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Can Inflammation-Based Indices Describe The Poor Prognosis in Palliative Care Patients?

İnflamasyon İlişkili İndeksler, Palyatif Bakım Hastalarında Kötü Prognozu Tanımlayabilir Mi?

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Abstract

Aim: Palliative medicine provides holistic care to increase the quality of life. Predicting prognosis is critical for personalized treatment plan. We aimed to investigate the survival prediction properties of routine biochemistry tests, complete blood count (CBC) and neutrophil/lymphocyte ratios, in addition to biomarker-based indices (the mGPS, PI, and PNI).

Material and Method: The laboratory parameter values, prognostic factor scores, diagnoses and survival time of 139 palliative care patients in the last five weeks of their life were evaluated retrospectively. Cross tables and chi-square tests were used to evaluate whether there was a relationship between qualitative variables, and Pearson's correlation coefficient was used to assess the relationship between quantitative variables.

Results: Ninety-one (65.5%) patients were male and the mean age was 65.9 years (28–91). Results of all three prognostic indices (the mGPS, PI, and PNI) investigated in this study were found to have a statistically significant relationship with the survival time of our patients. In addition, NLR, neutrophil percent, hemoglobin, serum albumin and CRP values were seen to have a statistically significant relationship with the scores of all three prognostic indices. Moreover, it is detected that WBC, NLR, albumin, and CRP values were associated with overall survival.

Conclusion: Our study showed that the PNI, PI, mGPS, and NLR, which are prognostic tools obtained from CBC and biochemistry tests and, which are frequently used, inexpensive, and accessible tests, can predict prognosis in palliative care.

Keywords: Palliative care, prognosis, inflammation

Öz

Amaç: Palyatif tıp, hastaların yaşam kalitesini artırmak için bütünsel bakım sağlar. Kişiselleştirilmiş bir tedavi planı için prognozu tahmin etmek çok önemlidir. Bu nedenle, biyobelirteç bazlı indekslere (mGPS, PI ve PNI) ek olarak rutin biyokimya testleri, tam kan sayımı (CBC) ve nötrofil/lenfosit oranlarının sağkalım tahmin özelliklerini araştırmayı amaçladık.

Gereç ve Yöntem: 139 palyatif bakım hastasının yaşamlarının son beş haftasındaki laboratuvar parametre değerleri, prognostik faktör skorları, tanıları ve sağkalım süreleri geriye dönük olarak değerlendirildi. Nitel değişkenler arasında ilişki olup olmadığını değerlendirmek için çapraz tablolar ve ki-kare testleri, nicel değişkenler arasındaki ilişkiyi değerlendirmek için Pearson korelasyon katsayısı kullanıldı.

Bulgular: Doksan bir (%65.5) hasta erkekti ve yaş ortalaması 65.9 yıl (28-91) idi. Bu çalışmada incelenen her üç prognostik indeksin (mGPS, PI ve PNI) sonuçlarının hastalarımızın sağkalım süreleri ile istatistiksel olarak anlamlı bir ilişkisi olduğu bulundu. Ayrıca NLR, nötrofil yüzdesi, hemoglobin, serum albümin ve CRP değerlerinin her üç prognostik indeksin skorları ile istatistiksel olarak anlamlı bir ilişkisi olduğu görüldü. Ayrıca WBC, NLR, albümin ve CRP değerlerinin genel sağ kalım ile ilişkili olduğu saptandı.

Sonuç: Çalışmamız CBC ve biyokimya testlerinden elde edilen prognostik araçlar olan ve sıklıkla kullanılan, ucuz ve ulaşılabilir testler olan PNI, PI, mGPS ve NLR'nin palyatif bakımda prognozu öngörebildiğini göstermiştir.

Anahtar Kelimeler: Palyatif bakım, prognoz, ınflamasyon

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INTRODUCTION

Palliative care practice, which is the basic principle of holistic patient care, provides symptom control to increase the quality of life of patients with advanced cancer and prevent unnecessary examinations and treatments. Many symptoms, particularly malnutrition and dyspnea are exacerbated in the last period of life. Describing the negative clinical prognosis using the prognostic information of patients with advanced cancer may provide a personalized treatment approach, especially for patients who cannot tolerate aggressive therapy. These predictions are critical for clinicians in recommending and planning medical support interventions such as nutrition and physiotherapy.[1]

Describing the poor prognosis enables the achievement of a dignified death which is the ultimate goal of palliative care. Numerous studies show that the prognostic predictive properties of many biomarkers in various cancers have been studied to contribute to planning the most efficient and patient-centered treatment protocols.[2,3] Instruments frequently used in palliative care for this purpose include the Palliative Prognosis Score (PaP score), Palliative Prognostic Index (PPI), Palliative Performance Scale (PPS) and the Glasgow Prognostic Score (GPS). These tools yield results by evaluating clinical and biomarker data.[4]

Many researchers have indicated that nutritional and immune status have a high relationship with the nascency, progression, and treatment of cancer. The inflammation parameters are appropriate tools to predict the prognosis of cancer. The poor prognosis of patients with malignant tumors is often associated with immune-related systemic inflammatory response.[5] Based on the relationship between inflammation and cancer progression, various inflammation-based indices have been developed as prognostic. Demirelli developed other different inflammatory based prognostic prediction instruments which are used in oncology clinics, are the Modified Glasgow Prognostic Score (mGPS), Prognostic Index (PI), Prognostic Nutritional Index (PNI), and Neutrophil-Lymphocyte Ratio (NLR). However, these tools are not used frequently for palliative care patients, especially in the last weeks of life.[6]

We think that it is important for patients with advanced cancer with a poor prognosis to spend quality time with their loved ones instead of spending their valuable time with unnecessary tests and treatments at the end of their lives. At the same time, this approach may enable cost-effective symptom treatment for terminal stage palliative care patients. In our study, we aimed to investigate the prognostic prediction properties of routine biochemistry tests, complete blood count (CBC), and NLR and biomarker-based indices (the mGPS, PI, and PNI), which are relatively less used in palliative care, in patients with advanced cancer in the last weeks of their life.

MATERIAL AND METHOD

The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.12.2020, Decision No: 20-KAEK-298). The universe of our study was constituted by the adult patients who were treated in our palliative care center and who died between July 1, 2018, and June 30, 2020. Patient records were scanned retrospectively and patient files with missing data were excluded from the study. Parameter values, prognostic factor scores, diagnoses and survival times (days) obtained from the examination results of their clinical controls in the last five weeks of their lives were compared.

Parameters

CBC and biochemistry test results were evaluated for patients with various symptoms treated in our palliative care clinic. Within the scope of biochemistry tests, electrolytes (Na, K, Cl, and Ca), kidney function tests, liver function tests, serum albumin, C-reactive protein (CRP) and procalcitonin values were screened. Neutrophil, lymphocyte, monocyte, platelet, and red blood cell count values were examined using CBC. NLR values obtained from CBC were examined.

Prognostic indexes

The mGPS is based on serum albumin and CRP values. It is scored as 2 if CRP is >10 mg/L and serum albumin is <3.5 g/dL, 1 if only CRP is >10 mg/L, and 0 if these parameters were normal.[2]

PI is based on CRP and leucocyte count. It is calculated as 2 if the CRP value is above 10 mg/L and the leukocyte count is above 10×10^9, 1 if one of the two values is higher, and 0 if both values are normal.[7]

PNI is scored using serum albumin level and lymphocyte count. It is calculated using the formula of 10×serum albumin value (g/dl) +0.005×lymphocyte count (per mm^3). It is scored as 0 if the result is 45 or above, and 1if the value is below 45.[6,8]

Statistical analysis

Descriptive analyses were conducted to provide information about the characteristics of the study groups. The data of continuous variables were in the form of mean ± standard deviation, and data of categorical variables were given as n (%). While comparing the means of quantitative variables between groups, the significance test of the difference between two means and the one-way analysis of variance were used for normally distributed data, and the Mann–Whitney U test and Kruskal–Wallis test were used for non-normally distributed data. Cross tables and chi-square tests were used to evaluate whether there was a relationship between qualitative variables, and Pearson's correlation coefficient was used to assess the relationship between quantitative variables. A p value of less than 0.05, was considered statistically significant, and a ready-made statistics software was used in calculations (SPSS 22.0 Chicago, IL, USA).

RESULTS

Ninety-one (65.5%) patients were male and the mean age of was 65.9 years (28–91). The three most common diagnoses in the patient files screened were lung (29.5%), stomach (12.2%), and colorectal (8.6%) cancers and the mean survival time of patients after their last palliative care visit was 16.5±7.9 days. Results of the three prognostic indices which investigated were found to be statistically significant concerning the survival time of our patients ($p<0.05$). On the other hand, there was no statistical relationship between gender and survival time statistically ($p>0.05$). Gender and prognostic index data are given in **Table 1**.

Table 1: Survival time data regarding gender and prognostic indexes

Variables		Survival time (day)*	p
Gender	Male	16 [10-21]	0.428
	Female	15.5 [10.5-24]	
mGPS	0	29 [16-30]	0.014
	1	18 [11.5-23]	
	2	15 [10-20]	
PNI	0	29 [15-31]	0.003
	1	15 [10-20]	
PI	0	29 [16-30]	0.027
	1	15.5 [10-20]	
	2	15 [10.5-20.5]	

*Median [Q1-Q3] mGPS: modified Glasgow prognostic index, PNI: prognostic nutritional index, PI: prognostic index

We analyzed laboratory data according to the index scores. NLR, neutrophil percent, hemoglobin, serum albumin and CRP values were seen to have a statistically significant relationship with the scores of all three prognostic indices ($p<0.05$). Laboratory parameters found to be statistically significant with prognostic index scores are given in **Table 2**.

The relationship between the parameters and overall survival was investigated using Pearson's correlation test. It is detected that white blood cell (WBC), NLR, albumin, and CRP values have a relationship with survival time, but it was determined to be weak or very weak. (**Table 3**)

Table 3: Statistical parameters correlated with overall survival

Parameters	r	p
NLR	-0.171	0.044
WBC	-0.207	0.015
Albumin	0.332	<0.001
CRP	0.171	0.044

WBC: white blood cell, NLR: neutrophil/lymphocyte ratio

DISCUSSION

Personalized treatment approaches are crucial in palliative medicine, whose primary goal is to increase the quality of life of palliative care patients. At the end of life, in addition to the priorities and expectations of the patients, treatment protocols are shaped by many factors such as the decrease in the benefit–harm ratio of aggressive treatments that have severe side effects. Predicting overall survival is central to planning treatment options, including invasive interventions such as palliative resection, total parenteral nutrition or permanent catheters, for various reasons.[1] In our study, the laboratory parameters (CBC, biochemistry tests) and, NLR, mGPS, PI, and PNI scale scores obtained using the data of patients treated in our palliative care clinic were compared with the life-spans of our patients. All three prognostic scale scores examined were found to have a statistically significant relationship with survival time. WBC, NLR, albumin, and CRP values were also found to be statistically significant with survival, but the correlations were weak.

Table 2: Comparing patients' age and laboratory data according to index scores

Parameters	mGPS				PI				PNI		
	0	1	2	p	0	1	2	p	0	1	p
Age	72.7±5.5*	63.7±13.2*	65.7±12*	0.188	72.6±5.5*	65.7±11.1*	65.3±13.2*	0.214	74.5±10*	65.1±11.7*	0.006
WBC	5.9 [4.3-6]**	8.2 [5.6-9.1]**	9.8 [6.6-13.2]**	0.002	5.9 [4.3-6]**	6.7 [5.1-8.2]**	13.2 [11.3-18]**	<0.001	7.3 [5.9-8.6]**	9 [6.3-13.1]**	0.095
NEU (%)	53.3±30.7*	77.4±13.1*	77.9±15.2*	<0.001	68.2 [12.8-78.8]**	78.8 [68.1-85.8]**	85.1 [76.6-90.1]**	<0.001	68.2 [50-76.4]**	82 [73.6-88.8]**	<0.001
NLR	4.7±1.4*	21.1±30.6*	12.3±11.6*	0.026	4 [3.5-6.6]**	6.5 [4.3-12.1]**	11.5 [6.9-20.3]**	<0.001	3.5 [1.3-5.9]**	9.5 [5.1-17.3]**	<0.001
LYM	13.2 [2.9-19.1]**	7.1 [3.9-13.1]**	9.2 [5.5-14]**	0.614	13.2 [2.9-19.1]**	11.8 [6.8-17.2]**	7.4 [4.3-11.2]**	0.013	26.7±18.5*	10.2±7.3*	<0.001
HGB	11.8±1.4*	11.6±1.6*	9.9±1.9*	0.001	12.6 [9.9-12.9]**	10.1 [9.04-11.3]**	9.7 [8.5-11.1]**	0.02	11.5±2.1*	10.1±1.8*	0.008
Serum Albumin	4 [3.6-4.3]**	3.7 [3.6-4]**	2.7 [2.3-3.1]**	<0.001	4±0.3*	2.8±0.6*	2.7±0.4*	<0.001	3.75±0.59*	2.74±0.58*	<0.001
CRP	5.5 [3.6-8.6]**	73.94 [40.6-138.3]**	106.9 [71.7-168.9]**	<0.001	5.2 [3.6-8.6]**	100.5 [62-149.6]**	124.8 [71.7-177.4]**	<0.001	29.3 [8.7-77.4]**	103.6 [64.6-166.3]**	0.002
Total Protein	6.2 [6-6.7]**	6.6 [6.2-7]**	5.9 [5.4-6.6]**	0.008	6.2 [6-6.7]**	5.8 [5.4-6.6]**	6.1 [5.6-6.7]**	0.135	6.7 [6.2-6.7]**	5.9 [5.5-6.6]**	0.013

*Mean ± SD, **Median [Q1-Q3], WBC: white blood cell, NEU: neutrophil, LYM: lymphocyte, HGB: hemoglobin, NLR: neutrophil/lymphocyte ratio, CRP: C-reactive protein, mGPS: modified Glasgow prognostic index, PNI: prognostic nutritional index, PI: prognostic index, *** Pearson chi-square test was used.

Studies in the literature show that systemic inflammation could play a crucial role in promoting cancer progression and metastasis, because, for example, inflammatory mediators increase vascular permeability and promote cancer cell infiltration through the lymphatic and blood vessels.[9] Hence, CRP, which increases due to tumor growth and tissue inflammation, has been used to determine cancer prognosis.[10] Amano et al., in their study with 1,511 palliative care patients in Japan, showed that high CRP level is associated with poor prognosis and high mortality.[11] In agreement with the literature, our study showed that CRP and overall survival were found to be statistically significantly inversely related; however, due to a low correlation, CRP was not accepted as an independent prognostic factor. This difference among results may be related to the small number of patients in our study.

Inflammation is the main factor in tumor initiation and progression, as it affects various stages of oncogenesis. Indeed, inflammatory cells orchestrate the neoplastic process, promoting tumor proliferation and migration.[12] Tumor-related leukocytosis has been reported in lung, breast, and cervical cancers in the literature.[13] In their study which was conducted with 103 patients, Schernberg et al showed that leukocytosis and neutrophilia are strong prognostic factors for overall survival, progression, and locoregional and distant-free survival in anal cancer treated with chemoradiation.[14] Our study shows that leukocytosis and overall survival have a statistically significant relationship (p=0.015); however, we think that WBC was not an independent prognostic factor due to a low correlation (r=0.207). Another parameter found to be statistically significantly associated with overall survival in our study was NLR. Similar to CRP and leukocytosis, NLR had a weak correlation due to a low regression value. Elevated NLR, another marker of a systemic inflammatory response, has been shown to be significantly associated with poor prognosis in various malignancies.[15] Ahn et al. in their study with 205 patients demonstrated that elevated NLR predicted worse survival in patients with terminal cancer.[16] Many studies have reported that NLR was a prognostic indicator in patients with early or advanced solid tumors in the literature.[15] Weak correlations according to regression analysis of CRP, WBC, and NLR, found to be statistically significantly associated with survival in our study, may be explained by the diversity of cancer diagnoses. The patients we studied were not a homogeneous group, consisting of patients with various cancer diagnoses. The PI which is calculated via CRP serum concentration and WBC, was studied first by Kasymjanova et al.in 2010. In the study, conducted with 134 advanced non-small-cell lung cancer patients, Kasymjanova et al. showed that the PI was a significant prognostic factor for survival.[7] Recently, Gruber et al. reported that the PI independently predicts survival in patients with pancreatic ductal adenocarcinoma undergoing resection.[17] Meanwhile, our study showed that the PI predicts survival in palliative care patients. This result is a strong aspect of our study as to our knowledge, the relationship between the PI and survival in palliative care patients with various cancers has not been studied before.

Inflammation which effects on various stages of cancer causes decreased serum albumin, a negative acute-phase protein.[18] The correlation between serum albumin value and prognosis has been studied by many researchers. Hypoalbuminemia is often detected in advanced cancer patients, and it usually indicates malnutrition and cachexia.[19] In their study with 604 patients, Danan et al. showed that a lower preoperative serum albumin value is associated with an increased rate of wound infection and poorer overall survival in patients with head and neck cancer.[20] It was seen that hypoalbuminemia and overall survival are associated in our study, which agrees with the literature.

The mGPS is a scoring system that works using serum albumin and CRP values to verify systemic inflammation and nutritional status.[21] Researchers posit that the mGPS has prediction value in pancreatic, esophagus, and lung cancers, and its prognostic ability in cancer was indicated by various studies.[22] Tsujino et al. reported that a preoperative measurement using the mGPS predicts survival in non-metastatic renal cell carcinoma prior to nephrectomy.[23] Further, the mGPS was emphasized as an independent prognostic marker in metastatic gastric cancer by Demirelli et al.[6] In our study, the mGPS was an independent prognostic marker in palliative care patients.

The PNI, which was initially identified to evaluate preoperative nutritional conditions and surgical complications in patients with gastrointestinal cancers, reveals nutritional and immunological status via albumin and lymphocyte values.[8] The efficiency of the PNI as a prognostic marker in colorectal, hepatocellular, and pancreatic cancers and renal cell carcinoma has been explained by many studies.[24,25] Okadome et al. found that a low PNI value was associated with poor prognosis in esophageal cancer in their study, which was conducted with 337 patients.[26] Meanwhile, our study showed that the PNI has a prognostic marker feature. In the literature, the PNI and mGPS prognostic tools have been studied with certain cancer types, and their survival prediction properties have been revealed. We believe the fact that the universe of our study includes patients diagnosed with various cancers renders our study effective and powerful. Regarding limitations, this single -center study was conducted in a tertiary palliative care center, so results may not be generalizable.

CONCLUSIONS

Predicting prognosis in advanced cancer, especially in palliative care, is of key importance in establishing a care plan and using available resources efficiently. We have shown that the PNI, PI, mGPS, and NLR, which are prognostic tools obtained from CBC and biochemistry tests and, which are frequently used, inexpensive, and accessible tests, can predict prognosis in palliative care. Finally, we would like to emphasize the importance using prognostic tools for survival prediction in palliative care about developing personalized treatment plans for patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.12.2020, Decision No: 20-KAEK-298).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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