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Original Article

The Efficacy of Inflammatory and Immune Markers for Predicting the Prognosis of Patients with Stage IV Breast Cancer

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Systemic therapy for stage IV breast cancer is usually an initial treatment and is based on findings regarding biomarkers (*e.g.*, hormone receptors and human epidermal growth factor receptor-2 [HER2]). However, the response to therapy and outcomes sometime differ among patients with similar prognostic factors including grade, hormone receptor, HER2, and more. We conducted retrospective analyses to evaluate the correlations between the overall survival (OS) of 46 stage IV breast cancer patients and (*i*) the peripheral absolute lymphocyte count (ALC) and (*ii*) composite blood cell markers. The peripheral blood cell markers included the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR), the systemic immune-inflammation index (SII), the systemic inflammation response index (SIRI), and the most recently introduced indicator, the pan-immune-inflammatory value (PIV). The SIRI and PIV showed prognostic impacts on the patients: those with a low SIRI or a low PIV showed significantly better OS than those with a high SIRI (5-year, 66.0% vs. 35.0%, $p<0.05$) or high PIV (5-year, 68.1% vs. 38.5%, $p<0.05$), respectively. This is the first report indicating the possible prognostic value of the PIV for OS in patients with stage IV breast cancer. Further studies with larger numbers of patients are necessary for further clarification.

Key words: breast cancer, pan-immune-inflammatory value, prognosis

Breast cancer is the most frequent malignancy among women worldwide [1]. As an initial treatment for breast cancer, systemic therapy is chosen based on the patient's values of biomarkers such as hormone receptors and human epidermal growth factor receptor-2 (HER2). However, the outcomes of breast cancer sometime differ among patients with similar prognostic factors including the tumor stage and grade, the hormone receptor status, HER2 value, and more [2]. Various inflammatory and immune markers (both single blood cell and composite markers) have been shown to be correlated with patients' prognoses and responses to systemic therapies in solid malignancies [3], and this may account for the difference in prognosis. Lymphocytes both in the circulation and the microenvironment have an important role in the immune responses against cancer [4]. Neutrophils have been shown to produce cytokines to promote cancer proliferation [5] and to suppress the cytotoxic activity mediated by immune cells [6,7]. Monocytes, which are the primary source of tumor-associated macrophages [8], have an essential role in cancer progression [9]. Platelets secrete growth factors including fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor that stimulate tumor proliferation and angiogenesis [10].

In the present study, we evaluated the correlations between the overall survival (OS) of patients with stage IV breast cancer and (*i*) the peripheral absolute lympho-

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cyte count (ALC) and (*ii*) composite blood cell markers. The peripheral blood cell parameters examined herein were the neutrophil-to-lymphocyte ratio (NLR) [11], the monocyte-to-lymphocyte ratio (MLR) [3], the systemic immune-inflammation index (SII) [12], and the systemic inflammation response index (SIRI) [13]. We also examined a recently introduced indicator, the pan-immune-inflammatory value (PIV) [14], which is composed of immune-inflammatory populations from peripheral blood that demonstrated prognostic relevance in breast cancer, *i.e.*, neutrophils, monocytes, lymphocytes, and platelets [15, 16].

Patients and Methods

We retrospectively analyzed the clinicopathological data of 46 patients with stage IV breast cancer diagnosed at our hospital between April 2008 and July 2020. This study was approved by the Institutional Review Board of our institution (approval no. 2020154), and the requirement to obtain informed consent was waived.

Protocol and evaluations. A pathological diagnosis and further evaluations of the primary tumor based on specimens obtained from a core needle biopsy were performed in all patients. The estrogen receptor (ER) and progesterone receptor (PgR) statuses were regarded as positive if their nuclear expression was found to be ≥ 1% by immunohistochemistry. The HER2 expression was scored according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. HER2 scores of 0 and 1 were defined as negative, and a score of 3 was defined as positive. An *in situ* hybridization analysis was carried out in HER2 samples with a score of 2+. Luminal disease was defined as ER- and/or PgR-positive and HER2-negative. HER2-positive disease was defined as HER2-positive irrespective of the ER/PgR expression, and triple-negative status was defined by negativity for ER, PgR, and HER2. Systemic therapy was selected according to the surrogate subtype (*i.e.*, ER, PgR, and HER2 statuses), patient age, extent of disease, and the patient's preference. Some patients underwent surgery with palliative intent.

The inflammatory and immune markers were assessed at baseline (*i.e.*, within 4 weeks before systemic therapy). Each marker was defined as follows according to previous reports: NLR = neutrophils (10^3/μL)/lymphocytes (10^3/μL); MLR = monocytes (10^3/μL)/lymphocytes; SII = neutrophils × platelets (10^3/μL)/lymphocytes; SIRI = neutrophils × monocytes/lymphocytes; and PIV = neutrophil × monocyte × platelet/lymphocyte. The median values were used as cut-off values (Table 1). Overall survival was defined as the length of time from the pathological diagnosis of breast cancer to the date of the last follow-up or death.

Statistical analyses. The data are presented as the median (range) unless otherwise stated. The Mann-Whitney *U*-test or *t*-test was used for comparisons of continuous variables between two groups. Fisher's exact probability test was used for the comparison of categorical variables. The OS was assessed using the Kaplan-Meier approach, with differences between groups examined by a log-rank test. A Cox proportional hazard model was used for the multivariate analysis of the OS. *P*-values < 0.05 were considered significant. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Japan).

Results

Patients' background characteristics. The median follow-up period was 30 months (1-146 months). The background characteristics of the patients are summarized in Table 2. The median age of the patients at the diagnosis of breast cancer was 57 years (38-73 years). The proportions of the subtypes of breast cancer were luminal, 52.2%; HER2, 34.8%; and triple-negative, 13.0%. The proportions of the patients who had metastasis were 47.8% in bone, 54.3% in lung, and 39.1% in

Table 1 Inflammatory and immune markers and their cut-off value

Markers	Cut-off value
ALC, absolute lymphocyte count ($\times 10^3/\mu$L)	1.4
NLR, neutrophil-to-lymphocyte ratio (= N/L)	2.77
MLR, monocyte-to-lymphocyte ratio (= M/L)	0.21
SII, systemic immune-inflammation index (= N × P/L)	829
SIRI, systemic inflammation response index (= N × M/L)	0.83
PIV, pan-immune-inflammatory value, (= N × M × P/L)	230

N, neutrophil; L, lymphpcyte; M, monocyte; P, platelet.

Table 2 Patient background characteristics

Median age (range), years	57 (38–73)
Subtype, n (%)	
Luminal	24 (52.2)
HER2	16 (34.8)
Triple-negative	6 (13.0)
Metastatic site, n (%)	
Bone	22 (47.8)
Lung	25 (54.3)
Liver	18 (39.1)

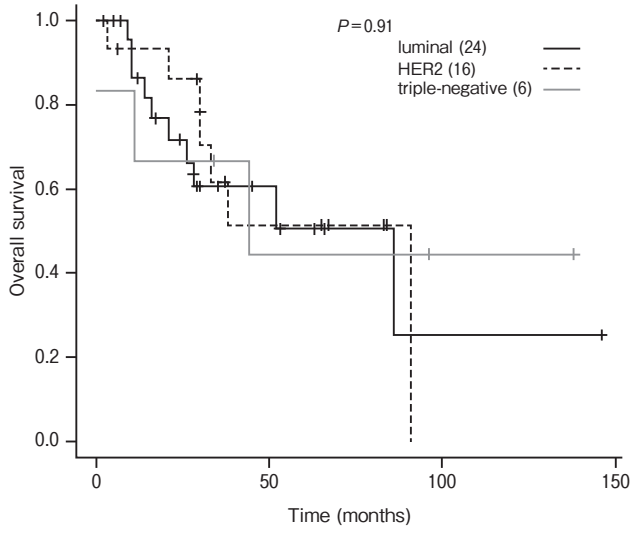

Fig. 1 Overall survival according to the subtypes of breast cancer.

liver.

Clinicopathological factors affecting the survival of the stage IV breast cancer patients. There were no significant differences in the 5-year OS according to the subtypes of breast cancer, as shown in Fig. 1: luminal vs. HER2 vs. triple-negative = 50.5% vs. 51.4% vs. 44.4%, $p = 0.91$. We next evaluated the OS according to the site of metastasis at the initial diagnosis. Although there was no significant difference in OS between the patients with versus without bone metastasis (Fig. 2A) or those with versus without lung metastasis (Fig. 2B), the patients with liver metastasis had significantly poorer OS than those without it (42.2% vs. 57.4%, $p < 0.05$) (Fig. 2C).

The correlation of the inflammatory and immune markers with survival in stage IV breast cancer patients. Figure 3 depicts the correlations between the inflammatory and immune markers at baseline and the patients' OS. The median values were used as cut-off values. There were no significant differences in OS between the high and low values of ALC (Fig. 3A), NLR (Fig. 3B), and SII (Fig. 3D). The patients with a low MLR tended to show better 5-year OS than those with a high MLR (59.7% vs. 41.0%, $p = 0.07$) (Fig. 3C). The patients with a low SIRI or a low PIV showed significantly better 5-year OS than those with a high SIRI (66.0% vs. 35.0%, $p < 0.05$) (Fig. 3E) or a high PIV (68.1% vs. 38.5%, $p < 0.05$), respectively (Fig. 3F). The multivariate analysis revealed that liver metastasis at the time of the initial diagnosis was correlated with the OS, but none of the inflammatory and immune markers were correlated with the OS (Table 3).

Discussion

The results of our retrospective analyses of the cases of 46 patients with stage IV breast cancer demonstrated that among the inflammatory and immune markers examined, the SIRI and the PIV could be used as prognostic markers in such patients. Various populations of blood cells have been reported to reflect microenvironmental as well as the systemic inflammatory and immune responses [4-10], and composite markers that are based on combinations of different types of blood cells have been demonstrated to have a prognostic impact on patients with various types of cancer. For example, we reported that a high NLR was associated with poor relapse-free survival in patients with stage III breast cancer [17]. In a systematic review, a high NLR was associated with poor OS and poor disease-free survival in breast cancer patients [11].

With regard to the subtypes of breast cancer, triple-negative breast cancer has appeared to show a strong correlation between the NLR and prognosis [11, 18, 19]. Increased tumor-infiltrating lymphocytes have been associated with good prognosis in triple-negative breast cancer [20]. We have thus speculated that the nature of triple-negative breast cancer, which is prone to be affected by the immune system, could be associated with the good correlation between prognosis and the NLR. However, in the present study's patients with triple-negative breast cancer, there was no correlation

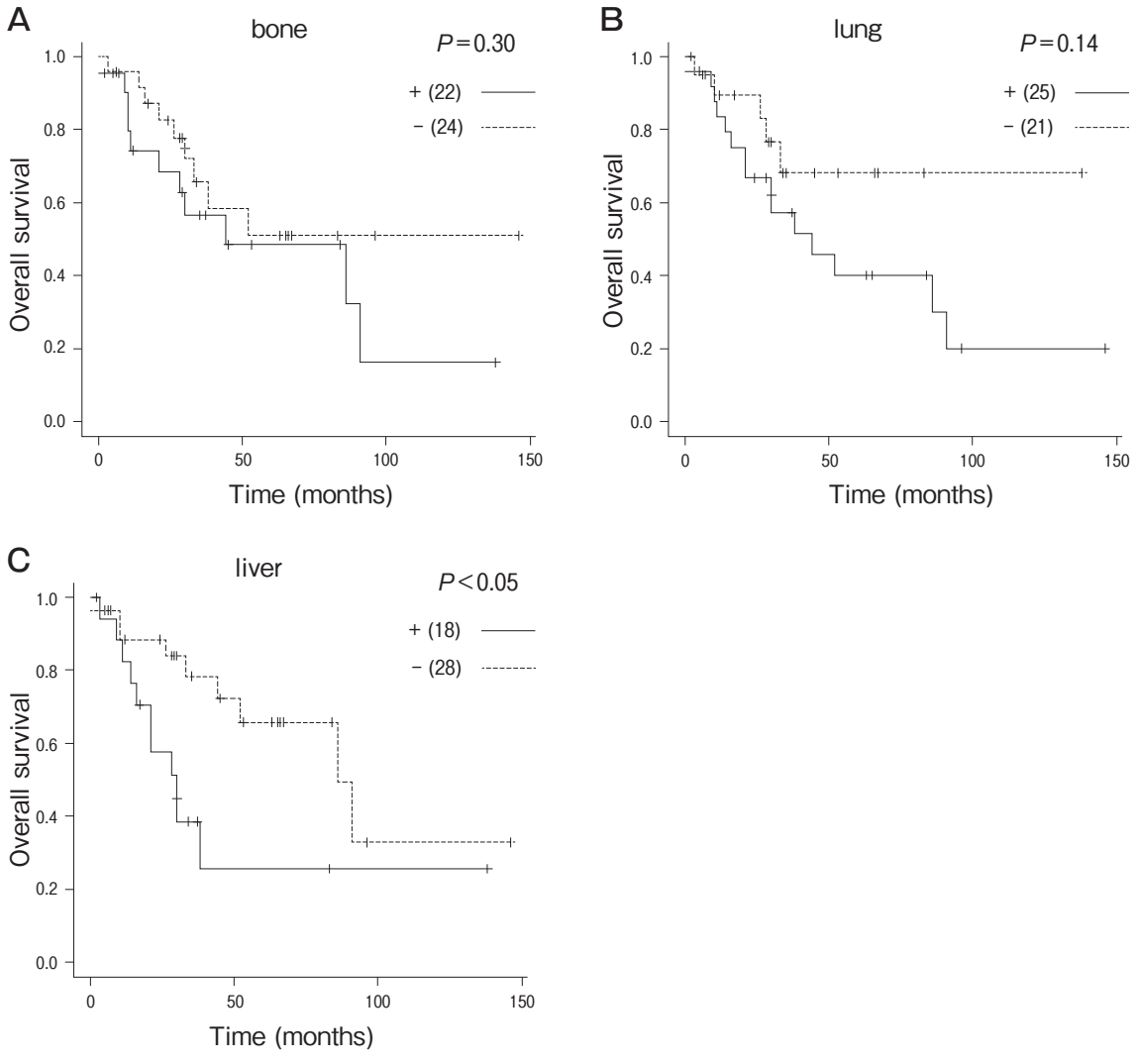

Fig. 2 Overall survival according to the site of metastasis at initial diagnosis. Bone (**A**), lung (**B**), and liver (**C**).

between the NLR and OS ($p=0.36$, data not shown), but only six patients comprised this subgroup.

Other than white blood cells, platelets and their composite markers have been reported to have prognostic and predictive impacts for solid malignancies. For example, a low pretreatment platelet-to-lymphocyte ratio, as well as a low NLR, were shown to be good prognostic markers in patients with nonmetastatic inflammatory breast cancer [21]. The preoperative SII was also shown to be independent predictor of OS and distant metastatic-free survival in patients with operable breast cancer [12].

As mentioned above, various composite blood cell markers have been described as prognostic and predictive factors in solid malignancies. The PIV was recently proposed as a new prognostic marker in metastatic colon cancer patients [14] and later in breast cancer patients [15,16]. Unlike the individual blood cell or composite markers reported previously such as the ALC, NLR, MLR, SII, and SIR, the PIV is composed of all of the blood cells that are components in the composite markers reported to date, and the PIV thus might capture a complex inflammatory and immune status more comprehensively since each cell type has different aspects of inflammatory and immune functions against tumors. In the multivariate analyses in previous studies, the PIV was shown to be an independent prognostic parameter for progression-free survival

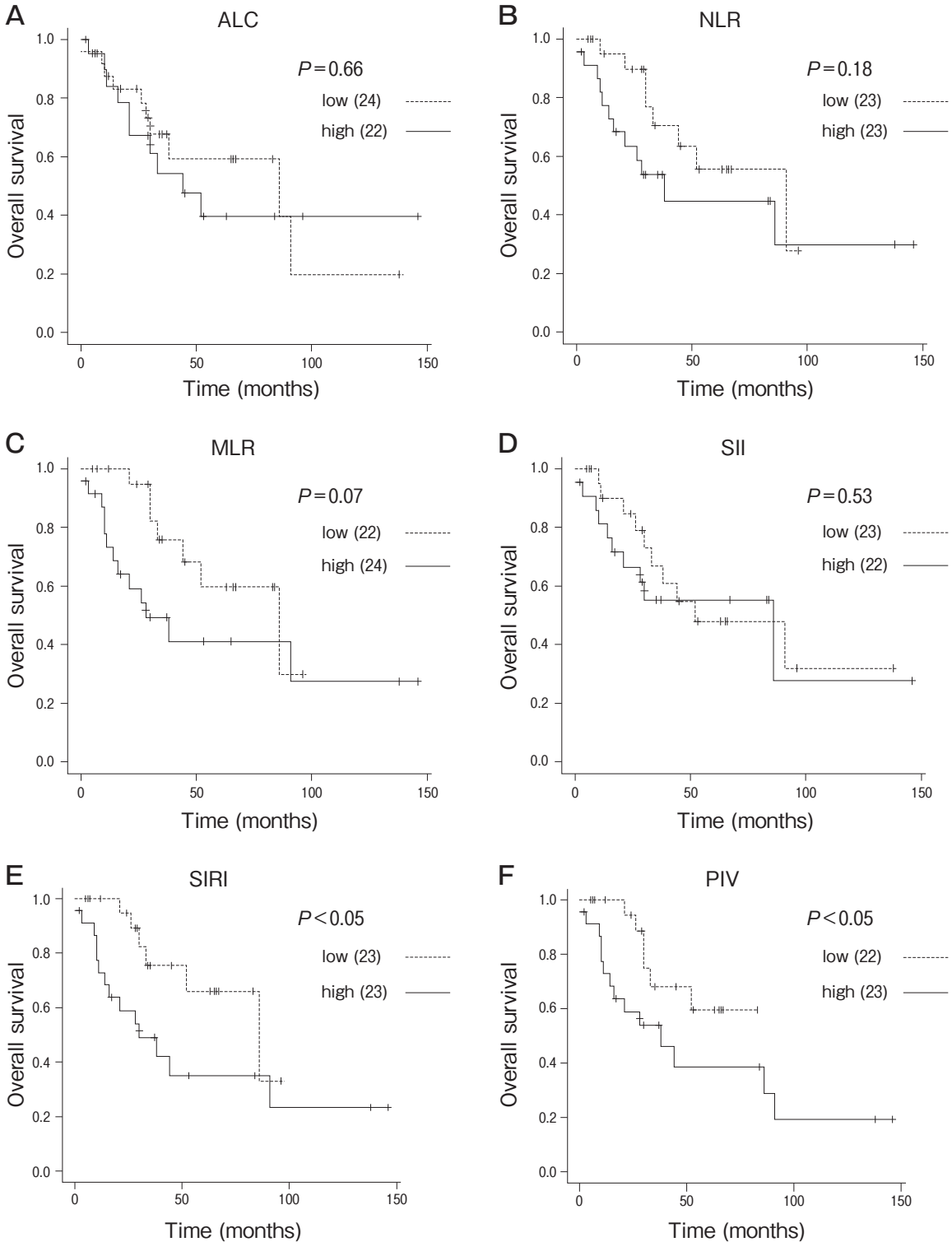

Fig. 3 Comparison of the overall survival between the patients with high and low values of the inflammatory and immune markers: the absolute lymphocyte count (ALC) (**A**), the neutrophil-to-lymphocyte ratio (NLR) (**B**), the monocyte-to-lymphocyte ratio (MLR) (**C**), the systemic immune-inflammation (SII) (**D**), the systemic inflammation response (SIRI) (**E**), and the pan-immune-inflammatory value (PIV) (**F**).

Table 3 Multivariate analysis for the overall survival

Variables		Hazard ratio (95% confidence interval)	*P*-value
Subtype			
	Luminal	2.06 (0.33–12.89)	0.44
	HER2	0.53 (0.13–2.18)	0.38
	Triple-negative	0.48 (0.08–3.03)	0.44
Metastatic site			
	Bone	1.31 (0.44–3.87)	0.63
	Lung	1.69 (0.44–6.55)	0.45
	Liver	6.74 (1.52–30.00)	<0.05
ALC (≤1.4 versus >1.4 × $10^3/\mu$L)		1.81 (0.44–7.42)	0.41
NLR (≤2.77 versus >2.77)		0.29 (0.03–2.54)	0.26
MLR (≤0.21 versus >0.21)		1.98 (0.31–12.89)	0.47
SII (≤829 versus >829)		1.11 (0.25–5.04)	0.89
SIRI (≤0.83 versus >0.83)		0.37 (0.03–4.38)	0.43
PIV (≤230 versus >230)		4.80 (0.29–78.26)	0.27

ALC, absolute lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammatory value.

and OS in advanced colorectal cancer [14] and HER2-positive breast cancer [15] and was described as outperforming other markers. In the present study, the multivariate analysis did not demonstrate statistical significance for the PIV, possibly due to the small number of patients examined.

To our knowledge, this is the first study to reveal prognostic value of the PIV for the overall survival of patients with stage IV breast cancer including all of its subtypes. The degree of the prognostic value of the PIV might differ among subtypes in patients with breast cancer, as is true for other markers. The PIV is the most recently introduced immune and inflammatory marker that may have a prognostic and predictive impact on survival in patients with breast cancer. Further studies with larger numbers of patients, including patients with different subtypes, are needed to clarify the detailed nature of the utility of the PIV.

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