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Neutrophil-to-lymphocyte ratio may guide the choice of treatment in metastatic cancer patients: Chemotherapy or best supportive care

Metastatik kanser hastalarında tedavi seciminde nötrofil-lenfosit oranı yol gösterici olabilir: Kemoterapi veya en iyi destekleyici bakım

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Abstract

Aim: We set out in this study to investigate whether the neutrophil-to-lymphocyte ratio is a predictor in deciding whether to either continue palliative chemotherapy or choose the best supportive care for advanced cancer patients.
Methods: Those with advanced solid tumors who had died after palliative chemotherapy were included the study. The patients were divided into two groups based on the time between the beginning of their last chemotherapy regimen and death, at ≤ 60 or > 60 days. Neutrophil-to-lymphocyte ratio was calculated using the laboratory values taken before the beginning of the last chemotherapy line. The determinant factors of ≤ 60-days survival were examined by logistic regression analysis, and a statistical significance level of alpha was accepted as $p < 0.05$.
Results: The study included 404 patients, with the mean age at diagnosis of 61.7±12.0 years. The mean neutrophil-to-lymphocyte ratio was calculated as 11.3±27.1. In the univariate analysis for determining ≤ 60-days survival, breast and colorectal cancers, ECOG status, single agent chemotherapy usage, neutrophil count, lymphocyte count and neutrophil-to-lymphocyte ratio were all found to be significant factors. The cutoff value determining the ≤ 60-days DCD, was determined as NLR ≥ 3.59. In logistic regression analysis, NLR ≥ 3.59, as well as ECOG status, were found to be significant factors.
Conclusion: The neutrophil-lymphocyte ratio, combined with ECOG, can predict survival in patients with solid advanced tumors and can therefore help clinicians in choosing to either administer chemotherapy to their patients or direct them to the best supportive care.

Keywords: neutrophil-to-lymphocyte ratio, solid tumors, palliative chemotherapy, best supportive care

Öz

Amaç: Bu çalışmada nötrofil-lenfosit oranının (NLO), metastaik kanser hastaları için palyatif kemoterapiye devam etme veya en iyi destekleyici bakımı (BSC) seçme konusunda bir belirleyici olup olmadığını araştırmayı amaçladık.
Yöntemler: Palyatif kemoterapi sonrası ölen metastatik kanser tanılı hastalar çalışmaya dahil edildi. Hastalar son kemoterapi rejimlerinin başlangıcı ile ölüm (DCD) arasındaki süreye göre ≤ 60 veya > 60 güne göre iki gruba ayrıldı. Nötrofil-lenfosit oranı, son kemoterapi hattı başlangıcından öncesindeki laboratuvar değerleri kullanılarak hesaplandı. ≤ 60 günlük DCD'nin belirleyici faktörleri lojistik regresyon analizi ile incelendi ve istatistiksel anlamlılık düzeyi alfa $p < 0,05$ olarak kabul edildi.
Bulgular: Çalışmaya ortalama tanı yaşı 61,7 ± 12,0 yıl olan 404 hasta dahil edildi. Ortalama NLO 11,3 ± 27,1 olarak hesaplandı. ≤ 60 günlük DCD belirlenmesi için tek değişkenli analizde, meme ve kolorektal kanser tanıları, ECOG durumu, tek ajan kemoterapi kullanımı, nötrofil sayısı, lenfosit sayısı ve NLO önemli faktörler olarak bulundu. ≤ 60 günlük DCD'yi belirleyen kesim değeri NLO ≥ 3,59 olarak belirlendi. Lojistik regresyon analizinde, NLR ≥ 3,59 ve ECOG durumu önemli faktörler olarak bulundu.
Sonuç: ECOG performans durumu ile kombine edilmiş nötrofil-lenfosit oranı, metastatik kanser hastalarında sağkalımı tahmin edebilir ve bu nedenle klinisyenlerin hastalarına kemoterapi vermeyi veya onları en iyi destekleyici bakıma yönlendirmeyi seçmelerine yardımcı olabilir.

Anahtar Kelimeler: Nötrofil-lenfosit oranı, solid tümörler, palyatif kemoterapi, en iyi destekleyici bakımı

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Introduction

The short- and long-term prognoses of cancer depend on patient and tumor features such as age, performance status, tumor site, grade, stage and treatment modality [1]. The tumor microenvironment and, in particular, the inflammatory response are thought to play important roles in cancer development and progression, and may be associated with systemic inflammation [2]. The neutrophil-to-lymphocyte ratio (NLR) is a novel marker of inflammation and is measured through routine blood count tests. It becomes elevated in metabolic and inflammatory conditions that are associated with chronic low-grade inflammation. These conditions include diabetes mellitus, thyroiditis, obesity and ulcerative colitis. NLR is even correlated with HbA1c levels in diabetic patients. Moreover, it helps in differentiating malignant nodules from benign ones in thyroid glands [3-8]. NLR has also been linked to a variety of malignancies such as lung, esophageal, colorectal, ovarian, and head and neck cancers [9-13].

For medical oncologists, determining a prognosis and life expectancy is critical to choosing either best supportive care (BSC) or chemotherapy. Survival estimates that clinicians make, usually guided only by their intuition and clinical experience, are often incorrect, and clinicians tend to believe that their patients have longer to live than they actually do [14]. This error sometimes results in treatment that is too aggressive [15, 16]. Although physicians appear to be wrong less often when assessing short- (<15 days) and long-term (>6 months) survival, there is a substantial period of uncertainty— a better prognostic assessment could help improve patient care [15]. While prognostic factors and predictive tools have been explored and developed to improve a clinician's ability to estimate life expectancy, they often require complex parameters, such as the inclusion of patient and tumor features [17, 18].

We investigated the NLR's ability to act as a predictor in deciding whether to continue palliative chemotherapy or to instead employ BSC in advanced cancer patients.

Material and methods

This trial was planned as a retrospective single-center study. Medical details were obtained from the archive files of patients with advanced solid tumors, who had died between January 2018 and December 2019 after palliative chemotherapy treatment in the medical oncology clinic of Prof. Dr. Cemil Taşçıoğlu City Hospital. These were patients who had been admitted to the oncology clinic and would routinely, after a 12-hour fast, have blood samples taken. The blood was drawn from the antecubital vein and a blood analysis was performed. Tubes containing ethylenediaminetetraacetate (for complete blood counts) and anticoagulant-free gel tubes (for biochemical parameters) were used to store the blood samples. The complete blood count parameters were tested in a hemogram autoanalyzer (Mindray, China), and the biochemical parameters were examined in an autoanalyzer (Beckman Coulter, USA), using a colorimetric method. Disease staging was performed according to the Tumor, Node, Metastasis (TNM) staging system. Patients with missing data were not included in the study. Patients with infectious diseases, other inflammatory diseases such as rheumatoid arthritis and ulcerative colitis, hematologic malignancies, and patients who had received granulocyte colony-stimulating factor ≤ 4 weeks before last chemotherapy line were excluded from the study. The patients were divided into two groups, according to DCD, as ≤ 60 or > 60 days [15].

The demographic features included age at diagnosis and death, histologic type, Eastern Cooperative Oncology Group (ECOG), status both at diagnosis and before beginning the last chemotherapy regimen, as well as stage, the number of total treatment lines, the last chemotherapy modality (single agent or combination) and the time between the beginning of their last chemotherapy regimen and death (DCD). Also noted were the laboratory values before the beginning of the last chemotherapy line, such as white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (HCT), mean platelet volume (MPV), total platelet count (TPC), total neutrophil count (TNC), total lymphocyte count (TLC), total monocyte count (TMC), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), and C reactive protein (CRP). The NLR was calculated by dividing the TNC count by TLC. Biochemical parameters were presented as either below or above the reference range, based on the reference intervals used in the laboratory.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were given as a number and as a percentage for categorical variables, average and standard deviation, and as a minimum and maximum for numeric variables. Comparisons of the numerical variables in two independent groups were made using the Mann Whitney U test, since the normal distribution condition was not met. Comparisons of the ratios in the groups were made using the Chi-Square test. The determinant factors which p value < 0.250 in univariate analysis, were examined by logistic regression analysis, the cutoff value was calculated by ROC curve analysis and a statistical significance level of alpha was accepted as $p < 0.05$.

Results

The study included 404 patients (68.8% men and 31.2% women) with solid tumors who had died after palliative chemotherapy. The mean age at diagnosis was 61.7±12.0 (22–89) years. The five most common cancer types were non-small-cell lung (33.4%), gastric (15.3%), small-cell lung (9.9%), colorectal (8.7%) and breast cancers (6.9%). The patient numbers for local, locally advanced and metastatic stage at the diagnosis were 22 (5.4%), 97 (24.0%) and 285 (70.5%), respectively. The mean number of chemotherapy lines was 1.40 (min-max 1–8). The number of patients that received single, doublet and triplet chemotherapy as a last chemotherapy regimen was 133 (32.9%), 228 (56.4%) and 43 (10.6%), respectively. The number of patients with an ECOG status of 0, 1, 2 and 3 before beginning the last chemotherapy regimen was 10 (2.5%), 40 (9.9%), 316 (78.2%) and 38 (9.4%), respectively. The mean DCD was 60.6±99.9 days (0–962). The number of patients in the two groups according to the DCD, whether ≤ 60 or > 60 days, was 291 (72.0%) and 113 (28.0%), respectively (Table 1).

The mean TNC and TLC counts were 7.32±5.52*103uL and 1.29±0.87*103uL, respectively. The mean NLR was calculated as 11.3%±27.1%. Other laboratory parameters are laid out in Table 2.

In the univariate analysis, breast and colorectal cancers were higher in patients who lived ≤ 60 days after the last chemotherapy than in those who lived > 60 days ($p = 0.035$ and $p = 0.040$, respectively). Also, single-agent chemotherapy usage was higher in the ≤ 60 days-group. There was a significant difference between the groups with respect to ECOG status. The number of ECOG 0/1 patients was higher in > 60-days group, and the ECOG 2/3 patient number was higher in the ≤ 60-day group ($p = 0.002$) (Table 1). The mean TNC was higher (7.75±5.76 103uL and 6.21±4.69 103uL, respectively, where $p = 0.014$) and the TLC was lower (1,22±0.87 103uL and 1,48±0.83 103uL, respectively, where $p = 0.003$) in the ≤ 60-days group

than in > 60-days group.

Table 1. Demographic and pathologic features of patients and univariate analysis for determining the 60≤days survival.

Variables		All patients (n= 404)		60≤days (n=291)		>60 days (n=113)		p
		n	%	n	%	n	%	
Gender	Male	278	68.8	202	69.4	76	67.3	0.674
	Female	126	31.2	89	30.6	37	32.7	
Age at diagnosis(year)	Mean+SD	61.7±12.0 (22-89)		62.0±12.2		60.8±11.8		0.350
Diagnosis	NSCLC	135	33.4	98	33.7	37	32.7	0.858
	SCLC	40	9.9	33	11.3	7	6.2	0.120
	Breast	28	6.9	25	8.6	3	2.7	0.035
	Colorectal	35	8.7	20	6.9	15	13.3	0.040
	Prostate	7	1.7	4	1.4	3	2.7	0.405
	Gastric	62	15.3	41	14.1	21	18.6	0.261
	RCC	1	0.2	1	0.3	0	0.0	1.000
	Sarcoma	8	2.0	6	2.1	2	1.8	1.000
	Pancreas	20	5.0	16	5.5	4	3.5	0.415
	Bladder	11	2.7	5	1.7	6	5.3	0.081
	Other	57	14.1	42	14.4	15	13.3	0.764
Last Ctx regimen	Single	133	32.9	109	37.4	26	23.0	0.024
	Doublet	228	56.4	157	54.0	72	63.7	
	Triplet	43	10.6	25	8.6	15	13.3	
Chemotherapy line number	Med (min-max)	2 (1-8)		2 (1-8)		1 (1-7)		0.684
ECOG before last Ctx regimen	0	10	2.4	6	2.1	4	3.6	0.002
	1	40	10.0	19	6.6	21	18.8	
	2	316	78.2	235	81.0	79	70.5	
	3	38	9.4	30	10.3	8	7.1	
DCD (days)	Mean+SD	60.6± 99.9						

ECOG: Eastern Cooperative Oncology Group scales, Ctx: chemotherapy, NSCLC: non-smallcelllungcancer, SCLC: small cell lungcancer, RCC: renal cell carcinoma, DCD: duration between last chemotherapy regimen and death, min: minimum, max: maximum, SD: standard deviation

The mean NLR values were 13.5±31.4% and 5.8±6.5%, respectively, in ≤ 60 days group and in > 60-days group ($p < 0.001$). Also, AST (51.1±85.8 and 39,2±89.6, respectively, where $p = 0.004$) and ALT values (36.7±45.2 and 27.0±63.2, respectively, where $p < 0.001$) were higher in the ≤ 60-days group than in > 60-days group. There was no difference in terms of CRP and LDH between the groups. (Table 2)

Table 2. Laboratory features of patients and univariate analysis for determining the 60≤days duration between last chemotherapy regimen and death

Variables	Allpatients (n=404) mean±SD	60≤ days (n=291) mean±SD	>60 days (n=113) mean±SD	p
WBC (10^3/uL)	9.36±5.99	9.69±6.22	8.52±5.30	0.146
Neu (10^3/uL)	7.32±5.52	7.75±5.76	6.21±4.69	0.014
Lym (10^3/uL)	1.29±0.87	1.22±0.87	1.48±0.83	0.003
NLR %	11.3±27.1	13.5±31.4	5.8±6.5	<0.001
Eos (10^3/uL)	0.11±0.27	0.10±0.3	0.14±0.24	0.019
Hgb (g/dL)	10.8±1.7	10.9±1.7	10.6±1.6	0.212
Plt (10^3/uL)	271.4±161.3	265.4±158.1	286.8±169.0	0.292
PDW (fL)	14.3±8.1	14.2±2.5	14.6±14.8	0.004
Crea (mg/dL)	0.87±0.58	0.85±0.57	0.90±0.60	0.205
	Median (min-max)	Median (min-max)	Median (min-max)	
AST (U/L)	24 (6-920)	26 (6-920)	20 (7-917)	0.004
ALT (U/L)	20 (3-645)	23 (3-411)	17 (5-645)	<0.001
LDH (U/L)	238 (22-4552)	237 (23-4478)	239 (22-4552)	0.987
CRP (mg/dL)	32 (0.75-1427)	34 (0.75-1427)	25 (1.92-375)	0.330

WBC: white blood count, Neu: neutrophil, Lym: lymphocyte, NLR: neutrophil to lymphocyte ratio, Eos: eosinophil, Hgb: hemoglobin, Plt: platelet, PDW: platelet distribution width, Crea: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, SD: Standard deviation

The receiver operating characteristic (ROC) curve was drawn using the NLR ratios at the time before the beginning of the last chemotherapy line; the corresponding area under the curve value was found to be 0.636 (95% Cl 0.577–0.694, $p < 0.001$). The cutoff value determining the ≤ 60-day DCD was determined as NLR ≥ 3.59%, with 70.0% sensitivity and 51.0% specificity (Fig. 1). The median DCD was lower in patients with NLR ≥ 3.59% than <3.59% (26 days and 42 days, respectively, where p= 0.001) (Table 3).

Table 3. Survivals differences between groups according to NLR cut-off value.

	NLR				
	<3.59		≥3.59		
	Mean ±SD	Min-Max (Median)	Mean ±SD	Min-Max (Median)	p
DDD (month)	13.8±20.6	0-150 (7)	9.4±14.5	0-148 (5)	0.002
DCD (day)	86.4±130.0	2-810 (42)	47.0±76.2	0-962 (26)	0.001

DDD: duration between diagnosis and death, DCD: duration between last chemotherapy regimen and death, NLR: neutrophil to lymphocyte ratio, Min: minimum, Max: maximum, SD: Standard deviation.

In multivariate logistic regression analysis for factors determining the ≤ 60-day DCD, an NLR ≥ 3.59%, as well as ECOG status, were found to be significant factors ($p < 0.001$, and $p < 0.009$, respectively) (Table 4).

Table 4. Multivariate analysis for determining the 60≤days duration between last chemotherapy regimen and death.

		p	OR	%95 CI	
ECOGs at before last ctx regimen		0.003			
	0	0.631	0.662	0.123	3.564
	1	0.009	0.225	0.074	0.685
	2	0.819	0.899	0.363	2.230
Stage at diagnosis		0.875			
	2	0.989	0.992	0.290	3.396
	3	0.787	1.211	0.301	4.869
Chemotherapy line number		0.627	1.106	0.737	1.658
WBC		0.902	1.003	0.956	1.052
NLR	≥3.59	<0.001	2.696	1.553	4.679
Hgb		0.419	1.068	0.911	1.252
MPV		0.722	0.963	0.785	1.183
Crea		0.484	0.864	0.574	1.300
ALT		0.167	1.004	0.998	1.009
Diagnosis	SCLC	0.511	1.382	0.527	3.626
	Breast	0.058	4.693	1.086	20.287
	Colorectal	0.251	0.616	0.270	1.409
	Bladder	0.525	0.620	0.142	2.710

ECOG: Eastern Cooperative Oncology Group scales, WBC: white blood count, NLR: neutrophil to lymphocyte ratio, Hgb: hemoglobin, MPV: mean platelet volume, Crea: creatinine, ALT: alanine aminotransferase, Ctx: chemotherapy, SCLC: small cell lung cancer,

Discussion

In this study, our aim was to investigate whether NLR is a predictor of survival in cancer patients that received palliative chemotherapy. We found that NLR and ECOG status were independent factors for ≤ 60 days' survival in patients with advanced solid tumors.

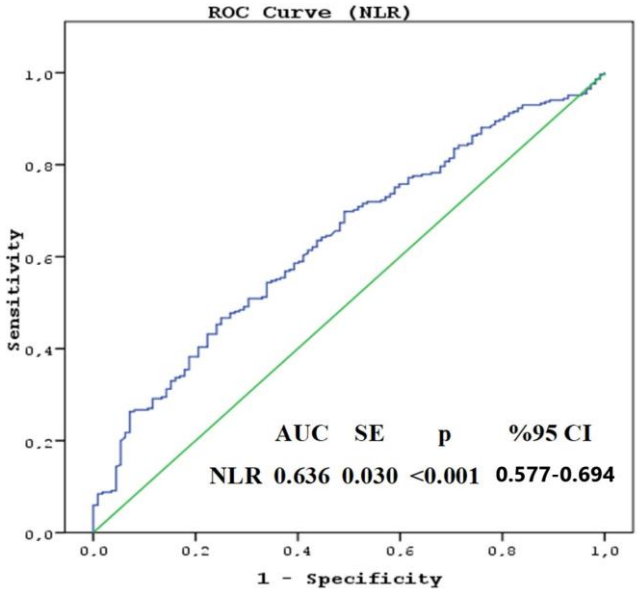


Fig. 1: Receiver operating characteristic curve analyses for ≤ 60day survival.
The cutoff value determining the ≤ 60 day DCD, was determined as NLR ≥ 3.59%, with 70.0% sensitivity and 51.0% specificity.

NLR is an indicator of inflammation and immune system response, and has been accepted as a prognostic factor in various malignancies. Based on the findings of current studies, it is relatively consistent to conclude that a higher NLR is a negative prognostic factor for many cancer types such as renal cell carcinoma, malignant melanoma, and gastric, pancreatic, breast and colorectal cancers [19-28]. But a few studies have focused on which parameter is a predictor of early death. In a trial published in 2007, with a total of 177 patients with solid tumors, two-month survival predictors were investigated, and the Karnofsky index, the number of metastatic sites, low serum albumin and LDH concentration were found to be independent factors in predicting two months' survival. Also, with univariate analysis, a high WBC was found to be a poor prognostic factor, but this relation was not observed with multivariate analysis. The neutrophil-to-lymphocyte ratio was not evaluated in this study [15].

Earlier studies have focused solely on performance status in terms of survival estimation. For example, one study set out to improve the ability to estimate the survival of terminally ill cancer patients and found that the factor most strongly associated with shorter survival was poor performance status [1]. However, these patients' NLR was not included in the analysis. Also, a palliative performance scale (consisting of the subheadings of mobility, activity/disease finding, self-care, nutrition and level of consciousness) was evaluated for estimating survival. The study's findings revealed that the palliative performance scale upon admission, along with gender and age, was a strong predictor of survival in patients already identified as palliative. However, survival had not been a significant part of the diagnoses [29]. A trial published in 2008 set out to derive and validate a simple predictive model for the survival of patients who had metastatic cancer and attended a palliative radiotherapy clinic. This model, different from older models (including six separate factors) needed three prognostic factors: primary cancer site, site of metastases and KPS. The study did not find a difference between the two models in terms of estimating survival [30]. In another study, which included a total of 299 patients, the prognostic value was based on a combination of performance status (PS) factors, with either the LDH level or the lymphocyte count being evaluated. This study found that a PS > 1, a lymphocyte count ≤ 700/μL and LDH > 600 UI/L were independent predictors of short-term survival, as well as the interleukin 6 (IL-6) level, the serum albumin concentration and the platelet count [31]. In the studies discussed above, the researchers either focused only on the PS or on models with complex components, but they did not evaluate NLR in terms of survival estimation. We found that easily accessible parameters such as NLR and ECOG status were independent factors for ≤ 2 months' survival in patients with advanced solid tumors. Also, we found that in the study's population, there was no relation between LDH and a ≤ two-months survival time.

This is a retrospective study with a specific limitation: We could not include albumin values in the analysis since not all patients had the respective data. But this is the first study to focus on the NLR as a predictor in terms of survival estimation in patients with advanced solid tumors, independent of tumor type.

In conclusion, NLR combined with ECOG PS appears to better predict survival in patients with solid advanced tumors and thereby can help clinicians either administer chemotherapy to their patients or direct them to the best supportive care.

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