ORIGINAL ARTICLE

Risk of Malnutrition and Its Effects on the Quality of Life of Hospitalized Cancer Patients

Hospitalize Kanser Hastalarında Malnütrisyon Riski ve Yaşam Kalitesine Etkisi

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ABSTRACT

Aim: Malnutrition is one of the most common clinical problems in cancer patients. Its frequency increases in hospitalized cancer patients. In this study, it was aimed to investigate the frequency of malnutrition and its effect on quality of life (QOL) in hospitalized cancer patients.

Materials and Methods: In this cross-sectional study, Nutrition Risk Screening-2002 (NRS-2002) and European Organization for the Research and Treatment of Cancer (EORTC)-QLQ C30 scales were completed for patients with cancer diagnosed in the medical oncology service. The relationship between clinical and laboratory parameters, malnutrition risk and QOL was analyzed by statistical methods.

Results: One-hundred thirteen patients were included in the study. According to the results of NRS-2002, 42.5% (n=48) patients were at risk of malnutrition. There was no difference between the groups in terms of gender and age. When the EORTC-QLQ C30 scale scores were compared, the risk of malnutrition had no effect on the overall health score (p=0.679). Physical function and role function scores were significantly lower in those at risk of malnutrition (worse QOL). There was no statistically significant difference between the groups in terms of other functional scales. When univariate logistic regression (LR) was applied to the factors affecting better general health score, only hemoglobin level was found to be a significant factor. Therefore, multivariate LR was not done.

Conclusion: Malnutrition risk assessment should be performed routinely in every hospitalized cancer patient. Early nutritional support should be given to patients at risk. It was observed that patients with malnutrition risk had worse QOL compared to the EORTC-QLQ C30 scale.

Keywords: Malnutrition, quality of life, NRS-2002, EORTC-QLQ C30

ÖZ

Amaç: Malnutrisyon kanser hastalarında en sık klinik sorunlardan biridir. Hospitalize kanser hastalarında sıklığı daha da artar. Bu çalışmada hospitalize edilmiş kanser hastalarında malnutrisyon sıklığı ve yaşam kalitesine (YK) etkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Kesitsel olarak dizayn edilen bu çalışmada medikal onkoloji servisine yatan kanser tanılı hastalar için Nutrisyon Risk Skorlaması-2002 (NRS-2002) ve "Avrupa Kanser Araştırma ve Tedavi Teşkilatı" (EORTC)-QLQ C30 ölçekleri dolduruldu. Klinik ve laboratuvar paramatreleri ile malnutrisyon riski ve YK arasındaki ilişki istatistik yöntemleri ile analiz edildi.

Bulgular: Çalışmaya 113 hasta dahil edildi. NRS-2002 sonuçlarına göre %42,5 (n=48) hastada malnutrisyon riski tespit edildi. Cinsiyet ve yaş açısından gruplar arasında fark yoktu. EORTC-QLQ C30 ölçek puanları karşılaştırıldığında malnutrisyon riskinin genel sağlık skoru üzerine etkisi yoktu (p=0,679). Fiziksel fonksiyon ve rol fonksiyon skorları malnutrisyon riski olanlarda anlamlı olarak daha düşüktü (daha kötü YK). Diğer fonksiyonel skalalar açısından gruplar arasında anlamlı istatistiksel fark yoktu. Daha iyi genel sağlık skoruna etki eden faktörlere tek değişkenli lojistik regresyon (LR) uygulandığında sadece hemoglobin düzeyi anlamlı faktör olarak bulundu. Bu yüzden çok değişkenli LR yapılmadı.

Sonuç: Malnutrisyon risk değerlendirmesi hastaneye yatan her kanser hastasına mutlaka yapılmalıdır. Malnutrisyon riski olan hastalarda EORTC-QLQ C30 ölçeğine göre daha kötü YK olduğu görüldü. Risk saptanan hastalara erken dönemde nutrisyon desteği verilmelidir.

Anahtar Kelimeler: Malnutrisyon, yaşam kalitesi, NRS-2002, EORTC-QLQ C30

INTRODUCTION

Malnutrition is a condition that causes changes in body components due to a decrease in food intake and leads to decreased physical and mental functions and poor clinical outcomes[1]. Basically, malnutrition is due to insufficient energy and/or protein intake or processing or increased catabolism. Malnutrition is common in cancer patients due to the tumor itself or the complications of treatment, and it has been reported to occur at a higher rate than expected in all stages of the disease[2,3]. The incidence of malnutrition, independent of cancer type, increases to approximately 40%[3]. Malnutrition and weight loss are an important poor prognostic factor in cancer patients[4]. Cachexia typically occurs with weight loss and decreased body mass index (BMI), and it can be prevented by early screening and intervention for malnutrition risk[5]. Malnutrition is also a very common problem for hospitalized cancer patients. In the literature, malnutrition has been reported to be an independent risk factor in terms of long hospitalization time, nosocomial infection, shorter survival, poorer quality of life (QOL) and chemotherapy toxicity in hospitalized cancer patients[4,6,7]. In addition, treatment costs of patients with malnutrition also increase[8].

Anamnesis, physical examination, screening scales, analysis of body components and blood biochemical markers (such as total protein, albumin, prealbumin, lymphocyte count, transferrin) are used in the evaluation of malnutrition. Definitive diagnostic criteria for the diagnosis of malnutrition are not clear and various nutritional evaluation methods have been described in the literature[6,9]. In this study, our aim is to investigate the effects of malnutrition on the QOL and on clinical problems encountered during hospitalization in cancer patients.

MATERIALS AND METHODS

Patients diagnosed with cancer and admitted to the medical oncology service were included in this study in which a cross-sectional study design was used. Before starting the study, İstanbul University-Cerrahpaşa Local Ethics Committee approval was obtained (date: 08.07.2020 number: 86049).

Patients who volunteered to participate in the study and signed the consent form were evaluated within the first 72 hours of their hospitalization with Nutrition Risk Score-2002 (NRS-2002). Those who were not pathologically diagnosed with cancer and those who did not have sufficient mental functions to answer the questions due to their general condition were excluded from the study. From the medical files of the patients included in the study and through a screening form, data about the disease and socio-demographic information were collected. Physical examination information at the time of hospitalization was recorded. BMI was calculated. Mid-arm muscle circumference (MAMC)[10,11] and calf circumference were measured[12].

The hemoglobin, C-reactive protein (CRP), albumin and thrombocyte values of all patients at the time of admission were retrospectively collected after completing the inclusion of patients to the study. Hospitalization epicrises were examined and the presence of infection requiring treatment and length of hospitalization were recorded. The survivability of each patient on the 90th day after the first day of hospitalization was examined and the 3rd month mortality rate was calculated. Nutrition Risk Index (NRI) and NRS-2002 were used to screen malnutrition risk. NRI was calculated by the formula: NRI=(1.519 × serum albumin, g/dL) + [41.7 × final weight (kg) / ideal body weight (kg)]. If the NRI score was >100, it was defined as no risk, 97.5-100 as mild risk, 83.5-97.5 as moderate risk, and <83.5 as severe risk[13]. The NRS-2002 scale, which was completed within the first 72 hours of hospitalization, was developed by Kondrup et al.[14,15] and it is used to identify patients who may benefit from nutritional support by screening the risk of malnutrition with reduced nutrition. The European Parenteral Enteral Nutrition Association recommended NRS-2002 for screening malnutrition risk in hospitalized patients[6]. NRS-2002 scale consists of three parts as "disease severity", "nutritional status" and "age". The points from each section are added up. A total score of 3 and above means an increased risk of malnutrition[15].

European Organization for the Research and Treatment of Cancer (EORTC)-QLQ C30 (Turkish version) QOL forms developed by the European Organization for the Research and Treatment of Cancer-EORTC were filled in by all patients. EORTC QLQ-C30 Version 3.0 is a QOL scale and consists of 30 questions. There are 2 questions in the "general health" questionnaire. "Functional scales" consists of physical function, role function, emotional function, cognitive function and social function. "Symptom scales" consists of weakness, nausea-vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties. Scoring was calculated according to the EORTC QLQ-C30 scoring manual. Each parameter has a score between 0 and 100.

A high score for general health and functional scales indicates good health, while a high score on the symptom scale indicates an excess of symptoms, that is, a worse QOL.

Statistical Analysis

Statistical analyses of the data obtained as a result of the evaluation were performed using a statistical package program (SPSS 21 for Windows, SPSS, Inc, Chicago, Illinois, USA) on the computer. Whether the data distribution was normal or not was checked with the Kolmogorov-Smirnov test. Results were expressed as median and interquartile range in all cases. In

ÇELİK et al. Malnutrition and Quality of Life

Nam Kem Med J 2021;9(1):84-90

subgroups formed based on socio-demographic characteristics, tumor characteristics, laboratory parameters, BMI, MAMC and calf circumference parameters, the difference between the 2 groups in terms of malnutrition risk was evaluated by the non-parametric Mann-Whitney U test, and the difference between more than 2 different groups was evaluated by the non-parametric Kruskal-Wallis test. The difference between qualitative groups was analyzed using the chi-square test. Fischer's correction was performed when necessary. It was planned to examine the differences between the patient groups with and without malnutrition risk in terms of all sub-parameters of the EORTC QLQ-C30 by using the Mann-Whitney U test. Later, it was planned to divide the patients into two groups according to the median value for the "general health status" score of the EORTC QLQ-C30 questionnaire. Patients above the median value constituted better overall QOL, patients below the median value constituted poorer overall

QOL group. In order to find the predictors of the better QOL group, univariate logistic regression (LR) analysis was planned first, followed by multivariate LR analysis for factors found to be significant. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 113 patients were included in the study. According to the results of NRS-2002, 42.5% (n=48) of the patients were found to have a malnutrition risk. The comparison results of patients with and without malnutrition risk are shown in Table 1. Gender and age were similar in both groups. The median age was 60 years in those at risk of malnutrition and 59 years in those without risk. Primary tumor was in the gastrointestinal system (GIS) in 21.2% of the patients and there was no statistically significant difference between the groups in terms of frequency. The rate of metastatic (tumor node metastasis

Table 1. Comparison of patients with and without malnutrition risk according to Nutrition Risk Screening-2002			
	With malnutrition risk (n=48)	**Without malnutrition risk (n=65)**	**p**
Variables	**n (%) or median [Q1-Q3]**		
Gender			
Male	28 (58.3)	37 (56.9)	0.881
Female	20 (41.7)	28 (43.1)	
Age	60 [49-70]	59 [48-63]	0.172
Smoking			
Smoker/quitted	34 (70.8)	41 (63.1)	0.388
Never smoked	14 (29.2)	24 (36.9)	
Location of tumor			
GIS	13 (27.1)	11 (16.9)	0.192
Non-GIS	35 (72.9)	54 (83.1)	
TNM stage			
3	1 (2.1)	9 (13.8)	**0.030**
4	47 (97.9)	56 (86.2)	
Presence of infection (during hospitalization)	34 (70.8)	42 (64.6)	0.486
Nutritional support before hospitalization	20 (41.7)	3 (4.6)	**<0.001**
Low MAMC	12 (25)	10 (15.4)	0.202
Low calf circumference	9 (18.8)	7 (10.8)	0.229
3rd month mortality after hospitalization	34 (70.8)	24 (36.9)	**<0.001**
Hemoglobin (g/dL)	9.7 [8.6-11]	9.5 [8.9-11]	0.691
Platelet (x10³)	281.5 [222.5-352.5]	271 [181-417]	0.81
CRP (mg/L)	67 [39-136]	49 [22-114]	0.193
Albumin (gr/dL)	2.78 [2.45-3.4]	2.8 [2.4-3.4]	0.543
Body mass index	22 [20.63-24.83]	24.69 [22.49-27.55]	**0.001**
Nutritional Risk Index	80 [71.5-87]	83 [78-92]	0.018
Length of hospital stay (day)	21 [11-39]	17 [12-29]	0.508
For quantitative variables M [Q1-Q3] (M: Median Q1: percentage 25, Q3: percentage 75).			
P-values for quantitative variables were obtained with the Mann-Whitney U test, p values for qualitative variables were obtained with the chi-square test. Statistically significant "p" values were stated in bold.			
GIS: Gastrointestinal system, MAMC: Mid-arm muscle circumference, TNM: Tumor node metastasis, CRP: C-reactive protein			

Nam Kem Med J 2021;9(1):84-90

ÇELİK et al. Malnutrition and Quality of Life

stage 4) patients was higher in those at risk of malnutrition (p=0.030). Eastern Cooperative Oncology Group-Performance Scores (ECOG-PS) of patients with malnutrition risk are shown in Figure 1. ECOG-PS values of all patients were between 2 and 4. Malnutrition risk was 33.8% in those with ECOG-PS 2, 60.7% in those with 3, and 45% in those with 4. The difference between the groups was not statistically significant (p=0.054). The rate of patients who received chemotherapy and/or radiotherapy within 30 days before hospitalization was 62.5% (n=30) in the group with malnutrition risk and 66.1% (n=43) in the group without malnutrition risk (p=0.121).

As expected, BMI at hospitalization was significantly lower in the group with malnutrition risk (p=0.001). However, there was no difference between the groups in terms of calf circumference and MAMC. There was no significant difference between the groups in terms of albumin, CRP, hemoglobin and platelet count obtained from laboratory tests. The median length of stay in the hospital was 21 days in those at risk of malnutrition, while it was 17 days in those without risk. Although there was a numerically longer hospitalization period in those with malnutrition risk, the difference was not statistically significant (p=0.508). The rate of infection requiring treatment was slightly higher in those at risk of malnutrition (70.8%), but the difference between the groups was not statistically significant (p=0.486). When the groups were examined in terms of 3rd month mortality rate, the mortality rate was 70.8% in those with malnutrition risk and 36.9% in those without malnutrition risk (p<0.001). While the rate of nutritional support before hospitalization was 41.7%

in patients with malnutrition risk at admission, it was 4.6% in those without risk (p<0.001).

Figure 2 shows the distributions for NRI in patients with and without malnutrition risk. The rate of patients with NRI<83.5, which indicates the risk of severe malnutrition (according to NRS-2002), was detected to be 69% in those with malnutrition risk and 52% in those without risk. The rate of patients with NRI>100, which indicates that there is no malnutrition (according to NRS-2002), was 6% in those with malnutrition risk, while it was 12% in those without risk. The patients were asked whether there was a decrease in food consumption in the last week (vv). In patients with malnutrition risk, food consumption was found to be less than half of normal in 50%, half of normal in 21% and normal in 29%. In patients without malnutrition risk, food consumption was found to be less than half of normal in 22%, half of normal in 23% and normal in 55%.

The comparison results of patients with and without malnutrition risk in terms of general health, functional scales and symptom scales are shown in Table 2. Malnutrition risk had no significant effect on overall health score (p=0.679). Physical function and role function scores were significantly lower in those at risk of malnutrition (poorer QOL). There was no statistically significant difference between the groups in terms of other functional scales. For symptom scales, scores for symptoms other than constipation and diarrhea were higher (poorer QOL) in patients at risk of malnutrition. The high scores detected for pain, nausea/vomiting, insomnia, and loss of appetite were also statistically significant. In Table 3, the characteristics of patients whose EORTC QLQ-C30 general health score was above the median value (better QOL) were investigated by univariate and multivariate LR analysis. According to the One-Way analysis results, only hemoglobin level was found as a significant factor.
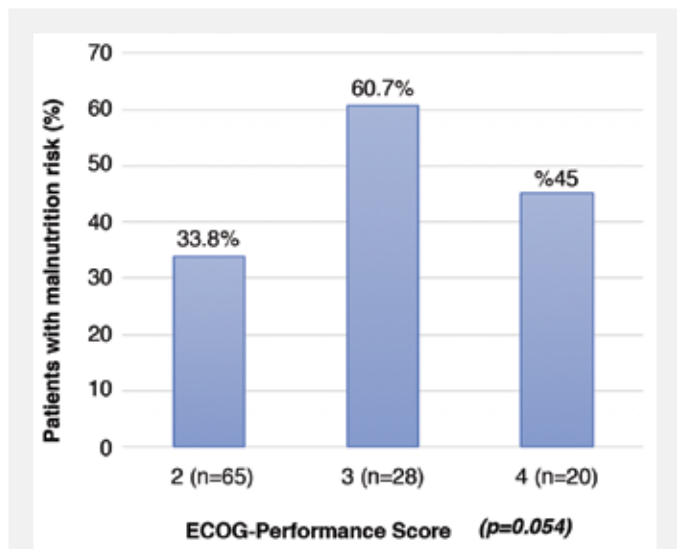

Figure 1. Distribution of patients with malnutrition risk according to Eastern Cooperative Oncology Group-Performance Score and Nutrition Risk Screening-2002
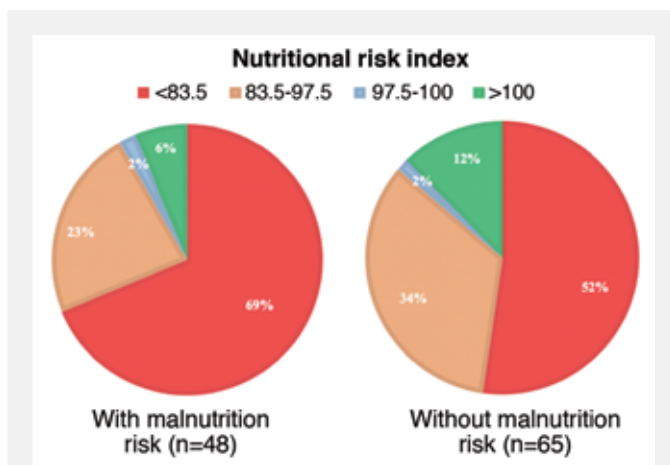
ECOG: Eastern Cooperative Oncology Group

Figure 2. Nutritional risk indexes of patients with and without malnutrition risk according to Nutrition Risk Screening-2002

ÇELİK et al. Malnutrition and Quality of Life

Nam Kem Med J 2021;9(1):84-90

A significant correlation was found between higher hemoglobin level and better general health score (p=0.028). It was observed that the risk of malnutrition, age, gender, ECOG PS and other variables given in Table 3 had no effect on the better overall health score. Multivariate LR analysis was not performed because only one factor had a significant effect.

Table 2. Comparison of EORTC QLQ-C30 quality of life scale scores of patients with and without malnutrition risk according to Nutrition Risk Screening-2002

	With malnutrition risk	Without malnutrition risk	p
	Median [Q1-Q3]		
Overall health	16.67 [0-33.33]	16.67 [0-33.3]	0.679
Functional scales			
Physical function	42 [33.3-53.3]	51.6 [40-73.3]	**0.019**
Emotional function	49 [33.3-66.7]	55.4 [41.7-75]	0.120
Role function	16.67 [0-33.3]	33.3 [0-50]	**0.017**
Mental function	53.7 [66.7-59.3]	59.3 [50-83.3]	0.218
Social function	33.72 [0-50]	44.5 [33.3-50]	0.057
Symptom scales			
Pain	83.33 [66.7-100]	66.7 [33.3-83.3]	**0.009**
Nausea or vomiting	56 [25-100]	33.3 [0-50]	**0.004**
Weakness	88.89 [77.8-100]	77.8 [55.6-100]	0.068
Dyspnea	58 [33.3-100]	48 [33.3-66.7]	0.155
Insomnia	68 [66.7-100]	54.5 [33.3-100]	**0.019**
Loss of appetite	100 [66.7-100]	66.7 [33.3-100]	**0.002**
Constipation	33.3 [0-83.4]	33.3 [0-66.7]	0.711
Diarrhea	22 [0-33.3]	24.8 [0-33.3]	0.890
Financial difficulty	55 [33.3-66.7]	33.3 [33.3-66.7]	0.155

P value was obtained with the Mann-Whitney U test. Q1: percentage 25, Q3: percentage 75.

Statistically significant "p" values were stated in bold.

EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer

Table 3. Univariate and multivariate logistic regression analysis for better overall health score variables on the EORTC-QLQ C30 scale

	Univariate LR		Multivariate LR	
Variables	**Odds ratio (95% CI)**	**p**	**Odds ratio (95% CI)**	**p**
With malnutritional risk	1.288 (0.584-2.84)	0.531		
Age	0.984 (0.954-1.016)	0.322		
Male gender	1.729 (0789-3.788)	0.171		
Smoking	1.167 (0.516-2.637)	0.711		
GIS tumor	0.847 (0.332-2.161)	0.729		
TNM stage 4	0.190 (0.023-1.559)	0.122		
ECOG-PS 3 (Ref: 2)	0.938 (0.362-2.431)	0.896		
ECOG-PS 4 (Ref: 2)	0.444 (0.160-1.236)	0.120		
Hemoglobin (g/dL)	1.318 (1.030-1.687)	**0.028**		
Platelet (x10^3)	1.000 (0.997-1.002)	0.873		
CRP (mg/L)	0.996 (0.991-1.001)	0.102		
Body mass index	0.978 (0.890-1.075)	0.648		
Low MAMC	1.517 (0.541-4.254)	0.428		
Low calf circumference	0.859 (0.287-2.571)	0.786		

Statistically significant "p" values were stated in bold.

CI: Confidence interval, LR, Logistic regression, GIS: Gastrointestinal system, MAMC: Mid-arm muscle circumference, TNM: Tumor node metastasis, CRP: C-reactive protein, EORTC-QLQ C30: European Organization for the Research and Treatment of Cancer, ECOG-PS: Eastern Cooperative Oncology Group-Performance Scores
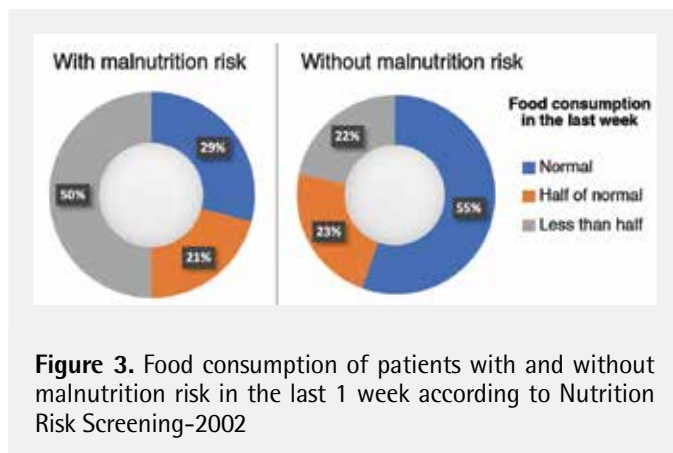
Figure 3. Food consumption of patients with and without malnutrition risk in the last 1 week according to Nutrition Risk Screening-2002

DISCUSSION

It is obvious how important it is to evaluate every hospitalized patient for malnutrition. In this cross-sectional study, nearly half of the 113 cancer patients hospitalized were found to be at risk of malnutrition, and it was observed that it negatively affected the QOL.

In the literature, while gender does not affect the frequency of malnutrition in cancer patients in general, it has been reported that the frequency of malnutrition increases in older patients[3,16]. In our study, no significant difference was found in terms of age and gender. It is known that malnutrition risk is higher in GIS cancers and tumors at the metastatic stage[6,16]. In our study, the rate of metastatic patients was significantly higher in those with malnutrition risk, in line with the literature. Although the frequency of GIS cancer was numerically higher, the difference was not significant. In Table 1, the comparison of patients with and without malnutrition risk was made to give information about the general patient population. Our primary aim in this study was not to investigate factors that increase the risk of malnutrition. For this reason, detailed and advanced statistical analyses (LR analysis etc.) were not performed for the factors affecting malnutrition risk. Rather, the effects of malnutrition risk on QOL and on clinical problems encountered during hospitalization were the topics to be examined.

In this study, scores of physical function, role function, pain, nausea/vomiting, insomnia and loss of appetite on the EORTC QLQ-C30 scale were found to be significantly associated with poorer QOL in those at risk of malnutrition (Table 2). In the literature, it has been reported that malnutrition impairs the QOL, in line with the results of our study[16,17]. The issue of QOL in cancer patients is an issue that needs to be handled in a multi-directional way. In addition to malnutrition, there are factors affecting QOL such as tumor type, tumor stage, patient's ECOG-PS and other defined risk factors[4,16,17]. For this reason, LR analysis was performed to determine the characteristics of patients with higher general health scores, that is, better overall QOL, on the EORTC QLQ-C30 scale. According to the

univariate analysis, it was observed that factors other than hemoglobin did not affect the overall health score (Table 3). The relatively small patient population may be the reason for the low number of significant factors. For validity of these results, it should be repeated with more participants using the same QOL scale and a similar patient population.

Although NRI is used to determine nutritional risk in cancer and non-cancer patients, its success in cancer patients is low[13]. Consistent with the results reported in the literature, NRI scores were generally found to be low in those with or without malnutrition risk. The albumin and weight loss used in the calculation of this index are more or less encountered in most cancer patients. Therefore, NRI does not appear to be useful in evaluating nutritional status in hospitalized cancer patients. In previous studies, it was reported that the length of hospital stay was longer in those with malnutrition[16]. In our study, the median hospital stay was four days longer in the group with malnutrition risk. However, the difference was not statistically significant. The relatively low number of patients may have caused this. It has been reported that providing nutritional support in the early period after hospitalization may shorten the length of stay[18]. One of the most common clinical problems in hospitalized cancer patients is the development of infection. We found the frequency of infection at the rate of 70.8% in those with malnutrition risk, which was slightly higher than in those without risk (p=0.486). The 3rd month mortality rate was significantly higher in those at risk of malnutrition (p<0.001). While interpreting these results, it should be kept in mind that the risk of malnutrition may develop during hospitalization, although not at the initial diagnosis. Therefore, the possibility of malnutrition risk that can develop later should be kept in mind while interpreting the duration of hospital stay, the frequency of infection and the mortality rates in the 3rd month.

Although it could not be done in this study, the effect of malnutrition on the problems that occur during hospitalization can be understood more clearly by repeating the NRS-2002 scale periodically during hospitalization.

Figure 3 highlights the important points in assessing malnutrition risk. Food consumption in the last one week was reported as normal in 29% of those at risk of malnutrition. In other words, nutritional evaluation made by questioning only oral intake means that an important patient group with malnutrition risk is overlooked. Again, in 45% of the patients without malnutrition risk, decreased oral intake was found. Re-application of the NRS-2002 scale at regular intervals, especially in these patients, may reveal the risk of malnutrition in the early period[18]. Consequently, decreased oral intake is common in hospitalized cancer patients and it should be kept in mind that malnutrition risk may develop without a decrease in oral intake.

ÇELİK et al. Malnutrition and Quality of Life

Nam Kem Med J 2021;9(1):84-90

Study Limitations

There are some limitations in our study. Although all cancer patients admitted to the medical oncology service were planned to be included in the study, some patients did not want to participate because of their poor general condition or being excessively symptomatic. Another limitation is that the effects of nutritional support given to patients on admission were not evaluated. In addition, the fact that each tumor type was not evaluated separately is another limitation. Considering the limitations we have reported may increase the strength of future studies to be carried out.

CONCLUSION

In conclusion, detailed nutritional assessment at the time of admission is an important issue in hospitalized cancer patients. Its frequency is quite high. It negatively affects the patients physically and emotionally and impairs the QOL. Patients having malnutrition at the time of admission have longer hospitalization periods and they have higher frequency of infection. Survival is shorter in patients with malnutrition. It should be kept in mind that malnutrition may develop without a decrease in oral food intake.

Ethics

Ethics Committee Approval: The study were approved by the İstanbul University-Cerrahpaşa University of Local Ethics Committee (date: 08.07.2020, protocol number: 86049).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Concept: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Design: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Data Collection or Processing: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Analysis or Interpretation: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Literature Search: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D., Writing: E.Ç., M.Ş.A., N.Ş.S., M.K., V.S., Y.Ç.Ç., N.S.D., F.H.D.

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