의학 석사 학위 논문

원격 전이를 동반한 유방암 환자에서 항암 치료 시작 후 호중구-림프구 비율 변화의 예후 인자로서의 가치

The prognostic value of Neutrophil-Lymphocyte ratio(NLR) change after initiation of chemotherapy in *de novo* stage IV breast cancer patients

울산대학교 대학원

의학과

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지도교수 안세현

이 논문을 의학 석사 학위 논문으로 제출함

2019년 8월

울산대학교 대학원

의학과

신해나

신해나의 의학 석사 학위 논문을 인준함

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Background

The *de novo* stage IV breast cancer has poor prognosis, predicting response to treatment in the affected patients is difficult. We investigated whether the initial neutrophil to lymphocyte ratio (NLR) at diagnosis and NLR change after the first palliative chemotherapy cycle can be a prognostic indicators.

Methods

We retrospectively reviewed 218 *de novo* stage IV breast cancer patients with available NLR values who underwent palliative chemotherapy as an initial treatment. We analyzed cancer specific survival (CSS) according to initial NLR (iNLR), NLR change after the first chemotherapy cycle (ΔNLR), and a combination of these two.

Results

The mean patient age was 47.2 years; the median follow-up period was 29.8 months. The mean iNLR and ΔNLR values were 2.83 ± 2.19 and 0.39 ± 3.74, retrospectively, amd were used as cut off points. There was no significant difference between low and high iNLR groups ($p = 0.431$); however, there was a significant correlation between ΔNLR and CSS ($p = 0.031$). The 1-, 3-, and 5- year CSS rates of patients in the increased ΔNLR group were significantly lower than those of patients in the stationary or decreased group. (78.4%, 35.4%, 20.8% vs 88.9%, 52.6%, 27.1%; $p = 0.031$). Multivariate analysis suggested that ΔNLR was an independent prognostic factor (hazard ratio (HR) = 1.748, 95% confidence interval (CI) = 1.084 - 2.818). The analysis of the combination of iNLR and ΔNLR showed that patients in the high iNLR and increased ΔNLR group had poorer

prognosis than those in the low iNLR and stationary or decreased ΔNLR group (HR = 4.294, 95% CI = 1.586 - 11.629).

Conclusion

Initial NLR alone was not a prognostic indicator among *de novo* stage IV breast cancer patients. However, patients with increased NLR after palliative chemotherapy exhibited worse CSS. Patients with high initial NLR and increased NLR after treatment might be a non responder to treatment.

Introduction

Screening has facilitated early diagnosis of breast cancer; however, the prevalence of *de novo* stage IV breast cancer is still 10%–25% in Asia and 3%–5% in Europe and United States [1,2]. The prognosis of such patients remains poor, with an average survival time no longer than 3 years [3]. Prognosis may be predicted based on factors such as age, metastatic site, tumor grade, and receptor status. However, the behavior of breast cancer is unpredictable, with markedly different clinical outcomes seen even among patients with similar classical prognostic factors [4,5]. Therefore, appropriate prognostic indicators that can facilitate treatment decisions are urgently needed.

Neutrophil-to-lymphocyte ratio (NLR) can be easily obtained from routine blood cell counts and is a good indicator that reflects the condition of a tumor-bearing host [6]. Neutrophils, reflecting an inflammatory response, play key roles in tumor growth, progression, invasion, and metastasis [7,8]. Lymphocytes, exerting immune response, have the potential for specific destruction of tumors without exerting toxicity on normal tissue and for possessing long-term memory that can prevent recurrence [9]. Thus, NLR may vary depending on the changes in inflammatory and immune states. The prognostic value of NLR in breast cancer patients has been examined through meta-analyses, which have indicated that patients with a high NLR have a short disease-free survival (DFS) [hazard ratio 1.46, 95% confidence interval (CI) 1.12–1.90, p = 0.044] and overall survival (OS) (hazard ratio 2.03, 95% CI 1.41–2.93, p = 0.001) [10]. Josee-Lyne et al. have shown that NLR greater than the cut-off value is associated with worse OR (hazard ratio 2.56, 95% CI 1.96–3.35, p < 0.001) and DFS (hazard ratio 1.74, 95% CI 1.47–2.07; p < 0.001) [11]. However, most studies have included stage I–III breast cancer patients and evaluated only baseline NLR mostly before treatment for prognostic impact.

In the present study, we aimed to investigate whether the initial NLR at the time of diagnosis and NLR change after the first palliative chemotherapy cycle can be prognostic indicators in *de novo* stage IV breast cancers.

Materials and Methods

Patients

Patients were recruited from the Department of Breast Cancer of the Asan Medical Center, Seoul, Korea. Between January 1997 and December 2012, 297 patients without previous primary breast cancer were diagnosed with breast cancer with distant metastasis confirmed by imaging and/or pathological findings. Of them, 238 patients received palliative chemotherapy as initial treatment; after excluding 20 patients without complete blood count at initial and/or after treatment time-point, 218 patients were analyzed in this study. Patients differed in age, histologic grade (HG), hormone (estrogen/progesterone) receptor (ER/PR)/human epidermal growth factor receptor 2 (HER2) status, subtype, and the number of metastatic sites. Clinicopathological information is described in Table 1.

Definition of NLR: initial NLR and NLR change

NLR was calculated from the differential leukocyte counts as a ratio of the percentage of neutrophils to that of the lymphocytes. The initial NLR (iNLR) was evaluated at the time of diagnosis before the initiation of palliative chemotherapy and was categorized based on the mean iNLR value (2.83)—low iNLR for values <mean value and high iNLR for values >mean value.

Follow-up NLR (fNLR) was calculated prior to the administration of the second chemotherapy cycle (~3–4 weeks after the first cycle). NLR change (ΔNLR) was the calculated difference between fNLR and iNLR (fNLR minus iNLR); if ΔNLR was above the mean value (0.39), NLR was considered to have increased, otherwise it was defined as stationary or decreased. By combining both iNLR and ΔNLR, patients were further categorized into four groups: A (low and stationary or decreased), B (high and stationary or decreased), C (low and increased), and D (high and increased).

Statistical analysis

Categorical data were compared using chi-square test, and continuous variables were compared using paired t-test. The 1-, 3-, and 5 year cancer-specific survival (CSS) and median survival were analyzed using Kaplan–Meier method, and the differences were analyzed using log-rank test. Multivariate Cox proportional hazards regression analysis was used to evaluate the prognostic factors. P value < 0.05 was considered statistically significant.

Results

The mean patient age was 47.2 years, and 11.0% of all patients (24/218) had a single metastatic site. The mean follow-up period was 29.8 (range, 1.5–176.4) months, during which 78.4% (171/218) deaths occurred. The mean iNLR and fNLR values were 2.83 ± 2.19 and 3.21 ± 4.18; there was no significant difference between these (p = 0.130). The mean ΔNLR value after systemic therapy was 0.39 ± 3.74.

Prognostic impact of initial NLR

Patients were divided into two groups on the basis of the mean iNLR value: the low iNLR group (iNLR < 2.83, n = 143) and the high iNLR group (iNLR ≥ 2.83, n = 75). Patients' characteristics according to iNLR are described in Table 1. There was no significant difference in age, HG, ER/PR/HER2 status, subtype, the number of metastatic sites, and endocrine therapy between the two groups.

The 1-, 3-, and 5- year CSS rates were 88.8%, 47.3%, and 26.9% in the high iNLR group and 78.7%, 45.3%, and 21.3% in the low group. There was no difference in survival rates between the two groups (p = 0.431) (Figure 1).

Table 1. Clinicopathological characteristics of *de novo* stage IV breast cancer patients according to iNLR

Variables		iNLR < 2.83 (n = 143)	iNLR ≥ 2.83 (n = 75)	P value
Age (mean ± SD)		47.3 ± 11.3	47.1 ± 9.3	0.855
HG	G2	58 (63.7%)	22 (56.4%)	0.431
	G3	33 (36.3%)	17 (43.6%)	
	unknown	52	36	
ER	(–)	61 (45.5%)	36 (50.7%)	0.480
	(+)	73 (54.5%)	35 (49.3%)	
	unknown	9	4	
PR	(–)	86 (64.2%)	44 (62.9%)	0.852
	(+)	48 (35.8%)	26 (37.1%)	
	Unknown	9	5	
HER2 (IHC)	0, 1+, 2+	73 (62.4%)	34 (64.2%)	0.826
	3+	44 (37.6%)	19 (35.8%)	
	unknown	26	22	
Subtype	HR+HER–	52 (44.4%)	21 (39.6%)	0.610
	HR+HER+	20 (17.1%)	11 (20.8%)	
	HR–HER–	21 (17.9%)	13 (24.5%)	
	HR–HER+	24 (20.5%)	8 (15.1%)	
	unknown	26	22	
Number of metastatic sites	Single	18 (12.6%)	6 (8.0%)	0.304
	Multiple	125 (87.4%)	69 (92.0%)	
Endocrine therapy	Yes	72 (50.3%)	33 (44.0%)	0.373
	No	71 (49.7%)	42 (56.0%)	

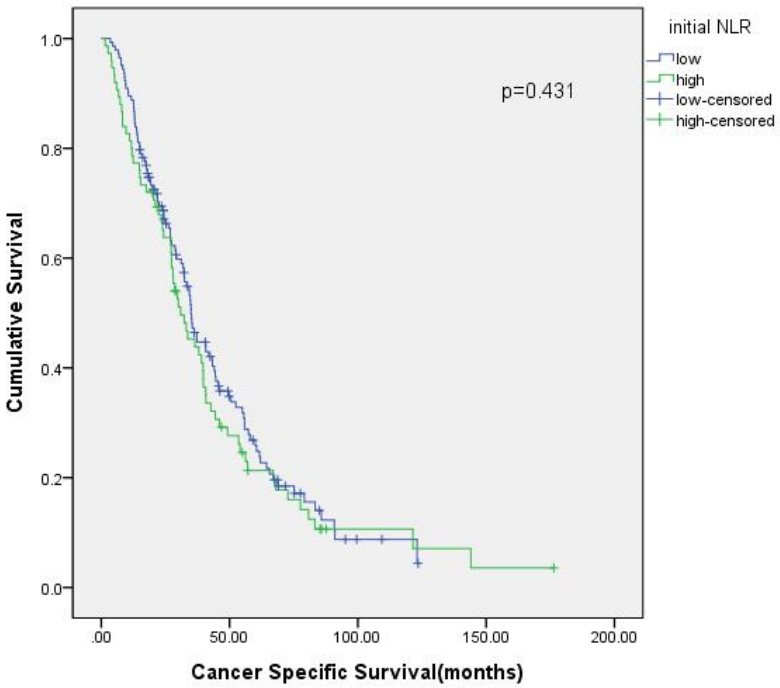


Figure 1. Cancer-specific survival curves in *de novo* stage IV breast cancer patients according to iNLR (initial neutrophil-to-lymphocyte ratio) showed no significant difference between the low and high iNLR groups (p = 0.431).

Prognostic impact of ΔNLR

Patients were divided into two groups on the basis of the mean ΔNLR value: the increased ΔNLR group (ΔNLR ≥ 0.39, n = 74) and the stationary or decreased ΔNLR group (ΔNLR < 0.39, n = 144). Patients' characteristics according to ΔNLR are described in Table 2. There was no significant difference between the two groups, except in the number of metastatic sites (p = 0.027). In the increased ΔNLR group, there were 13 (17.6%) patients with a single and 61 (82.4%) with multiple metastatic sites. In the stationary or decreased ΔNLR group, there were 11 (7.6%) patients with a single and 133 (92.4%) with multiple metastatic sites.

The 1-, 3-, and 5- year CSS rates were 78.4%, 35.4%, and 20.8% for patients in the increased ΔNLR group and 88.9%, 52.6%, and 27.1% for those in the stationary or decreased ΔNLR group, respectively. Survival rates plotted by Kaplan–Meier curve between the two groups were significantly different (p = 0.031) (Figure 2).

Table 2. Clinicopathological characteristics of *de novo* stage IV breast cancer patients according to ΔNLR

Variables		Increased ΔNLR ≥ 0.39 (n = 74)	Stationary or decreased ΔNLR < 0.39 (n = 144)	P value
Age (mean ± SD)		47.7 ± 10.7	47.0 ± 10.7	0.665
HG	G2	23 (52.3%)	57 (66.3%)	0.120
	G3	21 (47.7%)	29 (33.7%)	
	Unknown	30	58	
ER	(−)	36 (51.4%)	61 (45.2%)	0.396
	(+)	34 (48.6%)	74 (54.8%)	
	Unknown	4	9	
PR	(−)	49 (70.0%)	81 (60.4%)	0.178
	(+)	21 (30.0%)	53 (39.6%)	
	Unknown	4	10	
HER2 (IHC)	0, 1+, 2+	38 (61.3%)	69 (63.9%)	0.736
	3+	24 (38.7%)	39 (36.1%)	
	Unknown	12	36	
Subtype	HR+HER−	23 (37.1%)	50 (46.3%)	0.633
	HR+HER+	12 (19.4%)	19 (17.6%)	
	HR−HER−	15 (24.2%)	19 (17.6%)	
	HR−HER+	12 (19.4%)	20 (18.5%)	
	Unknown	12	36	
Number of metastatic sites	Single	13 (17.6%)	11 (7.6%)	0.027
	Multiple	61 (82.4%)	133 (92.4%)	
Endocrine therapy	Yes	35 (47.3%)	70 (48.6%)	0.854
	No	39 (52.7%)	74	

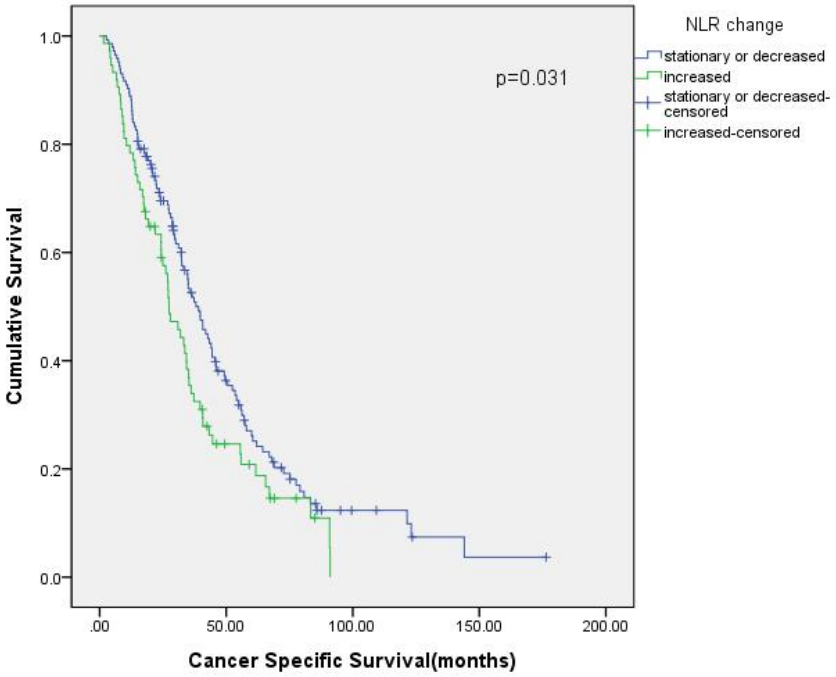


Figure 2. Cancer-specific survival curves in *de novo* stage IV breast cancer patients according to ΔNLR (change in neutrophil-to-lymphocyte ratio). There was a significant difference between the stationary or decreased group and the increased NLR group (p = 0.031).

Among other variables, age (p = 0.023), HG (p = 0.024), ER (p < 0.001), PR (p < 0.001), and the number of metastatic sites (p = 0.046) were significantly related to CSS (p < 0.05) (Table 3).

Multivariate analysis was performed using Cox regression analysis, which showed that factors associated with worse outcome were having multiple metastatic sites (hazard ratio 3.433, 95% CI 1.416–8.324), negative progesterone receptor (hazard ratio 2.050, 95% CI 1.172–3.585), and increased ΔNLR (hazard ratio 1.748, 95% CI 1.084–2.818) (Table 3).

Table 3. Uni- and multivariate analyses showing associations between clinicopathological characteristics and survival in *de novo* stage IV breast cancer patients

Variables		Univariate P	Multivariate hazard ratio	95.0% CI	P
Age (years)	<35 (ref)	0.023			
	35–50		0.836	0.358–1.952	0.679
	>50		1.346	0.560–3.237	0.506
Number of metastatic sites	Single (ref)	0.046			
	Multiple		3.433	1.416–8.324	0.006
HG	G2 (ref)	0.024			
	G3		1.562	0.983–2.484	0.059
ER	(+) (ref)	<0.001			
	(–)		1.659	0.963–2.858	0.059
PR	(+) (ref)	<0.001			
	(–)		2.050	1.172–3.585	0.012
ΔNLR	<0.39 (ref)	0.031			
	≥0.39		1.748	1.084–2.818	0.022

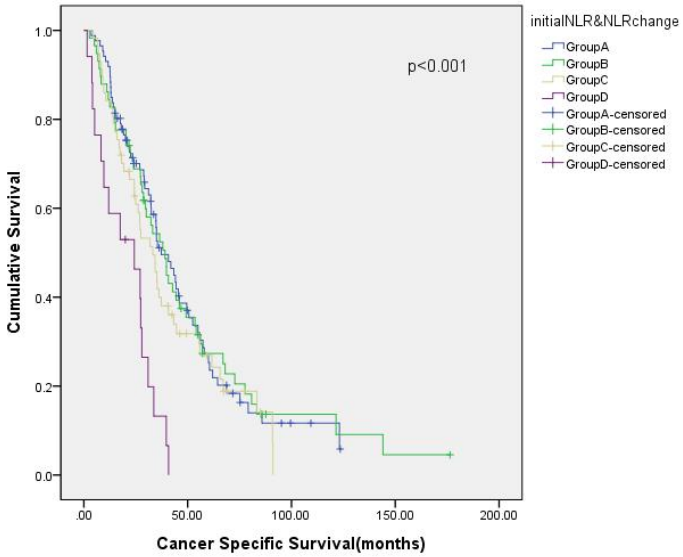
Prognostic impact of combining both initial NLR and ΔNLR

Combining both iNLR and ΔNLR led to four groups: A, B, C and D, wherein the median patient survival in each group was 37.3, 39.0, 33.2, and 24.2 months, respectively, and was significantly different among the groups ($p < 0.001$) (Table 4, Figure 3). Multivariate analyses adjusted for age, number of metastatic sites, HG, ER, and PR showed that patients in group D (high iNLR and increased ΔNLR; hazard ratio 4.294, 95% CI 1.586–11.629) exhibited poorer prognosis than those in group A.

Table 4. Multivariate analysis for the association among four groups (combining iNLR and ΔNLR) and survival in *de novo* stage IV breast cancer patients

Group (n)		Median survival (months)	Hazard ratio	95% CI	P
A (86)	iNLR < 2.83 & ΔNLR < 0.39	37.3			
B (58)	iNLR ≥ 2.83 & ΔNLR < 0.39	39.0	0.874	0.480–1.592	0.660
C (57)	iNLR<2.83 & ΔNLR ≥ 0.39	33.2	1.495	0.859–2.600	0.155
D (17)	iNLR ≥ 2.83 & ΔNLR ≥ 0.39	24.2	4.294	1.586–11.629	0.004

A.



B.

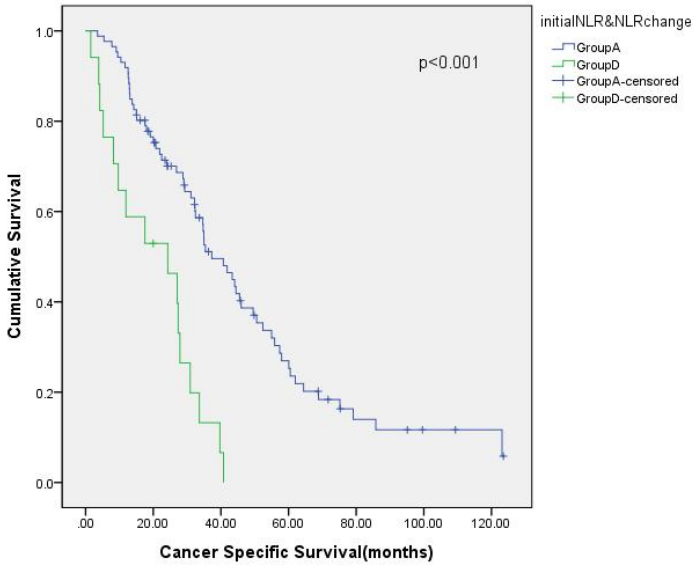


Figure 3. Cancer-specific survival curves in *de novo* stage IV breast cancer patients according to four risk groups (combining iNLR and ΔNLR) (A) all groups (B) group A versus group D. There was a significant difference among the four risk groups according to the combination of iNLR and ΔNLR ($p < 0.001$).

Discussion

The results of our study showed no significant difference in iNLR among the analyzed groups of patients with *de novo* stage IV breast cancer. Conversely, ΔNLR of patients receiving palliative chemotherapy appeared to have significant clinical value. Group D with high iNLR and increased ΔNLR had a significantly higher risk than group A with low iNLR and stationary or decreased ΔNLR ($p = 0.004$), which is indicative of patients' potential resistance to treatment and prediction of poor survival. Our results are inconsistent with those of previous meta-analyses showing a correlation between high baseline NLR and poor survival in patients with breast cancer [10,11]. These meta-analyses suffered from significant heterogeneity due to variations in region, race, stage composition, and cut-off point of baseline NLR. Furthermore, only few patients with *de novo* distant metastasis were included in these studies.

Several studies have been conducted to determine the correlation between NLR and cancer stage [12,13]. Elyasinia et al. [12] have suggested a significant correlation between NLR and the N stage in breast cancer patients ($p = 0.001$). A study has reported that patients in the highest NLR quartile (NLR > 75th percentile) have more advanced American Joint Committee on Cancer stages than those in the lowest NLR quartile (NLR <25th percentile) ($p = 0.001$) [13]. Similarly, in our preliminary study, the mean NLR values and cancer stage were found to be positively correlated; however, in patients with *de novo* stage IV breast cancer who are expected to have a high mean NLR, a single time-point NLR may not be a significant predictor of prognosis.

We also found that increased NLR after the initiation of palliative chemotherapy predicted worse CSS in patients with *de novo* stage IV breast cancer. To the best of our knowledge, this is the first study to evaluate ΔNLR after systemic treatment in breast cancer patients, although this prediction tool has been used to analyze the prognosis of other malignancies [14-19]. For example, increased NLR has helped predict worse overall and recurrence-free survivals in patients with small hepatocellular carcinoma who underwent curative resection (OS

hazard ratio 2.637 95% CI 1.356–5.128; recurrence-free survival hazard ratio 2.372 95% CI 1.563–3.601) [14]; increased NLR after two chemotherapy cycles has been reported to be associated with higher risk in patients with advanced pancreatic cancer (hazard ratio 1.894 95% CI 1.160–3.091) [17]; relative NLR change by ≥25% from baseline to 6 weeks after immune checkpoint blockade therapy (anti-programmed cell death protein (PD)1/PD-L1 therapy) has been used as a prognostic factor for objective response rate, progression-free survival and OS in patients with metastatic renal cell carcinoma [19].

Changes in NLR with systemic therapy may result from therapy-associated changes in tumor burden through interactions between the pro-tumor environment and anti-tumor immune response. A decreased tumor burden resulting from a response to therapy may improve tumor-associated systemic inflammation, thereby reducing NLR. Conversely, an increased tumor burden from a lack of response to therapy could perpetuate the recruitment of cells with pro-oncogenic functions, thereby resulting in a high NLR.

Tumor-associated neutrophils promote extracellular matrix remodeling through enzymatic action, resulting in the release of basic fibroblast growth factor, migration of endothelial cells, and dissociation of tumor cells. In addition, neutrophil-derived reactive oxygen species further reduce the adhesion-promoting properties of the extracellular matrix and inhibit tumor cell apoptosis through nuclear factor-kB activation, all of which increase angiogenesis, tumor growth, and progression to a metastatic phenotype [20]. Neutrophil-derived oncostatin M has been shown to increase vascular endothelial growth factor in human breast cancer cells, thereby increasing breast cancer cell detachment and invasiveness [21].

Cytotoxic T lymphocytes (CTLs) are known to induce cancer cell apoptosis through two pathways: (1) interaction between CD95L molecule (Fas ligand) on the CTL and CD95 (Fas) molecule on target tumor cells and (2) action of perforin and serine proteases present in the lymphocyte-specific granules [22]. While lymphopenia has been associated with negative outcomes in pancreatic cancer

patients [23], tumor-infiltrating lymphocytes have been shown to inhibit tumor growth, reduce tumor recurrence, and improve prognosis in some cancers including melanoma, colorectal cancers, and ovarian cancers [24-27].

This study has some limitations. First, this was a single-center retrospective study with a small sample size, which restricts the generalizability of the results. Second, we could not analyze chemotherapy regimens and several confounding variables, including smoking [28] and co-morbidities (cardiovascular disease, inflammatory disease, hematological disease, etc.[29-31]), which may affect NLR. To generalize the ΔNLR value as a prognostic predictor, additional studies with large sample sizes, standardized treatment, and laboratory follow-up should be conducted.

Conclusions

High initial NLR was not a poor prognostic marker among *de novo* stage IV breast cancer patients. However, patients with increased NLR after palliative chemotherapy exhibited worse CSS. Taken together, ΔNLR may be an index of response to systemic treatment.

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원격 전이를 동반한 유방암 환자에서 항암 치료 시작 후 호중구-림프구 비율 (NLR) 변화의 예후 인자로서의 가치

연구 배경

4기 유방암 환자의 예후는 불량하며, 치료에 대한 반응 예측이 어렵다. 그래서 우리는 고식적 항암 화학 요법 전후에 호중구-림프구 비율(NLR)의 변화가 예후 인자로서의 가치가 있는지 조사하였다.

연구 방법

우리는 4기 유방암 환자 중 초기 치료로 고식적 항암 화학 요법을 시행 받고, NLR 값을 모을 수 있는 환자 218명을 대상으로 연구 진행하였다. NLR 값은 진단시와, 첫번째 항암 화학 요법 후의 값을 추출하였고, 암 특이 생존과의 연관성을 분석하였다.

연구 결과

대상 환자의 평균 연령은 47.2세이며, 추적 기관의 중앙값은 29.8개월이었다. 평균 초기 NLR과 NLR 변화값은 각각 2.83±2.19, 0.39±3.74로, 우리는 이 값을 기준값으로 정하였다. 유의한 차이를 보이지 않은 초기 NLR군별 분석 ($p = 0.431$)과 달리, NLR 변화에 따른 암 특이 생존률에는 통계적으로 유의한 차이가 나타났다 ($p = 0.031$). 치료 후 NLR 값이 증가한 군의 1, 3, 5년 암 특이 생존률은 78.4%, 35.4%, 20.8% 였고, 변화없거나 감소한 군에서의 생존률은 88.9%, 52.6%, 27.1% 였다. 다변량 분석에서 NLR 변화는 독립적인 예후 인자로 나타났다. (위험도 = 1.748, 95% 신뢰 구간 = 1.084 – 2.818) 초기 NLR과 NLR 변화의 조합을 분석한 결과, 높은 초기 NLR에서 치료 후 증가한 환자는 낮은 초기 NLR에서 감소하거나 변화 없는 환자보다 불량한 예후를 보였다. (위험도 = 4.294, 95% 신뢰 구간 = 1.586 – 11.629)

연구 결론

초기 NLR 단독은 4기 유방암 환자의 예후 인자가 아니었다. 고식적 항암 화학 요법 후 NLR이 증가한 환자는 더 불량한 예후를 보였다. 초기 NLR 값이 높고 치료 시작 후에도 증가한 NLR 값을 보인 환자는 치료에 불응하는 환자일 수 있을 것이다.

Key words: Breast neoplasm, Neutrophils, Lymphocytes, Prognosis