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Original article

Can Neutrophil/Lymphocyte Ratio be a Predictor for Bone Metastases of Solid Tumors?

Billur Caliskan, Ayşe Nurdan Korkmaz

Department of Nuclear Medicine, Abant Izzet Baysal University, Bolu, Turkey

Abstract

Cancer-associated inflammation has been receiving increased attention due to its role in cancer development. It is known that tumors can cause an inflammatory reaction and inflammatory cells play an important role in neoplastic growth. In this study, we aimed to investigate any relationship between bone metastases and the neutrophil-to-lymphocyte ratio (NLR). Patients who were referred for bone scintigraphy to investigate bone metastasis were enrolled in the study. Patients' hematological parameters were obtained from the hospital database retrospectively. Patients with a nonmetastatic bone scan were categorized as Group A (*N* = 171), patients who had metastatic bone disease without any other organ metastases were categorized as group B (*N* = 25), and patients who had metastatic bone disease with the other organ metastases were categorized as Group C (*N* = 48). The median NLR of the patients in Group A was 2.55 (range: 0.38–20.7), in Group B was 2.83 (range: 1.56–31.8), and in Group C was 4.12 (range: 1.79–38). NLR was significantly higher in Group C patients compared to Group A and B patients ($P < 0.001$). In conclusion, the NLR is significantly associated with the other organ metastases but has no significant correlation with bone metastases.

Keywords: Bone metastasis, bone scintigraphy, neutrophil-to-lymphocyte ratio (NLR), solid tumor

Introduction

Bone metastasis of various neoplasms affects patients' quality of life as well as their morbidity and mortality. Bone scintigraphy is generally used to detect bone metastasis in most cancers including breast cancer, lung cancer, prostate cancer, and gastrointestinal system cancer. Although bone scintigraphy has a high sensitivity for detecting bone lesions, it has limitations in determining if bone lesions are benign or malignant. Other imaging modalities such as fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET/CT) or a NaF bone scan may be suggested, but these modalities are not cost-effective and they are also not suitable in most centers. Recently, some hematological indices, such as neutrophil counts and neutrophil-to-lymphocyte ratios (NLR) have been investigated and introduced as prognostic indicators in cancer patients.[1] The tumor's inflammatory response plays an important role in the development and survival of tumor cells.[2] NLR is determined as a hematological inflammatory marker that can be measured easily in the peripheral blood of patients. NLR has been associated with the prognosis of cancers of the colorectal region, lungs, breasts, and pancreas.[3-6] Wang *et al.* reported that NLR was an independent prognostic factor in patients with bone metastasis.[7] Consequently, we aimed to investigate whether NLR can be used as a predictor for bone metastasis before they appear on bone scintigraphy. We also wanted to show any relationship between NLR, hematological parameters, and bone scintigraphy findings.

Address for correspondence:
Dr. Billur Caliskan,
Department of Nuclear Medicine,
Faculty of Medicine, Abant Izzet Baysal University,
Bolu - 14210, Turkey.
E-mail: billurcaliskan@gmail.com

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Materials and Methods

Research Ethics Committee approval was obtained for performing this study. Patients who were referred for bone scintigraphy between January 2012 and December 2013 were reviewed retrospectively. There were 267 patients with histologically verified primary malignancy as solid tumors, who were referred for bone scan to evaluate bone metastasis. Patients were categorized into three groups based on metastatic bone disease with or without the other organ metastases. Twenty-three patients with suspicious metastatic bone disease were excluded from the study. Complete blood counts (CBC) of all patients obtained within the same week of the bone scan date were obtained from medical records. Patients with chronic inflammatory disease and hematological disease were excluded from the study, as were patients who had been using antiinflammatory medications and those who had no blood count data.

Patients received an intravenous injection of 740–925 MBq technetium-99m (^{99m}Tc) methylene diphosphonate (MDP). Approximately 3 h later, they underwent a whole-body planar image in the anterior and posterior views on a dual-headed gamma camera (Siemens; e-cam signature, USA) fitted with a low-energy, all-purpose, parallel-hole collimator. The photopeak of ^{99m}Tc was 140 keV with a 15% pulse height analyzer window. Planar spot images and single photon emission computed tomography (SPECT) images were added for certain patients whenever deemed necessary. SPECT was reconstructed using an iterative reconstruction method in which a Gaussian filter was implemented. Two experienced nuclear medicine physicians interpreted bone scintigraphy scans. Patients with suspicious bone lesions were interpreted as metastatic disease only when a correlation with other radiological modalities could be identified. Patients were divided into three groups as follows: Group A had nonmetastatic bone scans, Group B had metastatic bone scans without any other organ metastases, and Group C had metastatic bone scans with other organ metastases.

Hematological parameters, including hemoglobin, white blood cell (WBC) count, neutrophil count, and lymphocyte count, were analyzed 30 min after blood collection using an automatic blood count system. The NLR was then calculated.

A statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). All normally distributed data were analyzed using unpaired sample *t*-tests. A comparison of the nonnormal numerical variables was performed using the Mann–Whitney *U* test. A *P* value of < 0.05 was considered statistically significant.

Results

The 244 subjects who were enrolled in this study were aged 28–90 years. Scintigraphy was normal in 147 patients, but 24 patients' scintigraphy results were suggestive of degenerative changes corroborated with PET/CT and other radiological findings. Patients' characteristics are given in Table 1.

NLR was significantly increased in patients with bone metastasis with other organ metastasis compared to the patients without bone metastasis and the patients with only bone metastasis ($P < 0.001$) [Figure 1].

Median neutrophil counts were 4.6 (range: 1.0–42.1) in Group A, 4.9 (range: 3.1–10.8) in Group B, and 6.2 (range: 1.9–44.4) in group C ($P = 0.003$). The median lymphocyte count of Group C was lower from that of Group B and Group A (1.4, 1.6, and 1.7 respectively; $P = 0.004$). WBC counts were higher in Group C than in Group A and Group B (10.8, 7.4, and 7.0 respectively; $P = 0.026$) [Figure 2].

Table 1: Characteristics and diagnosis of the patients

	Group A (*N*:171)	Group B (*N*:25)	Group C (*N*:48)	*P*
Sex (male/female)	98/73	19/6	36/12	0.028
Age (mean±SD)	61.7±11.8	72.1±12.2	65.5±10.9	<0.001
Diagnosis, *N* (%)				
Bladder cancer	5	1	4	
Breast cancer	40	3	6	
Pancreatic cancer	5	0	3	
Gastrointestinal tract cancer	50	3	7	
Prostate cancer	29	15	10	
Lung cancer	30	3	18	
Other	12	0	0	

SD: Standard deviation. Other includes renal cell cancer (*N*=5), gynecological cancer (*N*=5), hepatocellular cancer (*N*=1) and malign mesenchymal tumor (*N*=1)

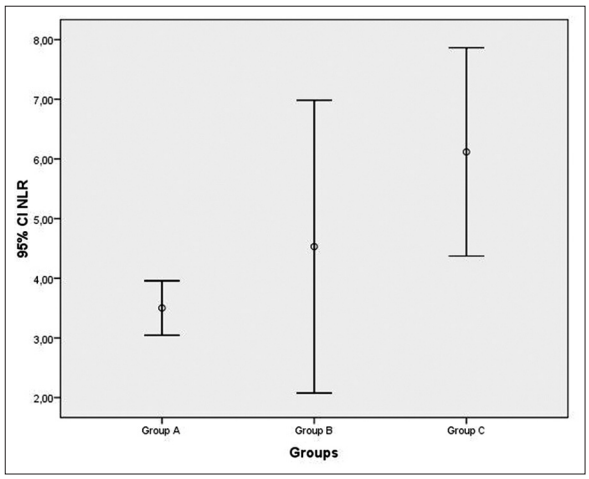

Figure 1: The box and whisker plot showing distrubutions of NLR for groups

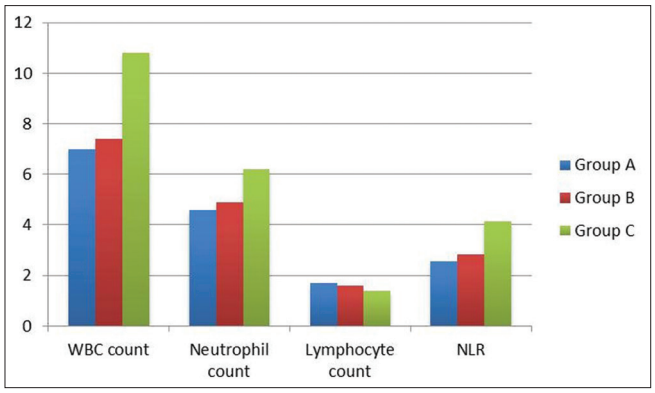

Figure 2: Hematological parametres of groups

There was no correlation between the number of metastatic bone lesions and NLR in groups B and C.

Discussion

The results of our study demonstrate that there is a relationship between metastatic disease and some hematological indices. When we compared the patients with normal bone scan and the patients with metastatic bone disease, we found that the NLR was slightly higher in the group of metastatic bone disease. However, the NLR of patients with bone metastases accompanied with other organ metastases was also significantly higher than that of the normal patients As mentioned above, neutrophil counts were higher and lymphocyte counts were lower in patients with bone metastasis and the other organ metastases. It is well known that there is a relationship between systemic inflammation and tumor development.[2,8,9] Although it is not clearly understood which mechanisms cause this relationship, some theories have been suggested. Tumor-related inflammation may cause direct or indirect increases in cytokines, inhibition of apoptosis, and increases in angiogenesis.[2,8] Tumor cells release granulocyte colony-stimulating factor (GCSF) that can trigger neutrophilia. Neutrophils play a role in tumor angiogenesis by producing proangiogenic factors such as vascular endothelial growth factor, matrix metalloproteinase, interleukin-8, and elastases.[1,2,8,10] These types of cytokines promote tumor growth, development, and metastasis. On the other hand, lymphocytes are important in providing antitumor immunity.[11] Increased lymphocytes have also been reported to be a good prognostic indicator in patients with colorectal cancer, breast cancer, and melanoma.[12-14] Both increased neutrophil counts and decreased lymphocyte counts can be a cause for increased NLR. In our study, neutrophil counts were significantly higher in patients with bone metastasis and other organ metastases, and also, lymphocyte counts were slightly lower in patients with bone metastasis and other organ metastases. Current studies have reported that NLR is a prognostic predictor for many types of cancer. Paramanathan *et al*. reported in a systemic review and meta-analysis that an elevated NLR correlated with poor prognosis in patients with solid tumors.[1] Unal *et al*. investigated the effects of the pretreatment NLR on survival in patients with non-small cell lung cancer and found that the overall survival rates were significantly associated with NLR.[4] They also found there was no significant relationship between chemoradiotherapy and NLR. Thus, the effect of inflammation on survival seemed independent from the response to chemoradiotheraphy. Another study reported that multiple myeloma patients with a NLR ≥ 2 at diagnosis were associated with worse outcomes compared with patients with a NLR <2.[15] Wang *et al*. reported that the prognosis of patients with malignant bone metastasis was independently associated with NLR; they found that a high NLR (>3) was associated with a poor prognosis.[7]

Bone scintigraphy is commonly used for detection of bone metastasis in many types of cancers including cancers of the prostate, breasts, lungs, and gastrointestinal tract. Most metastatic bone lesions are asymptomatic and there is controversy about whether asymptomatic cancer patients should be scanned. There is a propensity of scanning asymptomatic patients with tumors that may metastasize to bones from areas such as the breasts, lungs, and prostate. On the other hand, tumors with low rates of bone metastases such as tumors from the colon, head, neck, and nasopharyngeal region could be out of preference for scanning in a cost-effective approach. In this study, we showed that there is a relationship between metastatic disease and NLR. Although it is more obvious that the other organ metastases are related with increase of NLR, the patients with only bone metastases showed a slight increase on NLR. Thus, it is still controversial if NLR can help the clinician make decisions about scanning asymptomatic cancer patients.

The limitations of this study include the relatively small numbers of patients and the wide range of various cancer types. Inflammation markers can also increase with certain inflammatory diseases and another limitation of our study was that we did not take into account this condition because it was a retrospective study. Further studies need to be performed to confirm our results. A large prospective study can demonstrate whether NLR can help to distinguish malignant and benign bone lesions. In conclusion, a high NLR is significantly associated with metastatic disease but it is not associated with only metastatic bone disease.

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Conflicts of interest

There are no conflicts of intrest.

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