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Do Inflammatory Indices Predict Neoadjuvant Chemotherapy Response in Hormone Receptor-positive, HER2-negative Breast Cancer?

Enflamatuvar İndeksler Hormon Reseptörü Pozitif HER2-negatif Meme Kanserinde Neoadjuvan Kemoterapi Yanıtını Predikte Eder Mi?

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ABSTRACT

Aim: The aim of this study was to evaluate clinical, pathological, and inflammatory markers that can predict pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 (HER2) HER2- breast cancer.

Materials and Methods: A retrospective analysis was conducted on 109 patients aged 18-80 years with HR+/HER2- breast cancer who underwent NACT at University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital between January 1, 2020, and May 1, 2025. All patients received standard anthracycline-taxane-based chemotherapy. Pre-treatment blood tests were used to calculate the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). pCR was defined as the absence of residual invasive tumor in the breast and axillary lymph nodes. Factors affecting pCR were evaluated using logistic regression analysis.

Results: pCR was achieved in 21.1% of patients. Most of the pCR group was under 50 years of age and had the luminal B subtype. ROC analysis showed that NLR, PLR, and SII were not significant predictors of pCR ($p>0.05$). In univariate analysis, luminal B subtype, low estrogen receptor (ER) levels, high Ki-67, and high tumor grade were significantly associated with pCR. In multivariate analysis, only low ER levels and high Ki-67 remained independent predictors.

Conclusion: Inflammatory markers are insufficient to predict pCR in HR+/HER2- breast cancer. Low ER levels and high Ki-67 are associated with a better response to NACT. The findings highlight the importance of biomarkers in personalizing treatment response.

Keywords: Breast cancer, neoadjuvant chemotherapy, pathological complete response, inflammatory markers, Ki-67, estrogen receptor

ÖZ

Amaç: Bu çalışmanın amacı, hormon reseptörü pozitif (HR+)/insan epidermal büyüme faktörü reseptörü 2 (HER2) HER2- meme kanseri olan hastalarda neoadjuvan kemoterapi (NACT) sonrası patolojik tam yanıtı (pCR) öngörebilen klinik, patolojik ve enflamatuvar belirteçleri değerlendirmektir.

Gereç ve Yöntem: 1 Ocak 2020 ile 1 Mayıs 2025 tarihleri arasında Sağlık Bilimleri Üniversitesi, Balıkesir Atatürk Şehir Hastanesi'nde NACT uygulanan 18-80 yaş arası HR+/HER2- meme kanseri olan 109 hasta üzerinde retrospektif bir analiz yürütülmüştür. Tüm hastalar standart antrasiklin-taksan bazlı kemoterapi almıştır. Tedavi öncesi kan testleri kullanılarak nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve sistemik immün-enflamasyon indeksi (SII) hesaplanmıştır. pCR, meme ve aksiller lenf düğümlerinde rezidüel invaziv tümör bulunmaması olarak tanımlanmıştır. pCR'yi etkileyen faktörler lojistik regresyon analizi kullanılarak değerlendirilmiştir.

Bulgular: Hastaların %21,1'inde pCR elde edildi. pCR grubunun çoğu 50 yaşın altındaydı ve luminal B alt tipine sahipti. ROC analizi, NLR, PLR ve SII'nin pCR'nin anlamlı öngörücüleri olmadığını gösterdi ($p>0,05$). Tek değişkenli analizde, luminal B alt tipi, düşük östrojen reseptörü (ER) seviyeleri,

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yüksek Ki-67 ve yüksek tümör derecesi pCR ile anlamlı şekilde ilişkiliydi. Çok değişkenli analizde, yalnızca düşük ER seviyeleri ve yüksek Ki-67 bağımsız öngörücüler olarak kaldı.

Sonuç: Enflamatuvar belirteçler, HR+/HER2- meme kanserinde pCR'yi öngörmede yetersizdir. Düşük ER seviyeleri ve yüksek Ki-67, NACT daha iyi yanıtla ilişkilidir. Bulgular, tedavi yanıtının kişiselleştirilmesinde biyobelirteçlerin önemini vurgulamaktadır.

Anahtar Kelimeler: Meme kanseri, neoadjuvan kemoterapi, patolojik tam yanıt, enflamatuvar belirteçler, Ki-67, östrojen reseptörü

INTRODUCTION

Breast cancer (BC) is the most common type of cancer found in women[1]. More than 90% of BCs are confined to the locoregional area at the time of diagnosis, allowing for curative treatment[2]. One such approach, neoadjuvant therapy, involves administering systemic therapy before primary surgery and has made significant advances in recent years[3]. This strategy aims to reduce tumor size, enabling less invasive surgical procedures and improving patient outcomes[3]. Despite this, approximately 20% of patients experience recurrence after initial treatment[2]. Prediction of patients at risk of recurrence is primarily based on clinicopathological risk factors such as receptor status, tumor size, and nodal status[2]. Studies have shown that patients who achieve a pathological complete response (pCR) after neoadjuvant therapy have better long-term outcomes[4].

Breast tumors behave differently depending on the biological properties of their originating cells[5]. The most commonly used clinical markers for tumor biology classification are estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)[5]. The commonly accepted molecular subsets include luminal A [ER+/PR+/HER2-, low proliferation]; luminal B (ER+, low PR, HER2-, elevated proliferation); HER2+) (ER+ and ER- comprise unique HER2 subsets); and basal-like (commonly ER-/PR-/HER2-, triple-negative BC)[6]. In general, hormone receptor negative (HR-) (ER and PR negative) or HER2+ tumors are sensitive to chemotherapy and respond well to neoadjuvant chemotherapy (NACT)[4]. However, the indication for NACT in HR-positive (HR+)/HER2- tumors is controversial[7]. Although NACT is a treatment option for early-stage HR+/HER2- BC, pathological response rates are generally lower in this subtype[8]. pCR rates range from 0% to 18%, while breast-conserving surgery (BCS) can be achieved in up to 60% of tumors[7].

BC treatment is heterogeneous, and understanding who benefits most from specific treatments is vital[9]. Molecular methods such as prosigna gene testing on biopsy samples can influence neoadjuvant treatment decision-making in early-stage HR+/HER2- BC[10]. BC gene mutation status can help personalize treatment decisions[9]. Unfortunately, there are currently no completely reliable predictors[11]. The medical need for reliable biomarkers to predict response to NACT has not been met[12].

Persistent subclinical inflammation is closely associated with cancer development and progression, and neutrophils, platelets, and lymphocytes are key mediators of chronic inflammation[13]. Systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been identified as potential prognostic and predictive indicators in various malignancies, including BC[14]. Studies in the literature support the hypothesis that NLR, PLR, and SII may serve as predictive biomarkers for pCR in BC patients receiving NACT[15]. However, there are still inconsistent research results regarding the value of peripheral blood inflammatory markers in assessing the efficacy of neoadjuvant therapy in BC[16].

The aim of this retrospective study was to evaluate factors, including inflammatory markers, that may predict pCR after NACT in HR+/HER2- BC patients.

MATERIALS AND METHODS

Selection and Description of Cases

In our study, we retrospectively analyzed the data of HR+/HER2- BC patients aged 18-80 who underwent NACT at University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital between January 1, 2020, and May 1, 2025. Patients who received standard chemotherapy regimens (4 cycles of 600 mg/m^2 cyclophosphamide + 60 mg/m^2 doxorubicin every 2 weeks, followed by either 4 cycles of 175 mg/m^2 paclitaxel every 2 weeks or 12 cycles of 80 mg/m^2 paclitaxel weekly) were included in the study. Patients with clinical node positivity before treatment were included in the study. Patients with metastatic initial status, male gender, a second primary cancer other than BC, and those who received chemotherapy regimens other than those considered standard were excluded from the study. Patients with diseases that could affect blood results (rheumatological disease, chronic renal failure, liver cirrhosis, infection) and those taking medications (steroids, immunosuppressive therapy, chemotherapy) were excluded from the study.

The protocol for this retrospective study was approved Ethics Committee of University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital (decision number: 2025/07/67, date: 24.07.2025). Since this study was a retrospective archive search, informed consent was not obtained from the patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Technical Information

Immunohistochemistry (IHC) for ER, PR, and HER2, and double-probe fluorescence in situ hybridization (FISH) for HER2 were evaluated according to the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines using Food and Drug Administration-approved tests[17,18]. ER and PR positivity was defined as at least 1% nuclear staining in tumor cells[17,18]. HER2 IHC was scored as positive (3+), equivocal (2+ or 1+ to 2+), or negative (0 or 1+) according to the 2018 ASCO/CAP guidelines[17,19]. All HER2 IHC equivocal (2+ or 1+ to 2+) cases underwent reflex HER2 dual-probe FISH testing (HER2 IQFISH pharmDx; DAKO). A positive HER2 FISH result was defined as a HER2/CEP17 ratio ≥2.0 or a mean HER2 copy number ≥6.0 signals per cell[17,19] . In our study and the 2021 St. Gallen update, ER-positive cancers are sometimes classified as "luminal A-like" (lower grade, lower Ki-67, strong ER/PR expression) or "luminal B-like" (higher grade, higher Ki-67, lower ER/PR expression levels)[20].

pCR was defined as no residual invasive carcinoma (ypT0/is ypN0) in the breast and axillary lymph nodes after surgical resection[17]. Patients with tumor and nodal pathologic stages of all other stages, including T1mi and N1mi, were considered the non-pCR group. Microinvasive BC was defined as an invasive component not exceeding 1 mm, most often in the setting of ductal carcinoma in situ[21]. Foci measuring ≤2 mm in the lymph node were also considered micrometastases[22]. Clinical and pathological tumor staging was performed based on the 8th edition of the International Union on Cancer TNM classification.

In our study, NLR, PLR, and SII were calculated according to the following equations: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count[23]. Laboratory examinations, including routine blood tests, for which data were recorded, were selected from examinations performed within the last month before the start of NACT.

Neoadjuvant treatment decisions were made in accordance with international guidelines and based on tumor biology, clinical stage, and patient-specific characteristics. All cases were evaluated in a multidisciplinary tumor board including medical oncologists, breast surgeons, radiologists, and pathologists, and treatment plans were finalized by consensus. Clinical staging was performed using the 8th edition of the American Joint Committee on Cancer staging system[24]. Diagnostic evaluation included physical examination, breast and axillary ultrasonography, and mammography, with breast MRI performed when indicated. To exclude distant metastasis, additional imaging such as chest computed tomography (CT), abdominal ultrasonography/CT, and bone scintigraphy or positron emission tomography-CT was used according to guideline-based indications.

Statistical Analysis

Statistical analyses and data processing were performed using the SPSS Statistics software, version 24 (SPSS Inc., Chicago, IL) and the R programming language (R Core Team, 2024). The ideal cutoff value for the logarithmic formula in distinguishing pCR from non-pCR, as well as specificity and sensitivity values, were determined using ROC analysis. Factors predicting pCR were calculated using univariate and multivariate analyses and binary logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported, and a p value of <0.05 was considered statistically significant.

RESULTS

A total of 109 patients were included in the study. pCR was achieved in 23 patients (21.1%). Among patients who achieved pCR, 14 patients (60.9%) were under 50 years of age. The majority of this group had the luminal B subtype (20 patients, 87.0%). The Ki-67 proliferation index was above 20% in 20 patients (87.0%), and 9 patients (39.1%) had grade 3 tumors. Histologically, ductal type carcinoma was observed in 21 patients (91.3%). PR levels were low (<20%) in 8 patients (34.8%) (Table 1).

ROC curve analysis was conducted to evaluate the performance of inflammatory markers (NLR, PLR, and SII) in predicting pCR. The area under the curve for PLR was 0.451 (95% CI: 0.310-0.591; p=0.469), for NLR 0.595 (95% CI: 0.465-0.726; p=0.162), and for SII 0.583 (95% CI: 0.460-0.706; p=0.223). These results indicated that NLR, PLR, and SII do not exhibit adequate diagnostic value for predicting pCR; therefore, an optimal cut-off value could not be established (Table 2, Figure 1).

Logistic regression analysis was performed to identify predictors of pCR in HR+/HER2- BC. In univariate analysis, the luminal B subtype demonstrated approximately a five-fold higher odds of achieving pCR compared with luminal A (OR: 5.03; 95% CI: 1.39-18.22; p=0.014). A significant negative association was found between ER level and pCR, indicating that higher ER levels reduced the likelihood of achieving pCR (OR: 0.97; 95% CI: 0.96-0.99; p=0.004). Additionally, patients with a high Ki-67 index had significantly increased odds of achieving pCR (OR: 1.05; 95% CI: 1.01-1.09; p=0.009). Higher tumor grade also increased the likelihood of pCR (OR: 3.04; 95% CI: 1.11-8.32; p=0.030) (Table 3).

In multivariate analysis, only ER level (OR: 0.97; 95% CI: 0.96-0.99; p=0.009) and Ki-67 (OR: 1.05; 95% CI: 1.01-1.09; p=0.024) remained independent predictors of pCR. Molecular subtype, tumor grade, histological type, menopausal status, body mass index, inflammatory indices (NLR, PLR, SII), and clinical T stage were not significant in the multivariate model (Table 3). As all VIF values were <5, no multicollinearity was detected in the regression model (Table 3).

Table 1. Clinical and pathological characteristics of patients who achieved and did not achieve a complete pathological response after neoadjuvant chemotherapy

	Number of patients (n=109)	%	Non-PCR (n=86)	Non-PCR %	PCR (n=23)	PCR %
Age						
<50	47	43.1	33	38.4	14	60.9
≥50	62	56.9	53	61.6	9	39.1
Molecular subtype						
Luminal A	40	36.6	37	43.0	3	13.0
Luminal B*	69	63.3	49	57.0	20	87.0
Histology						
Ductal	89	81.7	68	79.1	21	91.3
Others	20	18.3	18	20.9	2	8.7
PR						
<20	32	29.4	24	27.9	8	34.8
≥20	77	70.6	62	72.1	15	65.2
Ki-67						
<20	40	36.6	37	43.0	3	13.0
≥20	69	63.3	49	57.0	20	87.0
Grade						
Grade 1-2	85	78.0	71	82.6	14	60.9
Grade 3	24	22.0	15	17.4	9	39.1
Clinical T stage						
T1	30	27.5	24	27.9	6	26.1
T2-T3	79	72.5	62	72.1	17	73.9
Menopause status						
Pre-peri menopausal	41	37.6	30	34.9	11	47.8
Postmenopausal	68	62.4	56	65.1	12	52.2
BMI						
<25	41	37.6	38	44.2	13	56.5
≥25	68	62.4	48	55.8	10	43.5
NLR (median)						
<3.3	53	48.6	45	52.3	8	34.8
≥3.3	56	51.4	41	47.7	15	65.2
PLR (median)						
<374	54	49.5	40	46.5	14	60.9
≥374	55	50.5	46	53.5	9	39.1
SII (median)						
<936	54	49.5	44	51.2	10	43.5
≥936	55	50.5	42	48.8	13	56.5

*:Ki-67 was determined as 20% for luminal A-B distinction. Cut-offs derived from literature, not ROC in this cohort

PCR: Pathological complete response, PR: Progesterone receptor, BMI: Body mass index NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

Table 2. ROC-curve analysis to determine cut-off for factors predicting pathological complete response

Test result variable (s)	Area under the curve	Area under the curve at 95% confidence interval		
		Lower limit	Upper limit	p
PLR	0.451	0.310	0.591	0.469
NLR	0.595	0.465	0.726	0.162
SII	0.583	0.460	0.706	0.223

ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

Table 3. Univariate and multivariate logistic regression analysis of clinical and pathological predictors of pathological complete response after neoadjuvant chemotherapy in HR-positive/HER2-negative breast cancer patients

Variable	Category	Univariate analysis		Multivariate analysis		
		OR (95% CI)	p	OR (95% CI)	p	VIF
Age	<50/≥50	0.40 (0.16-1.03)	0.057	-		
Molecular subtype	Luminal A/luminal B	5.03 (1.39-18.22)	**0.014**	2.37 (0.48-11.80)	0.293	1.058
Histology	Ductal/others	0.36 (0.08-1.68)	0.193			
ER (%)	Continuous	0.97 (0.96-0.99)	**0.004**	0.97 (0.96-0.99)	**0.009**	**1.051**
PR (%)	Continuous	1.00 (0.98-1.01)	0.606	-		
Ki-67 (%)	Continuous	1.05 (1.01-1.09)	**0.009**	1.05 (1.01-1.09)	**0.024**	**1.106**
Grade	1-2/3	3.04 (1.11-8.32)	**0.030**	1.66 (0.54-5.16)	0.378	1.069
Clinical T stage	T1-2 /T3	1.10 (0.39-3.11)	0.862	-		
Menopause status	Pre/peri/post	0.61 (0.24-1.54)	0.295	-		
BMI	<25/≥25	0.58 (0.23-1.48)	0.258	-		
NLR	Continuous	1.00 (0.91-1.09)	0.959	-		

HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, OR: Odds ratio, CI: Confidence interval, ER: Estrogen receptor, PR: Progesterone receptor, BMI: Body mass index, NLR: Neutrophil-to-lymphocyte ratio,

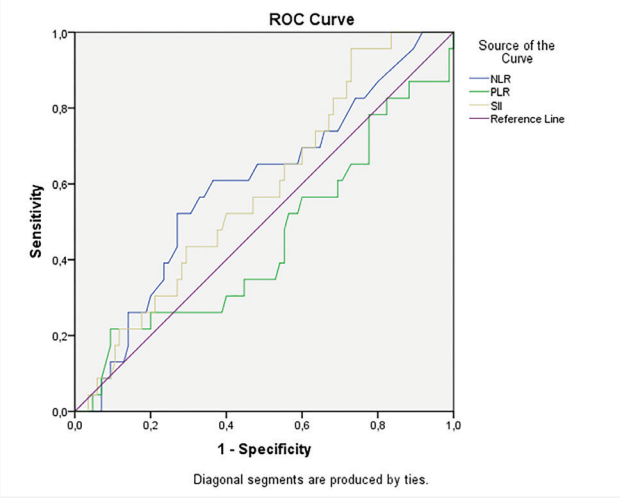

Figure 1. ROC-curve analysis for cutoff predicting complete response for NLR, PLR, and SII

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic inflammation index

DISCUSSION

This study investigated the factors predicting pCR after NACT in patients with HR+ BC. Univariate analysis revealed increased pCR in patients with luminal B, low ER, high Ki-67, and high-grade tumors. Multivariate analysis identified ER level and Ki-67 as independent predictors of pCR. NLR, PLR, and SII were found to have insufficient diagnostic value in predicting pCR.

pCR rates after NACT are lower in HR+/HER2- BC compared to other subtypes (7-16% in HR+/HER2- BC; 26-43% in HR+/HER2+ BC; 39-55% in triple-negative BC; and 46-90.5% in HER2+ BC)[25].

The 21.1% pCR achieved in our study may be attributable to the selection of patients who were relatively more suitable for NACT, with 63.3% having luminal B disease, 77.1% having Ki-67 ≥14, and 72.5% having cT2-cT3. The importance of pCR lies in the fact that large clinical trials of NACT have demonstrated improved disease-free survival (DFS) and overall survival (OS) rates in patients with pCR compared to those with residual disease[26]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18, patients achieving pCR had a DFS and OS of 75% and 85%, respectively, at a median follow-up of 9 years, compared to 58% and 73% in patients with residual disease[26].

It has been reported that luminal tumors with high Ki-67 expression respond well to chemotherapy, likely reflecting their high proliferative activity[27]. In a study by Aktas et al.[28] the Ki-67 level was identified as a guide for personalized treatment. Our study results are consistent with the literature in this regard. However, it should be noted that the European Society for Medical Oncology states that there is no consensus on a definitive cut-off value for Ki-67, but that values less than 10% are considered low and values greater than 30% are considered high[29]. Although stage, menopausal status, age, Ki-67, grade, HER2 expression, HR status, and even multiple gene expression analyses are used to assess whether neoadjuvant therapies will benefit a patient, identifying patients who will respond to NACT remains a challenging decision[30].

The recommendation that NACT can be used instead of adjuvant chemotherapy in HR+/HER2- BC is based on data from the NSABP B-18 study, which showed no difference in DFS or OS between adjuvant and neoadjuvant treatment in patients with stage II-III BC[31]. Factors guiding the decision-making process for adjuvant systemic therapy (e.g., lymph node status, tumor

grade, and comorbidities) can also be used to select patients with HR+/HER2- BC for whom NACT is appropriate, although it should be recognized that some factors, such as lymph node status, may be better assessed following definitive surgery[31]. The benefit of NACT in luminal subtype BC include performing BCS; however, whether neoadjuvant therapy improves prognosis in luminal subtype BC is controversial[32].

Yang et al.[13] reported that pretreatment NLR, PLR, and SII predicted pCR in BC patients undergoing NACT. Cullinane et al.[33] reported in their meta-analysis that NLR was a predictor of pCR in BC patients. A study by Kaytaz Tekyol et al.[34] demonstrated that low PLR levels were associated with higher chemotherapy sensitivity in NACT-treated BC, independent of molecular subtypes, but no association was found between NLR levels and pCR. A study by Eryilmaz et al.[35] also found no association between pCR and pretreatment NLR values. In the study by Hu et al.[36] lower pretreatment PLR was associated with higher pCR rates after NACT, but no such association was demonstrated with NLR. In the study by Wang et al.[37] higher pretreatment NLR and PLR were associated with a higher probability of achieving pCR, but pretreatment SII was not associated with a higher pCR.

In our study, no association was found between NLR, PLR, and SII and pCR. In the literature, different studies use different cutoff values for inflammatory markers, and the lack of a standard cutoff value may explain the discrepancies in the results of the studies[34]. Furthermore, many studies evaluated BC patients of all molecular subtypes together. Our study evaluated only HR+/HER2- patients to obtain more reliable results.

Study Limitations

Limitations of the study include the small number of patients conducted at a single center and its retrospective design. In addition, due to its retrospective design, it is possible that some conditions such as diseases and medication use that could affect blood values could not be evaluated due to incomplete records and could affect the results.

CONCLUSION

Predicting patients who will respond well to NACT in BC treatment is important. Inflammatory indices are inexpensive, reproducible, and easily accessible parameters that can be calculated with routine blood count analysis. However, given the conflicting results in the literature, negative studies including ours, and the multitude of factors that can influence blood parameters, their suitability for routine use in predicting chemotherapy response is questionable. Prospective clinical studies of sufficient size are needed to determine whether inflammatory indices can be a significant prognostic indicator of pCR.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee of University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital (decision number: 2025/07/67, date: 24.07.2025).

Informed Consent: This study is a retrospective cross-sectional analysis of medical records of patients experiencing neoadjuvant chemotherapy at University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital from January 2020 to May 2025.

Footnotes

Authorship Contributions

Concept: S.S., Design: S.S, Data Collection or Processing: S.S., Y.İ., Analysis or Interpretation: S.S., Z.E., Literature Search: S.S., Writing: S.S., Y.İ.

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