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Prognostic Nutritional Index Is Superior to Neutrophil-to-lymphocyte Ratio as a Prognostic Marker in Metastatic Breast Cancer Patients Treated With Eribulin

TAKAAKI OBA, KAZUMA MAENO, MAYU ONO, TOKIKO ITO, TOSHIHARU KANAI and KEN-ICHI ITO

Division of Breast and Endocrine Surgery, Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Abstract. *Background/Aim: The prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR) are prognostic markers for operable breast cancer. However, their importance in patients with metastatic breast cancer (MBC) remains unclear. This study aimed to evaluate these parameters as prognostic markers in MBC patients treated with eribulin. Patients and Methods: A total of 60 patients with MBC treated with eribulin were included. Results: Although high PNI and low NLR were correlated with better progression-free survival (PFS) and overall survival (OS), PNI had stronger impact as prognostic marker than NLR (PNI: HR=0.35, p=0.0008 for PFS and HR=0.27, p=0.0068 for OS; NLR: HR=0.71, p=0.081 for PFS and HR=0.63, p=0.14 for OS). Multivariate analysis demonstrated that PNI was an independent predictor of PFS (HR=0.30, p=0.0009). Conclusion: PNI could be a more reliable prognostic marker for MBC patients treated with eribulin than NLR.*

Breast cancer is the most commonly diagnosed cancer and the major cause of cancer-related deaths in women (1). Once the metastatic disease has developed, sequential therapy including endocrine, molecular targeted therapy, and chemotherapy are recommended for prolonging the survival and maintaining the quality of life (2). While treatments considered more effective for patients with metastatic breast cancer (MBC) are being sequentially selected among several anti-cancer agents based on the reported evidences, clinicians often face difficulties in deciding which agents to choose. To date, several studies have investigated the usefulness of predictive biomarkers for response to the anti-cancer drugs and prognosis after breast cancer treatment (3, 4), but their usefulness in clinical practice has not been validated.

Increasing evidence suggests that the prognosis of various solid malignancies is associated with the systemic nutritional and immunological status of patients (5). Prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR), which are calculated *via* simple formulae using serum albumin levels, lymphocyte count, and neutrophil count in the peripheral blood, are widely used as systemic nutritional and immunological parameters (6). A number of clinical studies in various operable malignancies have indicated that high PNI and low NLR could be predictors of longer prognosis (7-10). In breast cancer patients, few reports demonstrated that preoperative PNI and NLR predict postoperative long-term survival, especially for early-stage breast cancer (11-14). However, the clinical significance of these parameters for patients with MBC remains unclear. Generally, patients with early-stage breast cancer might exhibit good and reasonable values of PNI or NLR except patients extensively treated for other diseases; hence, these values among them tend to be normally distributed (15). However, PNI or NLR values are expected to vary among the MBC patients owing to the diversity of systemic conditions in each patient, which are affected by the extent of metastatic disease and previous systemic therapy. Therefore, there could be a possibility that the impact of PNI or NLR value in patients with MBC is not equivalent to that in patients with operable early-stage breast cancer.

Eribulin mesylate (eribulin) is currently used as one of the key chemotherapeutic drugs for MBC patients (16). Kashiwagi *et al*. reported that progression-free survival (PFS) of patients with high frequencies of tumor infiltrating lymphocytes (TILs), which represent the local immune response, was significantly longer than that of patients with low frequencies among triple negative breast cancer patients treated with eribulin (17). However, several studies have

Correspondence to: Kazuma Maeno, Division of Breast and Endocrine Surgery, Department of Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan. Tel: +81 263372657, Fax: +81 263372721, e-mail: kmaeno@shinshu-u.ac.jp

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indicated that the density of TILs positively correlated with PNI (18, 19), indicating an association between systemic immunological status and local immune response. Therefore, we hypothesized that systemic nutritional and immunological status could be associated with treatment outcomes of MBC patients who received eribulin therapy.

In this study, we investigated the association between patients' systemic nutritional and immunological status and prognosis after eribulin treatment. To this end, we calculated PNI and NLR as systemic nutritional and immunological factors at the first administration of eribulin; we analyzed the correlation of these values with patient outcomes and sought to compare the usefulness of PNI and NLR as prognostic markers.

Patients and Methods

Patients and study design. In this retrospective study, we examined a cohort of MBC patients, with a performance status (PS, Eastern Cooperative Oncology Group performance status) (20) 0 and 1, who received eribulin treatment at Shinshu University Hospital from 2011 to 2018. Metastatic breast cancer was confirmed by radiographic imaging examination, including computed tomography, magnetic resonance imaging, and/or 18F-fluorodeoxyglucose positron emission tomography. Patients without detailed clinical data were excluded. Finally, a total of 60 MBC patients were included.

Treatment protocol of eribulin. Eribulin was administered intravenously at 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle. If the patients developed grade 3 or 4 adverse effects of hematological toxicity and febrile neutropenia according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. on day 8 or 15, the dose was step-wise reduced to 1.1 or 0.7 mg/m^2.

Data collection. The clinical information including the age, menopausal status, PS, estrogen receptor (ER) status, progesterone receptor (PgR) status, human epidermal growth factor receptor type 2 (HER2) status, previous treatment, number of chemotherapy regimens prior to eribulin treatment, and metastatic sites were retrospectively collected from the patients' medical records. Neoadjuvant or adjuvant chemotherapy with anthracycline and/or taxane based regimens was excluded from the chemotherapy regimens prior to eribulin treatment. The metastatic sites were classified into visceral metastases, involving the lung, liver, and brain and non-visceral metastases such as the locoregional soft tissues, skin, and bone.

To determine the clinical response to eribulin treatment, we assessed the tumor lesions according to the RECIST version 1.1 (21) before and at week 6 (±3 weeks) after the first administration of eribulin. PFS was defined as the days from the first day of eribulin administration to the end of treatment owing to disease progression. Overall survival (OS) was assessed from the first eribulin administration to the date of death from any cause.

Calculation of prognostic nutritional index and neutrophil-to-lymphocyte ratio. The PNI values were calculated from the results of routine blood examination performed several days before or on the day of first administration of eribulin by using the following formula: 10× serum albumin value (g/dl) + 0.005× total lymphocyte count in the peripheral blood/mm3 (6). The NLR values were calculated by dividing the total neutrophil count by the total lymphocyte count from the same blood examination used for PNI (22). The receiver operating characteristics (ROC) curve was analyzed for determining the best cut-off values of PNI and NLR on PFS.

Ethics statement. This study complied with the provisions of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). The study was approved by the local ethics committee on clinical investigation of Shinshu University (no. 4672). Because this was a retrospective study of anonymized data, the need for informed consent was waived.

Statistical analysis. Categorical and continuous variables were analyzed using the Chi square or Fisher's exact test and Mann-Whitney *U*-tests, respectively. PFS and OS were estimated using the Kaplan–Meier method, and significant differences in survival were assessed using the log-rank test. Univariate and multivariate analyses with the Cox proportional hazards model were performed for determining significant factors. Multivariate analysis was performed for parameters with $p<0.3$ in the univariate analysis. All statistical analyses were carried out using StatFlex ver. 6 (Artech Co., Ltd., Osaka, Japan), and $p<0.05$ was considered statistically significant.

Results

Clinicopathological characteristics of all the patients included in this study. The clinicopathological characteristics of all the 60 patients are shown in Table I. The mean age (±standard deviation) was 58.6±11.9 years. Twenty patients (33.3%) were premenopausal, whereas 40 patients (66.7%) were postmenopausal. Furthermore, 49 patients (81.7%) had ER positive breast cancer, while 54 patients (90.0%) had HER2 negative breast cancer. Fifty-one patients (85.0%) had been previously treated with anthracycline and/or taxane based chemotherapy in either neoadjuvant, adjuvant, or metastatic settings [both, n=45 (75.0%); only anthracycline, n=3 (5.0%); only taxane, n=3 (5.0%)]. Before eribulin treatment, 53 patients had been treated with other chemotherapy regimens, including chemotherapy alone (n=49, 81.7%) and chemotherapy plus anti-HER2 therapy (n=4, 8.3%). Sixteen patients (26.7%) received either 1 chemotherapeutic regimen or none, while the other 44 patients (73.3%) progressed after at least 2 regimens. Visceral metastases were present in 48 patients (80.0%). As for clinical response, 18 patients (30.0%), 19 patients (31.7%), and 23 patients (38.3%) showed partial response (PR), stable disease (SD)/long SD, and progression disease (PD), respectively. The median follow-up period was 411 days (range=49-1,625 days).

PNI and NLR values and their correlation. The PNI values showed significantly inverse correlation with the NLR values ($p<0.0001$, R=-0.4974) (Figure 1). The optimal cut-off

Table I. *Patients' clinical features and comparison between high and low groups in PNI and NLR.*

Variables	Total (%)	PNI		*p*-Value	NLR		*p*-Value
		High (%)	Low (%)		High (%)	Low (%)	
	60	17 (28.3)	43 (71.7)		33 (55.0)	27 (45.0)	
Age (mean±SD)	58.6±11.9	55.6±12.6	58.9±10.9	0.42	57.1±10.3	58.9±10.9	0.52
Menopausal status							
Premenopausal	20 (33.3)	7 (41.2)	13 (30.2)	0.90	11 (33.3)	9 (33.3)	1
Postmenopausal	40 (66.7)	10 (58.8)	30 (69.8)		22 (66.7)	18 (66.7)	
ER							
Positive	49 (81.7)	13 (76.5)	36 (83.7)	0.51	24 (72.8)	25 (92.5)	0.09
Negative	11 (28.3)	4 (23.5)	7 (16.3)		9 (27.2)	2 (7.5)	
PgR							
Positive	44 (73.3)	11 (64.7)	33 (76.7)	0.34	23 (69.7)	21 (77.7)	0.56
Negative	16 (26.7)	6 (35.3)	10 (23.3)		10 (30.3)	6 (22.3)	
HER2							
Positive	6 (10.0)	2 (11.8)	4 (9.3)	0.77	4 (12.1)	2 (7.5)	0.68
Negative	54 (90.0)	15 (88.2)	39 (90.7)		29 (87.9)	25 (92.5)	
Previous anthracycline and taxane based therapy							
Both	45 (75.0)	14 (82.3)	31 (72.2)	0.15	27 (84.8)	18 (66.7)	0.27
Anthracycline only	3 (5.0)	2 (11.8)	1 (2.3)		1 (0)	2 (7.4)	
Taxane only	3 (5.0)	0 (0.0)	3 (6.9)		2 (6.1)	1 (3.7)	
None	9 (15.0)	1 (5.9)	8 (18.6)		3 (9.1)	6 (22.2)	
Treatment type before eribulin							
Chemotherapy	49 (81.7)	13 (88.2)	36 (83.6)	0.71	26 (78.7)	23 (85.2)	0.49
Chemotherapy and anti-HER2 therapy	4 (8.3)	2 (17.8)	2 (4.7)		2 (6.1)	2 (7.4)	
Anti-HER2 therapy	2 (1.7)	0 (0)	2 (4.7)		2 (6.1)	0 (0)	
Endocrine therapy	2 (3.3)	0 (0)	2 (4.7)		1 (3.0)	1 (3.7)	
None	3 (5.0)	2 (17.8)	1 (2.3)		2 (6.1)	1 (3.7)	
Number of chemotherapy regimens prior to eribulin							
0-1	16 (26.7)	7 (41.2)	9 (20.9)	0.11	8 (24.3)	8 (29.6)	0.77
≥2	44 (73.3)	10 (58.8)	34 (79.1)		25 (75.7)	19 (70.3)	
Metastatic site							
Visceral	48 (80.0)	14 (82.4)	34 (79.1)	0.77	27 (81.8)	21 (77.8)	0.75
Non-visceral	12 (20.0)	3 (17.6)	9 (20.9)		6 (18.2)	6 (22.2)	
Performance status							
0	40 (66.7)	13 (76.5)	27 (62.8)	0.37	23 (69.7)	17 (63.0)	0.59
1	20 (33.3)	4 (23.5)	16 (37.2)		10 (30.3)	10 (37.0)	
Clinical response							
PR	18 (30.0)	8 (47.1)	10 (23.2)	0.02	9 (47.1)	9 (33.3)	0.59
SD or long SD	19 (31.7)	7 (41.2)	12 (27.9)		10 (41.2)	9 (33.3)	
PD	23 (38.3)	2 (11.7)	21 (48.9)		14 (11.7)	9 (33.3)	

ER: Estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor type2; PR: partial response; SD: stable disease; PD: progressive disease; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.

values of PNI and NLR for PFS determined by the ROC analysis were 48.3 [Area under the curve (AUC)=0.87, sensitivity/specificity=0.85] and 2.32 [AUC=0.63, sensitivity/specificity=0.57], respectively. We segregated the patients into high and low groups for each parameter according to those cut-off values. There were no significant differences in the clinical features between the high and low groups of PNI. Regarding the clinical responses, significantly higher rates of PR and SD/long SD in high PNI and significantly higher rates of PD in low PNI were observed (p=0.02). However, there was no significant difference in the clinical features, including clinical responses between the high and low NLR groups (p=0.59) (Table I).

Association between PNI and NLR and patient outcomes after eribulin therapy. To evaluate the correlation between the values of PNI and NLR and patient outcomes, we compared the PFS and OS in the high and low groups for both parameters. The high PNI patients had significantly longer PFS than the low PNI patients [hazard ratio

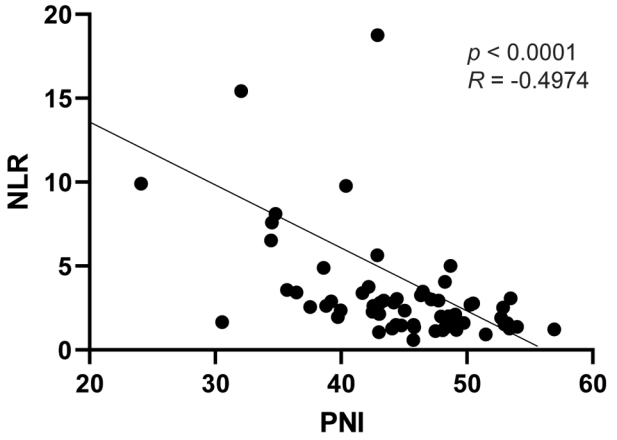

Figure 1. *Scatter plot of PNI against NLR at the first administration of eribulin. Correlation is shown using Pearson correlation coefficients (R), and significance was determined using the Spearman correlation. PNI: Prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.*

(HR)=0.35, 95% confidence interval (CI)=0.20-0.60; p=0.0008] (Figure 2A). The low NLR patients also showed a trend of longer PFS than the high NLR patients with marginal significance (HR=0.71; 95%CI=0.41-1.23; p=0.081) (Figure 2B).

In line with the PFS, the OS was significantly longer in the high PNI group than the low PNI (HR=0.27; 95%CI=0.13-0.53; p=0.0068) (Figure 2C). In contrast, no significant difference in the OS was observed between the high and low NLR groups despite the tendency of longer OS in the low NLR group (HR=0.63; 95%CI=0.34-1.18; p=0.14) (Figure 2D). These results indicated a stronger impact of PNI for better outcomes than that of NLR.

The effect of various clinical factors on the association between prognosis and PNI. Given the stronger impact of PNI than NLR on PFS and OS, we focused on PNI for further analysis. To assess whether the differences in various clinical factors could affect the association between PNI and prognosis after eribulin treatment, we segregated the patients according to menopausal status, ER expression, number of previous chemotherapies (early line: 0, 1 or late line: ≥2), and metastatic site (visceral or non-visceral), and compared the PFS and OS in the high and low PNI groups with each factor.

In both premenopausal and postmenopausal patients, the patients with high PNI showed significantly longer PFS than those with low PNI (HR=0.35; 95%CI=0.14-0.88; p=0.045 for premenopausal and HR=0.33; 95%CI=0.17-0.64; p=0.0068 for postmenopausal) (Figure 3A and B). Regarding the ER status, the high PNI group showed significantly longer PFS than the low PNI group regardless of ER expression (HR=0.33; 95%CI=0.18-0.62; p=0.0026 for ER positive and HR 0.27; 95%CI=0.06-1.22; p=0.031 for ER negative) (Figure 3C and D). When eribulin was administered after 2 or more chemotherapies (late line), the PFS was significantly prolonged in the high PNI patient group compared to that in the low PNI group (HR=0.31; 95%CI=0.17-0.56; p=0.0028). Similarly, in patients treated with eribulin after 0 or 1 chemotherapy regimen (early line), PFS was longer in the high PNI group, but the statistical significance was marginal (HR=0.40; 95%CI=0.14-1.18; p=0.064) (Figure 3E and F). In patients with non-visceral metastasis, no high PNI patient showed disease progression with eribulin therapy, whereas all the low PNI patients showed progression (p=0.0106). Even in patients with visceral metastasis, the high PNI group showed significantly longer PFS than the low PNI group (HR=0.49; 95%CI=0.27-0.90; p=0.034) (Figure 3G and H).

Univariate and multivariate analyses of PFS. Univariate analysis revealed that PNI was significantly associated with better PFS (HR=0.33, 95%CI=0.17-0.65, p=0.0015). On multivariate analysis using the Cox hazard model, PNI was an independent risk factor for PFS (HR=0.30, 95%CI=0.15-0.61, p=0.0009) (Table II).

Discussion

The present study demonstrates that high PNI before eribulin treatment is significantly associated with better clinical response and longer survival after eribulin treatment in patients with MBC. In addition, the results of this study suggest that high PNI might be a prognostic marker of patient outcomes after eribulin treatment independent of various clinical factors, including menopausal status, ER status, number of previous chemotherapies, and metastatic sites. To the best of our knowledge, this is the first study to identify PNI as a prognostic marker for MBC patients treated with eribulin.

This study also indicated the association between NLR and prognosis in MBC patients treated with eribulin. In line with this, Miyagawa *et al.* recently reported the association between low NLR and improved PFS of patients with locally advanced or metastatic breast cancer treated with eribulin when the cut-off value was set at 3.0 (23). This reproducibility of the results regarding NLR, demonstrated in the present study, underscores the importance of assessing the systemic immunological status of MBC patients. In addition, our results showed that PNI had stronger association with longer PFS and OS than NLR. One possible explanation for this advantage of PNI might be the exclusion of neutrophil count from the PNI calculation and its inclusion in the NLR calculation. In our cohort study, 90.0% of the total patients were treated with other chemotherapy before eribulin administration. Chemotherapeutic agents generally cause neutropenia. Although the decrease in neutrophils induced by

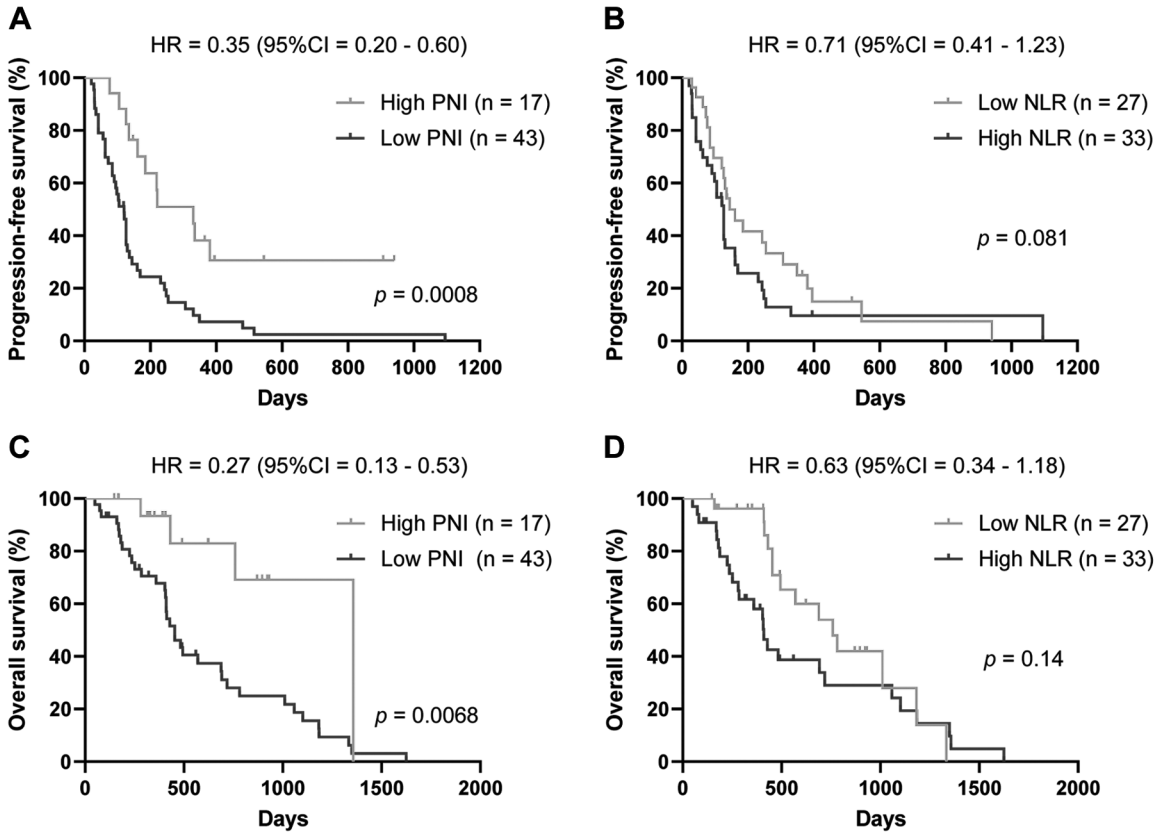

Figure 2. *Kaplan–Meier curves for PFS (A: PNI, p=0.0008, B: NLR, p=0.081) and OS (C: PNI, p=0.0068, D: NLR, p=0.14) according to PNI and NLR. PFS: Progression-free survival; OS: overall survival; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio.*

Table II. *Univariate and multivariate Cox proportional hazards regression analysis of progression-free survival.*

	Univariate			Multivariate		
	p-Value	HR	95%CI	*p*-Value	HR	95%CI
Menopausal status (postmenopausal *vs*. premenopausal)	0.086	0.60	0.33-1.07	0.056	0.53	0.27-1.01
ER (positive *vs*. negative)	0.29	0.70	0.34-1.40	0.34	0.69	0.32-1.48
Previous chemotherapy regimens (≥2 *vs*. 0, 1)	0.31	1.38	0.73-2.60	NA	NA	NA
Metastatic site (visceral *vs*. non-visceral)	0.16	1.76	0.79-3.91	0.33	1.49	0.65-3.37
PNI (high *vs*. low)	0.0015	0.33	0.17-0.65	0.0009	0.30	0.15-0.61

ER: Estrogen receptor; PNI: prognostic nutritional index; NA: not applicable; HR: hazard ratio; CI: confidence interval.

the previous chemotherapy is transient and expected to be recovered by the time of administration of eribulin, it would still be possible for neutrophil counts to be affected by the hematological toxicity of the previous chemotherapy. In contrast, serum albumin levels, which were used for PNI calculation, are less affected by previous chemotherapy and are rather stable. Such differential responses to the previous chemotherapy between neutrophils and serum albumin levels may make PNI a superior parameter compared to NLR for evaluating the systemic conditions of MBC patients treated with sequential chemotherapy.

We previously demonstrated that a decrease in PNI during neoadjuvant chemotherapy can be a marker of poor prognosis in patients with operable breast cancer, which highlights the importance of maintaining the nutritional and immunological status of patients during chemotherapy (15).

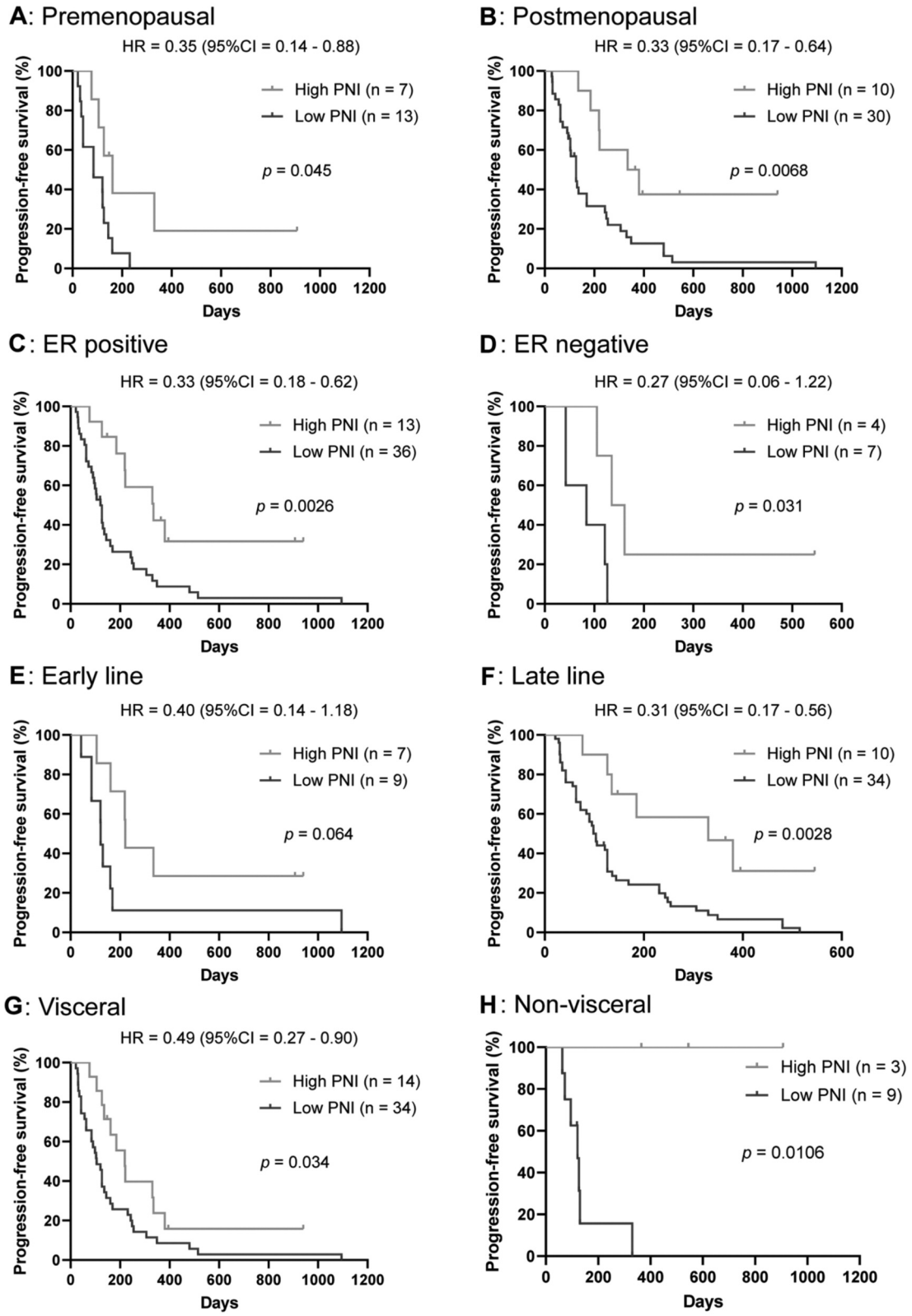

Figure 3. *Kaplan–Meier curves for PFS stratified by menopausal status (A, B), ER status (C, D), number of previous chemotherapies (early line=0, 1; late line≥2) (E, F), and metastatic site (visceral metastasis or non-visceral metastasis) (G, H). PFS: Progression-free survival; ER: estrogen receptor; PNI: Prognostic nutritional index.*

Therefore, it is possible that maintaining high PNI during sequential therapies for MBC improves the outcomes after eribulin treatment. Furthermore, nutritional intervention for maintaining PNI might provide better clinical benefits for MBC patients. Indeed, several ongoing clinical trials are examining whether nutritional intervention could improve the treatment outcome in MBC patients (NCT03045289, NCT03535701). Therefore, in the near future, we will be able to verify the hypothesis that improving systemic nutritional and immunological conditions may contribute to better prognosis of MBC patients.

There are several limitations of this study. First, this study is a single-center retrospective cohort study and only a small number of patients were enrolled. Second, this study investigated only patients treated with eribulin. Therefore, it may be possible that PNI is only a prognostic marker in MBC patients, and not a predictive marker of the response to eribulin treatment. Further studies which include patients treated with other chemotherapeutic agents are needed to elucidate whether PNI is a truly predictive marker of the treatment response to eribulin.

In conclusion, the present study indicates that PNI is a more reliable prognostic marker than NLR for MBC patients treated with eribulin. Our results imply that improving nutritional and immunological status in metastatic settings may contribute to better patient outcomes.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare in relation to this study.

Authors' Contributions

TO and KM designed the study. TO, MO, TI, TK, KM, and KI collected the clinical data. TO performed the statistical analysis. The draft manuscript was prepared by TO and KM. All the Authors read and approved the final manuscript.

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