anecdotal reports indicate that the pH measurement of fluid aspirated from tubes in the esophagus can be as low as 1 (perhaps as a result of reflux of acidic gastric juice) or as high as 7 (as a result of swallowing alkaline saliva). Therefore, it is stated that the pH value of the fluid is limited in detecting esophageal localization.[42] On the other hand, a difficulty of the application is that the patient is fed enterally with continuous infusion and the result is not reliable as some drugs may affect the pH value. For example, Histamine-2 receptor antagonists, antacids, and proton pump inhibitors can suppress stomach acid, causing measurement of high pH (pH > 5.5) values that raise concerns about tube misplacement.[11,19,42,43]

In a study, it was determined that gastric pH value was higher in patients using acid-inhibiting drugs (4.34 ± 0.14) compared to non-users (43.33 ± 0.2).[42] In the study of

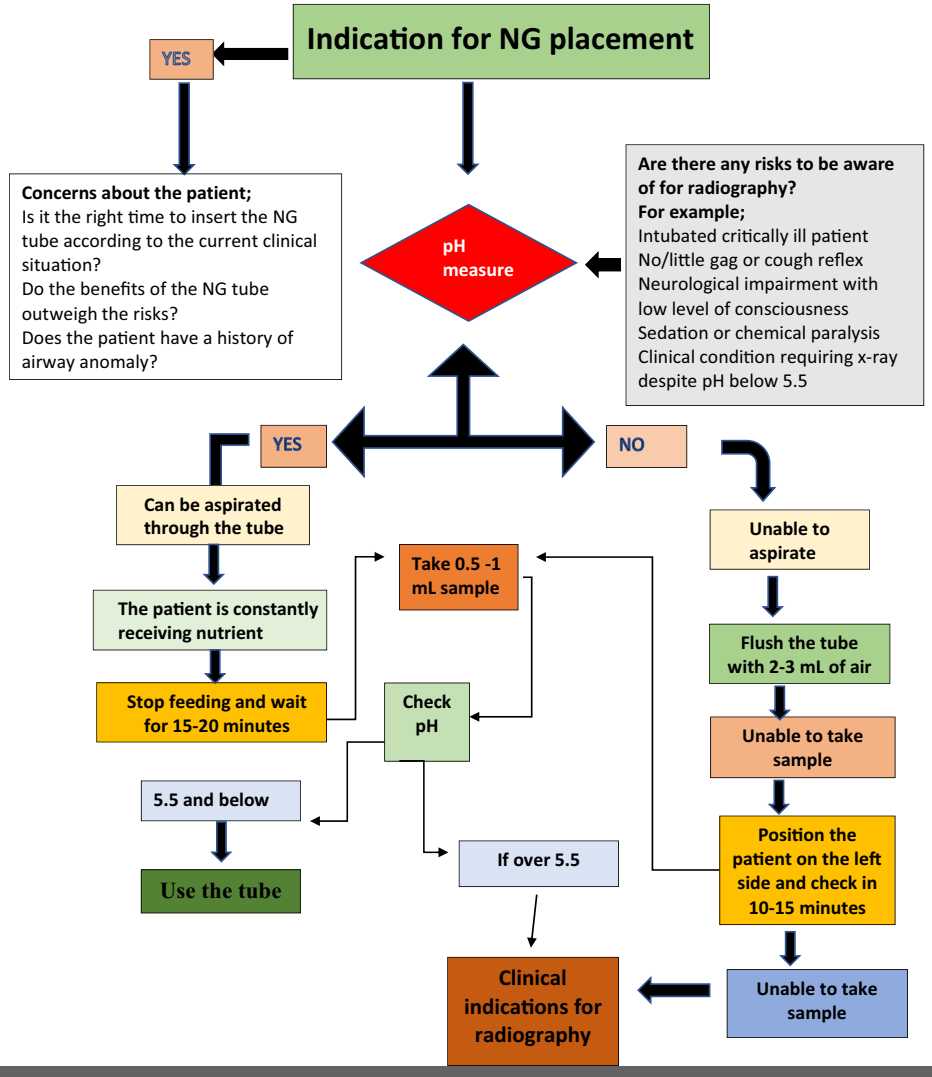

Figure 1. Placement of nasogastric feeding tube and verification of its location. mL, milliliter; NG, nasogastric. Adapted from Irving SY, et al. Pediatric nasogastric tube placement and verification: Best practice recommendations from the NOVEL Project. *Nutr Clin Prac.* 2018;33:921–927.

Boeykens et al.,[43] gastric pH_1 value was reported as 4.6 in people using H2 receptor antagonists and proton pump inhibitors and as 3.5 in non-users. Moreover, the inability to take gastric aspirate is another limitation of the application. Borsci et al[44] reported that gastric contents could not be obtained in 45% of the cases, 11% of the personnel participating in the study misinterpreted the strips, and the possibility of misreading the strips could lead to wrong decisions. In another study, gastric contents could be aspirated from only 48.6% of the patients. In the same study, in 33.5% of the cases, gastric content could be taken in line with additional measures such as providing air from the NG tube and lateral positioning. This situation caused a delay in feeding in 33.5% of the patients. The method could not be used because gastric contents could not be obtained from 18.4% of the patients. For accurate evaluation of pH measurements, pH sensors or guide wire with pH sensors in clinics and NG tube placement are recommended.[45]

Recently, some devices that can be used to evaluate the pH of the stomach contents without the need for pH strips to determine the gastric tip placement of the tube have been produced. On the other hand, with the fiberoptic sensor technology that can measure pH without the need for gastric aspirate, measurement devices that easily verify the location of the tube by turning on the green light on the device accompanied by a guide placed in the tube have been produced. In addition, some measuring devices have been produced in which CO_2 and pH measurement are made together. Although clinical studies on these devices are not yet available, they are seen as very promising technologies in determining the placement of the NG tube. In general, although the pH method has some limitations, it is accepted as an alternative to radiography, which is considered as gold standard, and as a practical application with the highest level of evidence. pH measurement is considered to be the most appropriate method to be used in clinics in terms of its ease of application, practicality, ability to give immediate results, cost-effectiveness, no exposure to radiation, and accurate results.[19,46]

Visual Evaluation of Fluid Aspirated From the Feeding Tube

This method is the visual examination of the fluid taken from the feeding tube. Gastric contents may be sedimented grass-green, brown (if blood is present and gastric acid has acted), clear and colorless (often snuff-colored with streaked grayish-white mucus or sediment), and rarely straw-colored. Since tracheobronchial fluids are actually composed of yellowish brown (snuff-colored) grayish-white mucus, the fluid in this appearance can be both respiratory fluid and gastric fluid. The pleural fluid is mostly clear and straw-colored. As a result of inadvertent insertion of the feeding tube into the pleura, the pleural fluid may appear bloody. When the infection develops, the pleural fluid may be seen as unclear. The contents of the small intestine are mostly clear and yellow to bile pigment in color. Therefore, it has been reported that the evaluation of the color of gastric contents taken with an injector is not an appropriate method without a high level of evidence to confirm the location of the feeding tube, and it has been reported that this method alone is inconvenient to use in clinics.[39]

Auscultation Method

This method involves injecting air through the tube with an injector and simultaneously listening to the "bubbling" or "gurgling-whining" sound over the epigastrium using a stethoscope. When the tube is placed in both the lung and upper gastrointestinal system (esophagus, stomach, duodenum, or proximal jejunum), the given air passes audible sounds through the epigastric region. Although this estimated sound is not an indication that the tube is directly in the stomach, it may be confused with intestinal, bronchial, or pleural sounds.[42] However, it is reported as the most frequently used method by nurses in clinics.[47]

A large-scale prospective study comparing the auscultation method and pH measurement with abdominal x-ray, which is accepted as the gold standard, examined 178 stomach contents and emphasized that the auscultation method was not a reliable method with 79% sensitivity and 61% specificity.[46] Although it is seen as an advantage that there is no need for gastric aspirate and measurement of aspirate, the reliability of the method is questionable and its use alone in clinics is not recommended.[31,43,48] In a review examining international guidelines, auscultation was reported as an unreliable method.[29]

Measurement of the Length of Tube

Once the NG feeding tube is in place, the tube is secured and marked with an indelible pen at the point where it exits the hole. In this method, the length of the tube outside the patient's body is measured and the line marked with this measurement is recorded in the patient file. These measurements are followed regularly. The majority of a previously correctly placed tube being left out is a clear indication for re-administration or replacement of the tube. However, in this method, although the tube is properly fixed, it may migrate, bend in the stomach, or extend to the first part of the duodenum. Especially in small diameter tubes, tube migration may occur more frequently. For this reason, it has been reported that it has no high level of evidence in confirming the location of the NG tube and it is inconvenient to use this method alone in clinics.[49,50]

Capnography and Calorimetric Capnometry

Capnography is an alternative method to confirm the position of the NG tube in mechanically ventilated patients. Capnography is the continuous analysis and recording of carbon dioxide (CO_2) using infrared technology. The result is expressed as the partial pressure of mercury in millimeters. In colorimetric capnometry, pH-sensitive filter paper impregnated with phenolsulfonephthalein is used and the strip color changes from purple to yellow in the presence of CO_2. The device, which is used to determine whether the placement of the tube is correct during the administration of NG tube, shows different colors according to the presence of CO_2 in the region where the tube is placed, after it is placed on the outer end of the tube. The purple color indicates the absence of CO_2 (indicating that the tube is in the stomach), and the brown or yellow color indicates the presence of CO_2 (indicating that the tube is outside the stomach). Since the lungs breathe CO_2, capnography/colorimetric capnometry is expected to detect CO_2 if the NG tube is placed in the lung rather than the stomach. The calorimetric capnography method is accepted as a valid method for confirming the placement of the NG tube for patients on mechanical ventilation.[5] On the other hand, this method confirms the accidental placement of the NG tube in the trachea, but it is not a useful method to distinguish between the placement of the tube in the esophagus or duodenum. Fizzy drinks or sodium bicarbonate may affect the result. When these methods are used in combination with radiology, they strengthen the accuracy of the tube location.[5,46]

In a systematic review examining studies comparing the placement of NG tube with capnography/calorimetric capnometry in adult patients, despite the high sensitivity and specificity of both methods, the limited sample size of the studies was reported as an important limitation and colorimetric capnometry method was reported to be more reliable than auscultation method for confirming the placement of the NG tube. Moreover, it was stated that it was compatible with the radiological method, but insufficient in distinguishing gastric or duodenal localization. It was emphasized that more studies on the subject were needed.[5] The use of these methods alone for locating the NG tube is not recommended.[1]

Biochemical Markers

In this method, bilirubin, trypsin, and pepsin levels are used together with pH measurement to confirm the location of the NG tube. Adding laboratory enzyme analyses to pH tests of fluid aspirated from feeding tubes increases the possibility of accurately distinguishing gastric, intestinal, and respiratory locations. Fluid withdrawn from the tube in the stomach contains mostly pepsin, and fluid withdrawn from the small intestine contains mostly trypsin, but little or no pepsin. Fluid drawn through misplaced tubes in the lungs usually contains little or no 2 of these gastrointestinal enzymes. Bilirubin level in the intestines is significantly higher than in the stomach. The major disadvantages are that there are not many studies on the subject, there are no simple bedside enzyme tests used in combination with pH measurements to confirm the tube position, it wastes time waiting for laboratory results, and it delays the feeding process. In addition, the necessity of removing gastric contents and the effect of factors that will influence the gastric pH result (continuous EN, some drugs, etc.) in this method are other disadvantages.[22,51]

CONCLUSION

The combined results of studies and guidelines show that x-ray is the most reliable and accurate method for distinguishing gastric and pulmonary location of the NG tube. Although it is not primarily used in all cases, it is supported to prefer the radiological method, especially for intensive care patients and critical patients with decreased consciousness levels and gag reflexes. Among the non-radiological methods, the common agreement of the guidelines and studies is the pH measurement of the gastric content. It is seen that the use of other non-radiological methods such as auscultation, examination of the color of the gastric contents, and monitoring of the length of the tube may cause distressing results in terms of patient safety and should not be used alone to confirm the location of the NG tube. Some methods alone have failed to provide an evidence base. For example, the absence of special bedside tests such as enzyme tests and the limitations of the use of CO_2 detectors in the routine clinical setting. Additional validation methods have been proposed for these applications.

In conclusion, a valid and comprehensive safety approach is required in verifying the placement of NG tubes. However, it is seen that there is no consensus on a standard method on this subject in studies and guidelines. More studies with a high level of evidence are needed to develop good practice protocols on the subject. Although the pH method is the most widely accepted method in order to increase safety and minimize radiological exposure in patients with NG tube, more studies are needed to standardize it as an application that health personnel can easily evaluate. Adequate training and competency of all healthcare personnel are extremely important in developing standards that include high-evidence practices that support patient safety and in determining the placement/location of the NG tube.

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CLINICAL SCIENCE OF NUTRITION

Case Report

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Nutritional Bicytopenia in the Context of a Very Low-Calorie Diet with Adequate Micronutrient Supplementation

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ABSTRACT

The aim of this study is to establish the ideal clinician's approach to nutritional bicytopenia in the context of adequate micronutrient supplementation. We present the case of a 27-year-old patient living with obesity, subjected for months to a very low-calorie diet and adequate supplementation with complementary vitamins and minerals, evaluated and treated for bicytopenia with iron-deficiency anemia and lymphocytopenia. The use of meal replacement supplements as nutritional sources replacing food items requires medical supervision as they can have consequences on the patient's micronutrient balance. Classically, and frequently, iron-deficiency anemias have been identified as the most common condition in these restrictive nutritional regimens. However, alterations in the white cell line are more frequent than believed and may be associated with multiple nutritional deficiencies including folic acid and vitamin B12. The diagnostic approach becomes complex when the most common nutritional causes are hidden by replacement supplements. The patient achieved an increase in hemoglobin after treatment (12.3 g/dL), recovering from anemia. When approaching nutritional cytopenias, the primary takeaway should always be the thinking process. Every patient with bicytopenia must be studied particularly meticulously, and the good clinician is forced to address it and reach the most likely diagnosis within the common and the rare.

Keywords: Anemia, folic acid, iron-deficiency anemia, leukopenia, lymphopenia, vitamin B12

INTRODUCTION

Iron, vitamin B12, and folic acid are the basic nutrients the bone marrow uses to build hematopoietic cells. When any of the above are no longer supplemented correctly, nutritional anemias can occur due to direct impairment in the synthesis and maturation of hematopoietic cells.[1] These cells begin to be reduced in quantity and size, having a clinical impact on the patient and causing specific symptoms to the affected cell line. Anemias are classified as microcytic when the mean corpuscular volume (MCV) is less than 80 fl.[2] Iron deficiency is by far the major cause of microcytic anemia, but pyridoxine and copper can cause it as well. Normocytic anemias are common in patients with protein-energy malnutrition and various chronic diseases, and macrocytic anemias can be caused by vitamin B12 or folic acid deficiencies.[3] The coexistence of iron and folic acid deficiencies is common and can be confirmed with a blood smear examination, measuring the suspected deficient nutrient blood level, or a bone marrow study. Therapeutic response to deficient nutrient replacement is the hallmark to define nutritional anemia.[4]

The etiology of anemia can be divided into 3: (i) hemolysis, (ii) blood loss, and (iii) diminished erythropoiesis. Once the first 2 options are evaluated and discarded, erythropoiesis must be studied by the first diagnostic test available in most laboratories: a complete blood count and smear. Iron deficiency occurs when serum ferritin is <30 ng/mL, transferrin saturation is <19%, the anemia resolves with iron replacement, or absence of stainable iron in the bone marrow.[5]

On the other hand, leukopenia associated with iron-deficiency anemia in the context of a very low-calorie diet, with adequate supplementation of folic acid, vitamin B12, copper, and zinc, should be evaluated as a nutritional consequence of iron deprivation.[6]

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CASE PRESENTATION

A 27-year-old female, previously healthy, with a body mass index of 30 g/m^2 and with no medical or pharmacological history, reports having undergone a very low-calorie diet (<800 kcal/day) for 6 months and supposedly adequate supplementation of vitamins and minerals.

She sought a second opinion for the symptoms she was experiencing for about 3 months and was managed in an outpatient clinic. Upon being questioned, she indicated she was experiencing dizziness, fatigue, pale integuments, and palpitation. She denied having a regular menstrual cycle. Physical examination showed pale mucous membranes and integuments, tachycardia, and postural weakness. No hepato-splenomegaly.

Initial hemoglobin (Hgb) 8.2 g/dL (normal value 12-15 g/dL), MCV 60 fL (normal value 80-95 fl), with hypochromia, leukocyte count of 3.5 × 10^9/µL (normal value 4.5-11.0 × 10^9/L), and normal platelets (normal value 150-400 × 10^3/µL). Additional lab tests were required on the same day. Complete results were red blood cell (RBC) count 5.0 × 10^6/µL (normal range 3.8-4.8 × 10^6/µL), Hgb 8.2 g/dL (normal range 12.0-15.0 g/dL), ferritin 12.5 ng/mL (normal range 15-204 ng/mL), transferrin saturation 5% (normal range 20%-50%), Iron 15 µg/dL (normal range 50-170 µg/dL), leukocytes 3.5×10^9/µL (normal range 4.5-11.0 ×10^9/L), platelets 322×10^3/µL (normal range 150-400×10^3/µL), vitamin B12 320 mIU/L (normal range 145.0-596.0), folic acid 15.1 nmol/L (normal range 2.70-16.30 nmol/L), thyroid-stimulating hormone 11.2 mIU/L (normal range 0.700-3.400 mIU/L), free thyroxine 4 fraction 10.7 mIU/L (normal range 7.9-13.9 mIU/L). One week and 2 weeks later, Hgb tests were made with 10.1 g/dL and 12.3 g/dL results, respectively.

This patient was treated in an outpatient clinic, and follow-up visits were held in the same place.

Main Points

- The use of supplementation in restrictive nutritional regimens requires meticulous medical supervision.
- Iron-deficiency anemia remains the most common deficiency in these nutritional regimens.
- When more than 1 blood cell line is affected, folic acid and B12 deficiencies should be addressed.
- In patients with bicytopenia and proper nutritional supplementation, autoimmune, infectious, and hormonal causes must first be ruled out.
- Patients with bicytopenia must be studied meticulously and addressed by the most likely etiology and the rare.

RESULTS

An iron deficiency of approximately 1.5 g was calculated. Due to intolerance of oral iron, this deficiency was managed with ferric carboxymaltose in 2 infusion sessions in an outpatient clinic. Additionally, the patient was orally supplemented with micronutrient complements, such as vitamin B12 and folic acid in the daily recommended dosage.

The patient achieved an increase in hemoglobin of 12.3 g/dL after a 2-week treatment, recovering from anemia (Table 1).

DISCUSSION

Bicytopenia can be a life-threatening condition if a proper diagnosis, treatment, and follow-up are not defined correctly. Although there may be transient cytopenias due to infections in the etiology, serious diseases related to the bone marrow can also be seen. Etiology ranges from inflammatory diseases, infections, transient suppression of the bone marrow, and of course, nutritional deficiencies.[7] According to the etiologic cause, cytopenias can be explained by maturation defects, ineffective hematopoiesis, infiltration of the bone marrow, and cell destruction.

Table 1. Laboratory Results

Laboratory Parameter	Value	Normal Range
RBC	5.0 × 10^6/µL	3.8-4.8 × 10^6/µL
Hgb	8.2 g/dL	12.0-15.0 g/dL
Ferritin	12.5 ng/mL	15-204 ng/mL
Transferrin saturation	5%	20%-50%
Iron	15 µg/dL	50-170 µg/dL
Leukocytes	3.5 × 10^9/µL	4.5-11.0 × 10^9/L
Platelets	322 × 10^3/µL	150-400 × 10^3/µL
Vit. B12	320 mIU/L	145.0-596.0 mIU/L
Folic acid	15.1 nmol/L	2.70-16.30 nmol/L
TSH	11.2 mIU/L	0.700-3.400 mIU/L
fT4	10.7 mIU/L	7.9-13.6 mIU/L
Hgb*	10.1 g/dL	12.0-15.0 g/dL
Hgb**	12.3 g/dL	12.0-15.0 g/dL

fT4, free thyroxine 4 fraction; Hgb, hemoglobin; TSH, thyroid-stimulating hormone; Vit. B12, vitamin B12.
*Before treatment.
**After treatment.

Iron deficiency is the most common cytopenia reported in malnutrition, and its approach to evaluation, diagnosis, and treatment is relatively simple when the suspicion of malnutrition is detected in the medical history.[8] In the face of significant malnutrition due to dietary restrictions, cell lines are theoretically affected by folic acid and vitamin B12 deficiency, and not only from iron.[9,10] The last thing to consider is the approach to leukopenia when we know in advance that the patient had adequate replacement of folic acid and vitamin B12 for at least 6 months when she underwent the caloric regime and that is when we have to think about studying the white cell line alone or collectively as bicytopenia.[11] Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) without any other manifestation in the physical exam would be extremely rare. Cancer and bone marrow failure should be considered and analyzed with a bone marrow aspirate and biopsy if no response to basic treatment is shown. The influence of medications is ruled out in medical history. Infections, especially those of viral etiology, can cause leukopenia to have at least some type of symptoms, which was not the case. Hypothyroidism can be ruled out with an initial thyroid exam.[12-15]

Clinical thinking of the internist always has to fully evaluate the patient, and define what is really probable, based on the most common causes, medical history, and physical examination. The association between iron-deficiency anemia and leukopenia has been related in the past, denoting bone marrow failure due to the deficiency itself.[16] However, the separate diagnostic approach to leukopenia does not confer a unique study purpose. It is here when the therapeutic test with iron has relevance, since when prescribed, bicytopenia can remit.

Nicotinamide adenine dinucleotide phosphate hydrogen-dependent oxidative burst, as well as other monocyte/macrophage differentiation processes, requires iron as a cofactor.[17] In vitro production of cytokines by lymphocytes studies have shown impairment to iron deficiency in the past.[5,18,19]

If the patient had not been adequately supplemented with vitamins and minerals, bicytopenia should no longer be considered clearly associated with nutritional deficiency due to inadequate intake. However, having 2 altered cell lines, which can be explained by different mechanisms, forces the clinician to go further in the diagnosis of leukopenia, and at least rule out the improbable and the most common within the logic and context of the patient.
When approaching nutritional cytopenias, the primary takeaway should always be the thinking process. First of all, the evaluation of possible nutritional deficiencies is primary cause of this condition. In certain cases in which there is evidence that the patient has been adequately supplemented nutritionally with the elements necessary to produce RBCs, white blood cells, and platelets, autoimmune, infectious, and hormonal causes must first be ruled out. If all of the above are within normality, the less frequent cases should be considered, such as bicytopenia, secondary to vitamin or mineral deficiency.

In this new era, in which restrictive diets with adequate vitamin and mineral supplementation are in vogue, every patient with bicytopenia must be studied meticulously, and a good clinician is forced to address it and reach the most likely diagnosis within the common and the rare.

Informed Consent: Informed consent has been obtained from the patient to process the information in the case report.

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