Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1162371

J Med Palliat Care 2022; 3(3): 216-220

Diagnostic value of delta neutrophil index in determining axillary metastases in breast cancer

Delta nötrofil indeksinin aksiller metastazları belirlemede tanısal değeri

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Cite this article as/Bu makaleye atıf için: Alkurt EG, Tutan MB. Diagnostic value of delta neutrophil index in determining axillary metastases in breast cancer. J Med Palliat Care 2022; 3(3): 216-220.

ABSTRACT

Aim: The delta neutrophil index (DNI), which shows the percentage of immature granulocytes (IG) in peripheral blood in inflammatory conditions, is an indicator of increased bone marrow activation. Its ability to predict prognosis has been demonstrated in many cancer studies. This study aims to investigate the value of DNI in predicting axillary metastases in breast cancer.

Material and Method: Patients diagnosed with breast cancer and operated on axillary lymph node dissection were screened and 127 patients were included in the study. The patient's age, gender, operation time, length of hospital stay, immature granulocyte (IG) percentages (IG#), and axillary lymph node pathology results were retrospectively scanned from the archive system.

Results: DNI and IG were statistically higher in the group with lymph node metastasis. When examined for IG#, the mean of the group with reactive lymph nodes was 0.02±0.02, while the mean of the metastatic group was 0.04±0.05. This statistically significant difference was high ($p<0.001$). Cut-off values of 0.035 (OR 4.133, CI 95% 0.589-0.777, $p<0.001$) were found with 40% sensitivity and 86.1% specificity for the differentiation IG# of metastasis among patients.

Conclusion: DNI and IG count may be new predictive markers with high sensitivity and specificity in detecting axillary metastasis of breast cancer.

Keywords: Breast cancer, axillary lymph node metastasis, delta neutrophil index, immature granulocyte

ÖZ

Amaç: İnflamatuar koşullarda periferik kandaki olgunlaşmamış granülositlerin (IG) yüzdesini gösteren delta nötrofil indeksi (DNI) artan kemik iliği aktivasyonunun bir göstergesi olarak kullanılabilir.Bu çalışmanın amacı meme kanseri prognozunda önemli rol oynayan aksiller lenf nodu metastazını klinik ve radyolojik tespitinden önce IG sayısı ve DNI ile belirlemektir.

Gereç ve Yöntem: Meme kanseri tanısı alıp opere edilen ve aksiller lenf nodu diseksiyonu yapılmış hastalar tarandı ve 127 hasta çalışmaya dahil edildi. Hastaların yaşı, cinsiyeti, operasyon süresi, hastanede yatış süreleri, immatür granülosit (IG) yüzdeleri (IG#) ve aksiller lenf nodu patoloji sonuçları retrospektif olarak arşiv sisteminden tarandı.

Bulgular: DNI VE IG lenf nodu metastazı olan grupta istatiksel olarak daha yüksekti. IG# açısından inceleme yapıldığında lenf nodu reaktif olan grubun ortalaması 0,02±0,02 iken metastatik grubun ortalaması 0,04±0,05 bulundu, istatistiki anlamlı farklılık gösterecek şekilde yüksekti ($p<0,001$). Hastalar arasında metastazın ayrımı IG#'sı için %40 sensitivite ve %86,1 spesifiteyle 0,035 (OR 4,133, CI%95 0,589-0,777, $p<0,001$) değerleri cut-off olarak bulunmuştur.

Sonuç: DNI ve IG sayısı, meme kanserinin aksiller metastazını saptamada yüksek duyarlılık ve özgüllüğe sahip yeni öngörücü belirteçler olabilir.

Anahtar Kelimeler: Meme kanseri, aksiller lenf nodu metastazı, delta nötrofil indeks, immatur granülosit

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Received/Geliş: 16.08.2022 **Accepted/Kabul:** 10.09.2022

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women and is an important global health problem (1). Although its incidence has increased recently, mortality rates have decreased due to advances in early diagnosis and neo-adjuvant therapy (2,3). Patient prognosis depends on many variables, including age, ethnicity, tumor biology (tumor size, nodal status, histological grade), and response to systemic therapy (polymerase chain reaction) (4).

In cancer, the clinical outcome may be influenced not only by the histopathological features of the tumor but also by the host response, including the inflammatory response. Therefore, biomarkers showing the inflammatory response in cancer patients may help guide treatment.

Recent studies have confirmed the role of host inflammatory responses in tumor development and the progression of cancers, including breast cancer (5). These studies demonstrated that the secretion of cytokines and chemokines produced by both tumor and associated cells such as leukocytes may contribute to the development of metastasis (6). Inflammatory cell stimulation occurs in lymph node metastases and distant organ metastases such as primary tumors. A neutrophilic response is associated with poor prognosis, as it can inhibit the immune system, for example by suppressing the cytotoxic activity of T cells (7). The presence of tumor-infiltrating lymphocytes (TILs) has been associated with a better response and prognosis to cytotoxic therapy in BC patients (8). Similarly, hematological indices such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and C-reactive protein (CRP) ratios between different cell types (7,9-11). Its relationship with malignant tumors has been studied in many studies.

Also, recent studies have defined the delta neutrophil index (DNI), which represents the percentage of immature granulocytes (IG) in peripheral blood due to increased bone marrow activation in inflammatory conditions (12). IG fractions are based on the count of granulocyte precursor cells such as promyelocytes, myelocytes, and metamyelocytes. With technological advances, IG count and DNI can be evaluated automatically from complete blood count parameters in automated systems (12,13).

IG count and DNI have been identified as prognostic factors in many inflammatory processes such as sepsis, cardiovascular events, and acute appendicitis (14-16). However, studies related to breast cancer with these parameters are limited. In this study, the utility of IG and DNI in the prediction of axillary lymph node metastasis, which plays an important role in breast cancer prognosis, was investigated.

MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Erol Olçok Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (Date: 11/08/2022, Decision No: 2022/74). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Our research was carried out retrospectively and cross-sectionally. Data were collected by examining patient files and computer records.

127 patients who were operated on with the diagnosis of breast cancer and underwent axillary lymph node dissection by the General Surgery clinic between 2019-2022 were included in the study.

Inclusion Criteria

Patients over the age of 18 were defined as those who were diagnosed with clinicopathologically breast cancer, did not receive neoadjuvant therapy, whose data could be accessed, and who did not have recurrence or distant metastasis. Exclusion criteria are; Patients with missing clinicopathological features, hematological and oncological diseases, under 18 years of age, whose data could not be reached, who were diagnosed with advanced breast cancer, and whose final pathology result was not reported as breast cancer were determined.

Statistical Analysis

IBM SPSS Statistics for Windows program was used for all statistical analysis (version 26; IBM Corp., Armonk, N.Y., USA). For categorical variables, descriptive statistics were provided using numbers and percentages, and numerical variables were reported with mean, standard deviation, and median in parentheses. The normal distribution of the data was evaluated with the Shapiro-Wilks test. Relationships between variables were investigated with Pearson or Spearman correlation coefficient by the data distribution. Comparison of numerical measurements for two independent groups according to research groups was evaluated with a two-sample t-test for age only, operation times, hospitalization times, IG percentages, and IG numbers were evaluated with Mann Whitney U test by data distribution. The ROC curve was used to show the discrimination of the statistically significant variables, and the cut-off values were found for the markers using the area under it and the Youden index. Sensitivity, specificity, PPV, NPV, and precision were calculated for these cut-off values. Odds ratio values were calculated according to these cut-offs. For the statistical significance level, $p<0.05$ was accepted.

RESULTS

A total of 127 patients were included in the study. All of the patients were women. The mean age of all patients was 58.31±13.11 years. The operation time was 119.37±65.05 minutes. The patients were hospitalized for an average of 9.59±8.48 days. The mean of IG% was calculated as 0.4±0.33, and the mean of IG# was calculated as 0.03±0.04.

Pathology results of 72 patients (56.7%) were reported as reactive lymph nodes. Metastatic lymph nodes were found in 55 patients (43.3%). The patients were divided into two groups according to axillary lymph node pathologies, reactive lymph node, and metastatic lymph node.

While the mean age of the lymph node reactive group was 57.96±12.42 years, the mean age of the metastatic group was 58.76±14.07 years. No statistically significant difference was observed between the two groups (p=0.733).

While the operations of non-metastatic patients lasted 106.94±64.11 minutes on average, this time increased to 135.64±63.19 minutes in metastatic patients. A statistically significant difference was observed (p<0.001). While patients without metastasis in the axilla were hospitalized for an average of 6.6±6.92 days, the duration of hospitalization in the metastatic group was found to be 13.51±8.78 days, which was statistically significantly higher (p<0.001).

The mean IG% of the lymph node reactive group was calculated as 0.28±0.15, and the mean of the metastatic group was calculated as 0.54±0.44, with a statistically significant increase in the metastatic group (p<0.001). In terms of IG#, the mean of the group with reactive lymph nodes was 0.02±0.02, while the mean of the metastatic group was 0.04±0.05, with a statistically significant difference (p<0.001).

To distinguish between patients with axillary lymph node reactive and metastatic patients with breast cancer, IG% and IG# markers with significant differences were evaluated in the area under the ROC curve and the Youden index. For differentiation of metastasis between patients, 0.55 (OR 7.072, CI 95% 2,438-20.518, p<0.001) for IG% with 34.5% sensitivity and 93.1% specificity, 40% sensitivity for IG# and specificity were found with 86.1%. Cut-off values of 0.035 (OR 4.133, CI 95% 0.589-0.777, p<0.001).

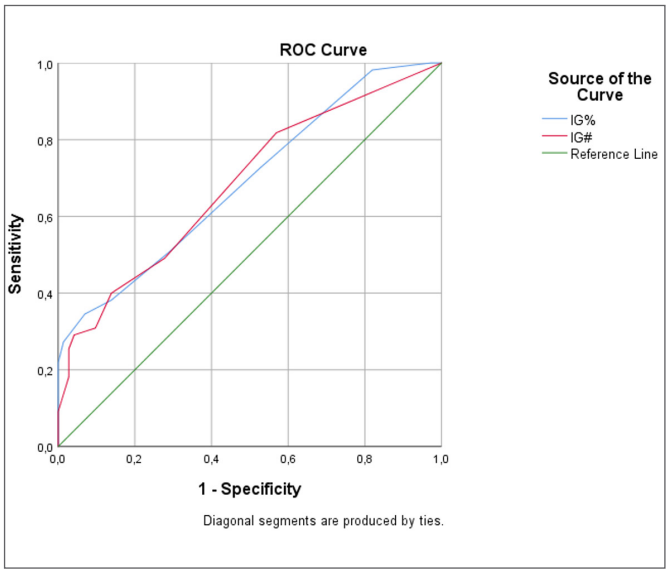

Figure 1.

DISCUSSION

DNI value showing the percentage of IG in peripheral blood in inflammatory conditions can be used as an indicator of increased bone marrow activation. In this study, it was found that DNI and IG values in patients diagnosed with breast cancer were increased in patients with axillary metastases and were a predictive marker in showing axillary metastases.

Table 1. All patients variables and comparison of variables between groups

Variables	All Patients (n=127)	Axilla Reactive (n=72)	Axilla Metastatic (n=55)	Statistical significance
Age	58.1±13.11	57.96±12.42	58.76±14.07	0.733
Operation duration	119.37±65.05	106.94±64.11	135.64±63.19	<0.001
Hospitalization	9.59±8.48	6.6±6.92	13.51±8.78	<0.001
IG%	0.4±0.33	0.28±0.15	0.54±0.44	<0.001
IG#	0.03±0.04 (0.02)	0.02±0.02	0.04±0.05	<0.001
Axilla LN				
Reactive	72 (%56.70)			
Metastasis	55 (%43.30)			

Table 2. Cut-off points and diagnostic values of variables for distinction between normal and appendicitis patients

Variables	Cut-Off	Diagnostic Values					ROC Curve			OddsRatio		
		Sensitivity	Specifity	PPV	NPV	Accuracy	Area (SE)	95% CI	p	Odds Ratio	95% CI	p
IG%	0.55	34.5%	93.1%	79.2%	65.0%	67.7%	0.688 (0.047)	0.596-0.781	<0.001	7.072	2.438-20.518	<0.001
IG#	0.035	40.0%	86.1%	68.8%	65.3%	66.1%	0.683 (0.048)	0.589-0.777	<0.001	4.133	1.752-9.754	<0.001

Predicting recurrence and survival after curative surgical resection for operable breast cancer patients has traditionally been based on standard clinicopathological criteria such as age, tumor size and grade, nodal status, and hormonal receptor status. However, it is known that inflammatory response can increase neoangiogenesis, cause tumor progression and metastatic spread, and further increase genomic instability by causing local immunosuppression. Other host-related factors, such as the systemic inflammatory response, have been previously shown to be associated with poor survival following potentially curative resection for a variety of cancers, including gastroesophageal and urinary tract cancers (17,18). Kim et al. (19) found that inflammatory markers were associated with low survival in patients who underwent cytoreductive surgery+hypec. Similarly, inflammatory response in pancreatic head cancers is associated with poor survival (20).

DNI is a new inflammatory marker that measures the percentage of circulating immature granulocytes as measured by next-generation automated devices. It indicates earlier bone marrow activation than neutrophil response and is a helpful indicator in the diagnosis and prognosis of different diseases (21–23). In a study by Yoonmi et al. (24), it was found to be an easy and useful marker for early diagnosis and prognostic evaluation of patients with sepsis. Bozan et al. (12) reported that preoperative DNI levels in patients with nodular goiter and thyroid malignancy were higher in the malignant patient group. They found the cut-off value for DNI to be 0.35%, with a sensitivity of 79.2% and a specificity of 78.9% in the diagnosis of malignant thyroid diseases. Also, in another study by Barut et al. (25), DNI was found to be a predictive factor in renal cell carcinoma. Another study reported that DNI is an early predictor of severe acute cholecystitis and is an inflammatory marker with a significantly higher predictive value than WBC count or CRP level to detect severe acute cholecystitis (26). Similarly, Shin et al. (27) reported that the preoperative DNI value helps the diagnosis of histologically normal appendicitis and is a useful parameter to distinguish between simple and complicated appendicitis.

As a result of our literature search, although many studies are showing that systemic inflammatory markers are associated with breast cancer prediction and prognosis, there is no comprehensive study revealing the relationship between DNI and axillary metastasis. With this study, we showed that an increase in serum DNI level, which can be processed by automated systems and included in CBC parameters, can be a useful marker for predicting axillary lymph node metastasis in patients with breast cancer.

Our study also has some limitations. First, our study had a retrospective design, and no subgroup analysis was performed according to breast cancer subtypes and receptor positivity or negativity. Also, the sample size was not large enough and outcome analysis with more patients may be required to further validate our model. We hope that in the future these parameters can be used as simple and inexpensive parameters for clinical decision-making and better prediction of axillary lymph node metastasis in breast cancer patients.

Finding a parameter that can predict axillary lymph node metastasis with simple blood values measurement, the absence of a similar breast cancer study in the literature, and the follow-up of patients with the same team and surgical discipline were the strengths of our study.

CONCLUSION

We showed that preoperative DNI and IG can predict axillary lymph node metastasis in patients with breast cancer. The conclusion we have reached as a result of our study is; The high sensitivity and specificity of these parameters can be used to predict preoperative axillary lymph node metastasis in patients with breast cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Erol Olçok Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (Date: 11/08/2022, Decision No: 2022/74).

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

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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