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Research

Is There a Relation Between Pretreatment CONUT Score and Neoadjuvant Chemotherapy Response in Breast Cancer Patients?

Meme Kanserinde Tedavi Öncesi CONUT Skoru Neoadjuvan Kemoterapi Yanıtı ile İlişkili mi?

Ayşe İrem Yasin, Atakan Topçu

Bezmialem Vakıf University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey

ABSTRACT

Objective: To evaluate the relationship between pre-treatment nutritional status and pathological complete response (pCR) rates in patients with breast cancer.

Methods: The study group consisted of 109 female patients. Clinicopathologic factors, pathological response status, and pre-treatment laboratory values of the patients were recorded retrospectively. CONUT score, consisting of total cholesterol, serum albumin, and total lymphocyte, was calculated to assess the nutritional status. Factors affecting pCR were evaluated, and the relationship between pCR and CONUT was analyzed.

Results: The mean age was 49.78±10.92. Thirty-two (29.4%) patients had pCR. The rate of pCR in the hormone-negative group was significantly higher than that in the hormone-positive group (p<0.001). Additionally, the pCR rate in the HER2+ group was significantly higher than that in the HER2- group (p<0.001). Patients with pCR had a significantly higher Ki67 index (p<0.001). There was no significant difference when the pCR rates of patients with high and low CONUT scores were compared.

Conclusion: This is the first study evaluating the association between pre-treatment CONUT score and pCR in breast cancer patients. There is a need for comprehensive studies to reveal the relationship more clearly.

Keywords: Breast cancer, CONUT score, neoadjuvant chemotherapy, nutrition, pathological complete response

ÖZ

Amaç: Neoadjuvan kemoterapi ile tedavi edilen meme kanseri hastalarında tedavi öncesi beslenme durumu ile patolojik tam yanıt (pTY) arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 109 kadın meme kanseri hastası dahil edildi. Hastalara ait klinikopatolojik faktörler, patolojik yanıt durumları ve tedavi öncesi laboratuvar değerleri hasta dosyalarından taranarak kaydedildi. Toplam kolesterol, serum albümin ve toplam lenfosit değerlerinden oluşan ve nutrisyonel durumu değerlendiren CONUT skoru valide edilmiş skorlama sistemine göre hesaplandı. pTY'yi etkileyen faktörler değerlendirildi. pTY ve CONUT arasındaki ilişki analiz edildi.

Bulgular: Ortalama yaş 49,78±10,92 idi. Otuz iki (%29,4) hastada pTY saptandı. Hormon negatif gruptaki pTY oranı, hormon pozitif gruptan anlamlı derecede yüksekti (p<0,001). Ek olarak, HER2+ grubundaki pTY oranı, HER2- grubundan anlamlı olarak yüksekti (p<0,001). pTY'li hastalarda Ki67 indeksi anlamlı olarak daha yüksekti (p<0,001). Hastalar yüksek ve düşük CONUT skoru gruplarına ayrıldığında gruplar arasında pTY açısından anlamlı fark yoktu.

Sonuç: Bu çalışma, meme kanserli hastalarda tedavi öncesi CONUT skoru ile pTY arasındaki ilişkiyi değerlendiren ilk çalışmadır. Geniş hasta gruplarında yapılacak kapsamlı çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Meme kanseri, CONUT skoru, neoadjuvan kemoterapi, beslenme, patolojik yanıt

Address for Correspondence: Ayşe İrem Yasin, Bezmialem Vakıf University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey
E-mail: ayseiremyasin@gmail.com ORCID ID: orcid.org/0000-0002-1528-8065

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INTRODUCTION

Neoadjuvant chemotherapy (NAC), which allows breast-conserving surgery and predicts chemotherapy response, is frequently used in breast cancer patients, the most common cancer among women (1-3). After NAC, a pathological complete response (pCR) is a validated prognostic survival factor (4). Survival times are longer in patients with pCR, particularly in triple-negative and HER2+ breast cancer (4). Response to NAC provides clinicians with prognostic information and guidance for further treatment options (5). Therefore, it is essential to define the factors affecting the NAC response.

Perioperative immune-nutritional status is considered a prognostic factor in different tumor types, including breast cancer (6). There are several scoring systems that evaluate the nutritional status of cancer patients (7). The prognostic nutritional index (PNI), one of these nutritional scoring systems, was predictive of pCR in breast cancer patients (8). Controlling nutritional status (CONUT), consisting of total cholesterol, total lymphocyte count, and serum albumin level, is another comprehensive scoring system that evaluates nutritional status (9). When CONUT and PNI were compared, CONUT was more predictive of the survival times of cancer patients (10). Several studies have demonstrated the impact of CONUT on survival outcomes in many types of cancer, including gastric cancer, lung cancer, esophageal cancer, mesothelioma, ovarian cancer, sarcoma, renal cell carcinoma, and hepatocellular carcinoma (9). Two recent studies from China identified that a high CONUT score was related to a worse prognosis in surgically treated breast cancer patients (10,11). Furthermore, preoperative high CONUT score was related to lower pCR in gastric cancer patients (12). This is the first study evaluating the relationship between pCR and CONUT score in patients with breast cancer.

METHODS

Patients

The data of patients followed up with breast cancer diagnosis in our Medical Oncology Clinic between January 2012-December 2021 were evaluated retrospectively. Of the 1,853 patients, 264 patients were treated with NAC. All biopsies and post-NAC surgical materials of the patients included in the study were evaluated at our center by experienced pathologists. Pre-treatment cholesterol, albumin, and lymphocyte values of 109 patients were obtained and recorded. All patients were female, aged between 18 and 80 years, had stage 2 or 3 breast cancer and underwent surgery. The tumor-node-metastasis staging was performed before NAC according to American Joint Committee on Cancer (13). NAC regimens they received before surgery were four cycles of doxorubicin and cyclophosphamide or epirubicin and cyclophosphamide every 21 days, followed by paclitaxel for twelve weeks. Trastuzumab was added to this regimen if the HER2 receptor was positive. HER2 positivity is defined as a 3+ score by immunochemistry or a 2+ score by immunochemistry and fluorescence *in situ* hybridization positivity (14). Scarff-Bloom-Richardson scheme was used for tumor grading (15). Estrogen (ER) and/or progesterone receptor positivity >1% in tumor nuclei by immunochemistry are accepted as hormone-positive disease (16). Miller-Payne criteria was used to assess the chemotherapy response, and no invasive disease was accepted as pCR (17). All demographic and clinicopathologic information of patients were recorded from the archive files. Two groups were created: pCR (+) and pCR (-). CONUT score was calculated according to the scoring system (Table 1) (18). Patients with a score ≥3 were defined in the high-CONUT group, and patients with a score <2 in the low-CONUT group (19). The data collection process was conducted according to the Helsinki Declaration. The study was approved by the Bezmialem

Table 1. CONUT scoring system

	Degree of malnutrition			
Parameter	**Normal**	**Mild**	**Moderate**	**Severe**
Serum albumin (g/dL)	≥3.50	3.00-3.49	2.50-2.99	<2.50
Albumin score	0	2	4	6
Total lymphocyte (/mm^3)	≥1,600	1,200-1,599	800-1,199	<800
Lymphocyte score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Cholesterol score	0	1	2	3

CONUT score = Albumin score + Total lymphocyte score + Cholesterol score, CONUT: Controlling nutrional status

Vakıf University Ethics Committee (no: 2021-393, date: 08.02.2022).

Statistical Analysis

The data were analyzed with SPSS 22 Statistics program (IBM Corporation, NY, USA) for Windows (Microsoft Corporation, WA, USA). Descriptive statistics are shown as mean ± standard deviation for variables with a normal distribution. Nominal variables were demonstrated as the number of cases and percentage. Two independent groups were compared with the independent sample t-test. Categorical variables were analyzed using the chi-square test or Fisher's Exact test. Results with $p<0.05$ were accepted as statistically significant.

RESULTS

One hundred nine female breast cancer patients were included in the study. The mean age was 49.78±10.92 in the patient group. Seventy five (68.8%) patients had a hormone-positive disease, and 34 (31.2%) patients had a hormone-negative disease. The number of HER2- patients was 82 (75.2%), and the number of HER2+ patients was 27 (24.8%). pCR was detected in 32 (29.4%) patients. The rate of pCR in the hormone-negative group was significantly higher than that in the hormone-positive group ($p<0.001$). Additionally, the pCR rate in the HER2+ group was significantly higher than that in the HER2- group ($p<0.001$). Ki67 proliferation index was significantly high in the patient group with pCR ($p<0.001$) (Table 2).

According to the CONUT scoring system, the scores were calculated. Patients with a score ≥3 were defined in the high-CONUT group and patients with a score <2 in the low-CONUT group. Eleven (10.1%) patients were in the high-CONUT group, and 98 (89.9%) patients were in the low-CONUT group. When the pCR rates of the two groups were compared, there was no significance (Table 3).

DISCUSSION

This is the first study evaluating the relationship between pre-treatment CONUT score and pCR in breast cancer patients. The results demonstrated no significant difference in pCR rates between the high-CONUT and low-CONUT groups. However, hormone receptor negativity, HER2 positivity, and a high proliferation index were related to high pCR rates.

Growing evidence revealed that tumor progression, treatment tolerance, and survival of cancer patients are closely related to the nutritional and immune-inflammatory status (20). Albumin is a reliable serum marker for nutritional status and the immune-inflammatory system (21). Low albumin levels in cancer patients are associated with poor survival and an increased risk of cancer-related death (22). Cholesterol plays an essential role in the cell membrane and in biochemical reactions related to the immune response (23). The correlation of low cholesterol levels with poor prognosis was demonstrated in various types of cancer (24). Furthermore, the host immune response was insufficient in patients with low peripheral lymphocyte count (25,26).

CONUT score consists of serum albumin, total cholesterol, and lymphocyte count in peripheral blood (18). Recently, in two studies, CONUT was found to be predictive of prognosis in breast cancer patients (10,11). In these studies, patients did not receive NAC, and the relationship between CONUT and pCR was not assessed. However, in gastric cancer patients who received NAC, high CONUT was associated with low pCR (12). This can be explained by the undernutrition degree of patients with gastrointestinal

Table 2. Clinicopathological factors affecting pathological complete response

	Patients with pathologic complete response (n=34)	Patients without pathologic complete response (n=75)	p
Age (mean ± SD)	47.91±10.98	50.56±10.86	0.952
Hormone receptor (ER/PR) status			
Positive	10 (31.2%)	65 (84.4%)	<0.001*
Negative	22 (68.8%)	12 (15.6%)	
HER2 receptor status			
Positive	16 (50%)	11 (14.3%)	<0.001*
Negative	16 (50%)	66 (85.7%)	
Ki67, % (mean ± SD)	52.39±26.87	30.51±21.8	<0.001*

*Significant results, SD: Standard deviation, ER: Estrogen, PR: Progesterone

Table 3. The association between pre-treatment CONUT score and pCR

	pCR + patients (n=34)	pCR - patients (n=75)	p
CONUT score			0.874
High	5	6	
Low	29	69	

CONUT: Controlling nutritional status, pCR: Pathologic complete response

system cancers being higher than that of patients with other types of cancer (27). Additionally, breast cancer patients are relatively in the younger age group (3), so they have better performance and fewer comorbidities, causing impaired nutritional and immune-inflammatory status.

PNI, another scoring system for nutritional status, was found to be predictive of pCR in breast cancer patients (8). CONUT is considered a more comprehensive scoring system with an additional parameter, total cholesterol, and was superior to PNI for predicting nutritional status (11). However, the role of cholesterol in breast cancer patients is controversial (28). The risk of developing breast cancer is related to various commodities such as metabolic syndrome (28). Hyperlipidemia is a common entity in this metabolic syndrome (29). It has been shown that oxysterol plays a mitogenic role in ER-positive breast cancer, and that low-density lipoprotein receptors are upregulated in cancer cells (30). Moreover, there are some differences in cholesterol function between hormone positive and negative breast cancer subgroups (31). This complex role of cholesterol in the pathophysiology of breast cancer may have influenced the relationship between the CONUT score and pathological response. However, significance might be observed when the histological subgroups were evaluated separately.

There were some limitations to our study. First, we calculated the CONUT score based on the pre-treatment laboratory values of the patients. However, side effects during NAC might impair the nutritional status, and preoperative values after NAC may yield different results. Second, breast cancer patients are a heterogeneous patient group because of their different receptor status (1). Because we had a relatively small sample size, we could not perform subgroup analyses of different histological breast cancer types.

CONCLUSION

It is important to discover markers that predict pCR associated with longer survival times in breast cancer. Although CONUT was not associated with pCR in this study, further investigation into different histological subtypes is needed to clarify the impact of immune-nutritional status on treatment response and prognosis of patients. Thus, the way for personalized treatment options will be paved.

ETHICS

Ethics Committee Approval: The study was approved by the Bezmialem Vakıf University Ethics Committee (no: 2021-393, date: 08.02.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.İ.Y., A.T., Concept: A.İ.Y., A.T., Design: A.İ.Y., A.T., Data Collection or Processing: A.İ.Y., A.T., Analysis or Interpretation: A.İ.Y., A.T., Literature Search: A.İ.Y., A.T., Writing: A.İ.Y., A.T.

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