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Integrated Evaluation of Inflammatory, Nutritional, and Sarcopenia Markers to Predict Survival in Metastatic Breast Cancer Patients

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Abstract. *Background/Aim: The prognosis of a cancer patient is influenced by the tumor-related factors, as well as by various patient-related factors. We evaluated the association between inflammatory and nutritional factors and their outcomes, including the prognosis and therapeutic course, in patients with metastatic breast cancer. Patients and Methods: In this observational retrospective study, we evaluated 35 patients. The inflammatory and nutritional markers before systemic therapy included the lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammatory index (SII), systemic inflammatory response index (SIRI), pan-immuno-inflammatory values (PIV), prognostic nutritional index (PNI), Glasgow prognostic score (GPS), and psoas muscle index (PMI). Results: Triple-negative, low PNI, and GPS 2 were correlated with worse overall survival in the univariable analysis. The GPS was the only independent predictor of overall survival [hazard ratio=5.85, 95% confidence interval=1.15-29.68, p<0.01]. The time to treatment failure of first-line therapy in patients with GPS 2 was significantly shorter than that in patients with GPS 0/1 (p<0.01). Conclusion: The GPS was an independent predictive marker for overall survival in patients with metastatic breast cancer.*

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Breast cancer is the most frequent malignancy in women worldwide (1). Patients with metastatic breast cancer (MBC) are generally treated with systemic therapy, selected based on biomarkers of breast cancer, such as hormone receptors and human epidermal growth factor receptor 2 (HER2) (2). However, even breast cancer patients with similar prognostic factors, including tumor stage, grade, hormone receptors and HER2, have different outcomes (3). In addition to the characteristics of the cancer itself, the patient's condition can influence the prognosis.

Systemic inflammation is frequently activated in cancer patients, leading to malnutrition and hypoalbuminemia (4). Various inflammatory and nutritional markers have been reported to be associated with the cancer prognosis. While lymphocytes are cytotoxic to cancer cells (5), neutrophils are known to have a positive impact on cancer progression (6). Additionally, composite hematological markers, such as the neutrophil-to-lymphocyte ratio (NLR) (7, 8), monocyte-to-lymphocyte ratio (MLR) (7), systemic immune-inflammatory index (SII) (9), systemic inflammatory response index (SIRI) (10), and pan-immuno-inflammatory values (PIV) (11), have been reported to be useful as prognostic indicators for breast cancer patients. Several nutritional markers, including the prognostic nutritional index (PNI) (4), Glasgow prognostic score (GPS) (12-14), and psoas muscle index (PMI) (15), have been reported to be associated with the prognosis, response to and side effects of treatment, and quality of life (QOL) in cancer patients.

The present study aimed to evaluate various markers of the inflammatory status, nutritional status, and sarcopenia in an integrated manner in patients with MBC and to identify the most relevant prognostic indicators.

Patients and Methods

Patients. We retrospectively analyzed the clinicopathological data of 35 patients with MBC who started systemic therapy at our institution between January 2012 and December 2021. This study

was approved by the Institutional Review Board of our institution (approval no. 4-88), and the requirement to obtain informed consent was waived.

Measurement and definitions. The estrogen receptor (ER) and progesterone receptor (PgR) status were regarded as positive if the 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 (16). 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 on HER2 samples with a score of 2+. Luminal disease was defined as ER- and/or PgR-positive and HER2-negative. HER2 disease was defined as HER2-positive, irrespective of the ER/PgR expression, and triple-negative 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.

Adverse events (AEs) due to treatment were evaluated by the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

The inflammatory and nutritional 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/lymphocytes (7); MLR=monocytes/lymphocytes (7); SII=neutrophils×platelets/lymphocytes (9); SIRI=neutrophils×monocytes/lymphocytes (10); PIV=neutrophil×monocyte×platelet/lymphocyte (11); PNI=10×albumin (g/dl)+0.005×lymphocytes (/μl) (4). GPS was derived as follows: GPS 0, C-reactive protein (CRP) ≤1.0 mg/dl and albumin ≥3.5 g/dl; GPS 1, CRP >1.0 mg/dl or albumin ≤3.5 g/dl; GPS 2, CRP >1.0 mg/dl and albumin <3.5 g/dl (17). Computed tomography scans were used to calculate the PMI. The PMI was calculated as both psoas muscle areas at the level of L5 divided by the body height squared (cm^3/m^2) (15). The median values were used as cut-off values. Overall survival (OS) was defined as the length of time from the diagnosis of metastasis to the date of the last follow-up or death. Time to treatment failure (TTF) was defined as the duration of administration of first-line therapy for MBC.

Statistical analyses. The data are presented as the median (range) unless otherwise stated. OS and TTF were assessed using the Kaplan-Meier approach, with differences between groups examined by log-rank test. Variables showing *p*-values of <0.10 in log-rank test were included in a multivariate Cox proportional hazard model. *p*-Values <0.05 were considered statistically significant. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Japan).

Results

Patient characteristics. The median follow-up period was 15 months (range=2-35). The background characteristics of the patients are summarized in Table I. The median age of the patients at the diagnosis of breast cancer was 64 years (range=37-98). The rates of stage IV disease and recurrence were 51.4% and 48.6%, respectively. The proportions of the subtypes of breast cancer were as follows: luminal, 57.1%; HER2, 17.1%; and triple-negative, 25.7%. The sites of metastasis were as follows: bone, 48.6%; lung, 37.1%; and liver, 31.4%.

Table I. *Patient background characteristics*.

Characteristic	n (%)
Age*, years	64 (37-98)
Stage IV/recurrence	18 (51.4)/17 (48.6)
Subtype	
Luminal	20 (57.1)
HER2	6 (17.1)
Triple-negative	9 (25.7)
Metastatic site at the time of the initial diagnosis	
Bone	17 (48.6)
Lung	13 (37.1)
Liver	11 (31.4)

*Data presented as median (range).

Correlation of the clinicopathological factors with survival in breast cancer patients. Table II depicts the correlation between clinicopathological factors at baseline and OS in the univariable analysis. Patients with a triple-negative status, low PNI, and GPS 2 showed significantly worse OS than those with luminal/HER2 [median 15 *vs*. 61 months, hazard ratio (HR)=3.62, 95% confidence interval (CI)=1.11-11.87, $p<0.05$], high PNI (17 *vs*. 84 months, HR=5.42, 95% CI=1.51-19.5, $p<0.01$), and GPS 0/1 (11 *vs*. 42 months, HR=7.06, 95% CI=1.72-28.98, $p<0.01$), respectively (Figure 1, Table II). The multivariable analysis revealed that GPS 2 at baseline was the only independent risk factor for worse OS (HR=5.85, 95% CI=1.15-29.68, $p<0.01$) (Table II).

Adverse events due to chemotherapy. Patients with GPS 0/1 and GPS 2 were evaluated for AEs attributable to initial chemotherapy. Only patients who received chemotherapy as first-line treatment for MBC were included in this evaluation. The occurrence of both hematological and non-hematological AEs (grade ≥2) during initial chemotherapy did not differ according to the GPS (Table III).

Comparison of time to treatment failure between the patients with GPS 0/1 and GPS 2. The TTF in patients with GPS 2 was significantly shorter than that of patients with GPS 0/1, in all patients (median 4 *vs*. 18 weeks, $p<0.01$) (Figure 2A) as well as in patients receiving chemotherapy as first-line treatment for MBC (median 3.0 *vs*. 12.0 weeks, $p<0.01$) (Figure 2B). In patients receiving chemotherapy as first-line treatment, the reasons for discontinuation of the initial therapy did not differ to a significant extent by GPS; however, all three patients with GPS 2 discontinued their initial therapy due to reasons other than disease progression, namely AEs and dementia (Table IV).

Table II. *Univariable and multivariable analyses for overall survival.*

	Univariate		Multivariate	
Variables	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (≤64 *vs.* >64 years)	0.92 (0.31-2.78)	0.88		
Subtype				
Luminal	0.75 (0.25-2.27)	0.60		
HER2	0.37 (0.08-1.78)	0.194		
Triple-negative	3.62 (1.11-11.87)	<0.05	4.38 (0.94-20.36)	0.06
Stage IV *vs.* recurrence	0.63 (0.22-1.84)	0.40		
Metastatic site at the time of the initial diagnosis				
Bone	1.95 (0.65-5.86)	0.22		
Lung	1.16 (0.40-3.36)	0.78		
Liver	1.63 (0.54-4.95)	0.38		
ALC (≤1.54 *vs.* >1.54×10^3/μl)	0.50 (0.15-1.62)	0.23		
NLR (≤2.67 *vs.* >2.67)	0.91 (0.32-2.64)	0.86		
MLR (≤0.19 *vs.* >0.19)	3.03 (0.84-10.95)	0.07	3.16 (0.73-13.74)	0.12
SII (≤672 *vs.* >672)	0.53 (0.18-1.55)	0.23		
SIRI (≤0.79 *vs.* >0.79)	1.45 (0.50-4.20)	0.49		
PIV (≤205.1 *vs.* >205.1)	1.17 (0.39-3.53)	0.77		
PNI (>48.7 *vs.* ≤48.7)	5.42 (1.51-19.5)	<0.01	0.43 (0.10-1.89)	0.26
GPS (0, 1 *vs.* 2)	7.06 (1.72-28.98)	<0.01	5.85 (1.15-29.68)	<0.05
PMI (≤555.7 *vs.* >555.7)	0.97 (0.33-2.83)	0.95		

HR, Hazard ratio; 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; PNI, prognostic nutritional index; GPS, Glasgow prognostic score; PMI, psoas mass index.

Discussion

In this study, we showed that the GPS is an independent predictor of OS in patients with MBC. Systemic inflammation is frequently activated in patients with cancer and is associated with the prognosis of these patients (4). Various blood cells have been reported to affect solid cancers, including breast cancer. For example, lymphocytes both in circulation and in the tumor microenvironment play an important role in the immune responses against cancer (5). On the other hand, neutrophils produce cytokines to promote cancer proliferation and metastasis (6, 18), and to suppress the cytotoxic activity of immune cells (19). Monocytes could suppress the activation of lymphocytes and promote cancer progression (20). Platelets secrete growth factors, such as fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor, which promote tumor growth and angiogenesis (21). These blood cells and their composite markers may have different inflammatory and immune functions against tumors.

Serum albumin levels are a nutritional indicator and are associated with immune status. Malnutrition and hypoalbuminemia, which are usually seen in cancer patients are caused in part by sustained cancer-associated systemic inflammation and the activation of inflammatory cytokines (4). CRP is synthesized by hepatocytes and is regulated by inflammatory cytokines (22). It enhances angiogenesis *via* vascular growth factors and interleukins, leading to cancer cell invasion and progression (23). Additionally, CRP levels indicate the aggressiveness of cancers and have been reported to be associated with resistance to treatment (24). CRP and albumin levels are usually linked, that is, elevated CRP levels are associated with decreased serum albumin levels due to suppression of the rate of albumin synthesis in the liver (22). Forrest *et al*. (25) first reported the prognostic value of the GPS in patients with advanced non-small-cell lung cancer in 2003. Subsequently, in a patient with MBC, the GPS was reported to be a predictor of cancer-specific survival (12), or progression-free survival or the response rate (26, 27).

Sarcopenia is accompanied by decrease in skeletal muscle mass, partly due to systemic inflammation (4, 28). The reported prevalence of sarcopenia among breast cancer patients ranges from 15.9% to 66.9% (29). Sarcopenia has been reported as a predictor of the prognosis in breast cancer; however, in this study, PMI, one of the indicators of sarcopenia, was not correlated with OS. To date, there have been few reports on the association between PMI and the prognosis of MBC (30), in comparison to other solid tumors. In patients with breast cancer, the skeletal muscle index or muscle strength—other

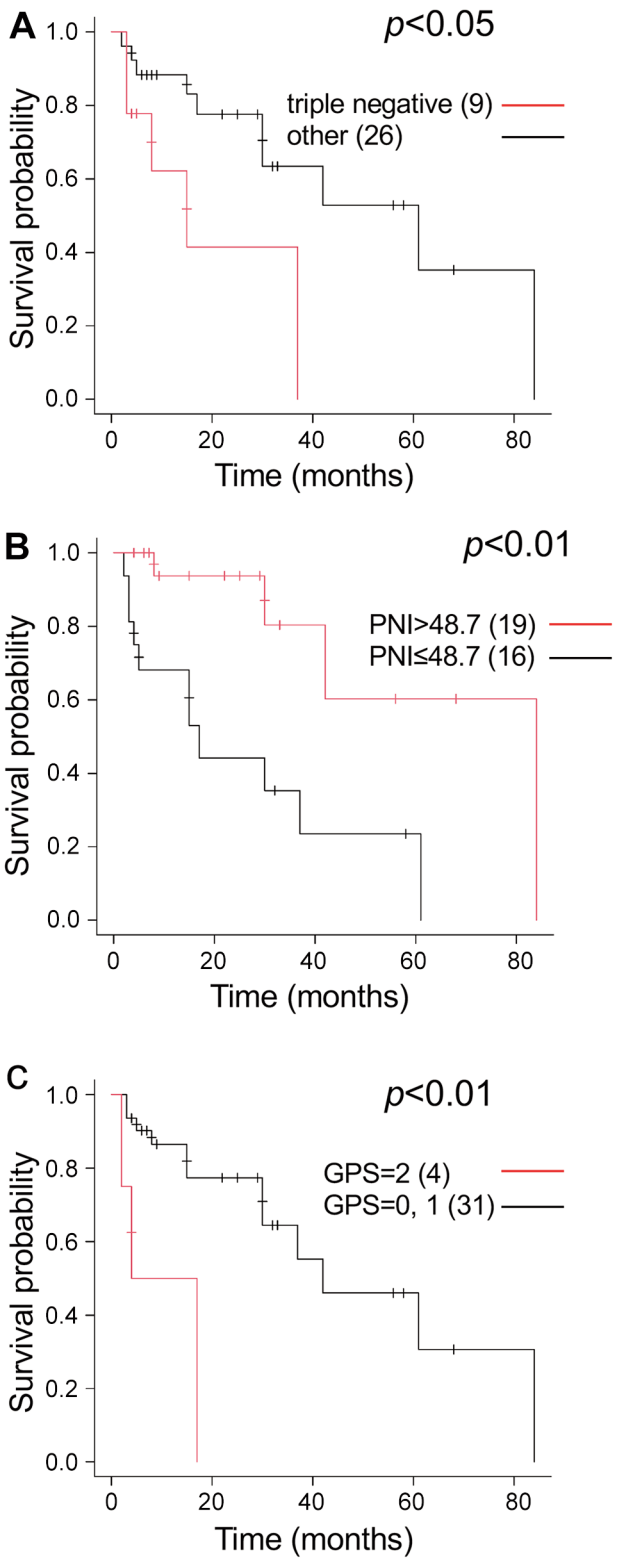

Figure 1. *Comparison of overall survival. (A) Triple-negative (n=9) vs. other subtypes (n=26). (B) Prognostic nutritional index (PNI) ≤48.7 (n=16) vs. >48.7 (n=19). (C) Glasgow prognostic score (GPS) 2 (n=4) vs. GPS 0/1 (n=31).*

makers of sarcopenia—may be more useful for predicting the prognosis (3, 31). While there have been reports on the integrated evaluation of inflammatory, nutritional, and sarcopenia markers in urologic cancer patients (32, 33), this is the first report to describe an integrated evaluation of these markers for predicting the prognosis of patients with MBC.

The GPS has been reported to be associated with chemotherapy-related toxicity in cancer patients (26, 34, 35). Thus, systemic inflammation and malnutrition are thought to adversely affect not only the prognosis and response rate of cancer patients, but also the toxicity of chemotherapy. Furthermore, the inflammatory and nutritional status has been known to affect the QOL of cancer patients. For example, the modified GPS was independently correlated with deteriorating QOL, as evaluated by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, including the summary QOL score, physical function, fatigue, and appetite loss in patients with incurable cancer (14). In patients with MBC, one of the basic goals of treatment is to maintain QOL; if prolonged survival is traded for reduced QOL, it may not be in the patient's best interest. Although our results showed that the occurrence of AEs (grade ≥2) did not differ between patients with GPS 0/1 and GPS 2, patients with GPS 2 had a shorter TTF in comparison to those with GPS 0/1 and discontinued first-line chemotherapy for reasons other than disease progression. One of the reasons for this result could be that AEs and QOL data may have not been recorded in all cases.

In the present study, we showed an association between inflammatory and nutritional markers at baseline and OS in patients with MBC, raising the question whether improvement of the inflammatory and nutritional status after the diagnosis or initiation of treatment could have positive impact on the outcomes of MBC patients. It is known that Western diet with high saturated fatty acid intake and low fiber intake is associated with inflammation and negatively affects the immune system (36). However, it is not yet clear whether anti-inflammatory and nutritional interventions affect the outcomes in patients with MBC.

The present study was associated with some limitations. First, the number of patients was too small to evaluate the results according to the subtype of breast cancer or type of treatment, while the number of patients with GPS 2 was particularly small (4 patients). Moreover, due to the retrospective design of the study, we could not obtain information for all the parameters that could have affected the outcomes of the patients (*e.g.*, AEs, comorbidities, performance status, and other details) from clinical records. In addition, we do not know the exact reason why anticancer therapy was avoided in patients with GPS 2.

To our knowledge, this is the first report on the integrated evaluation of inflammatory, nutritional, and sarcopenia markers in patients with MBC to show that the GPS was an

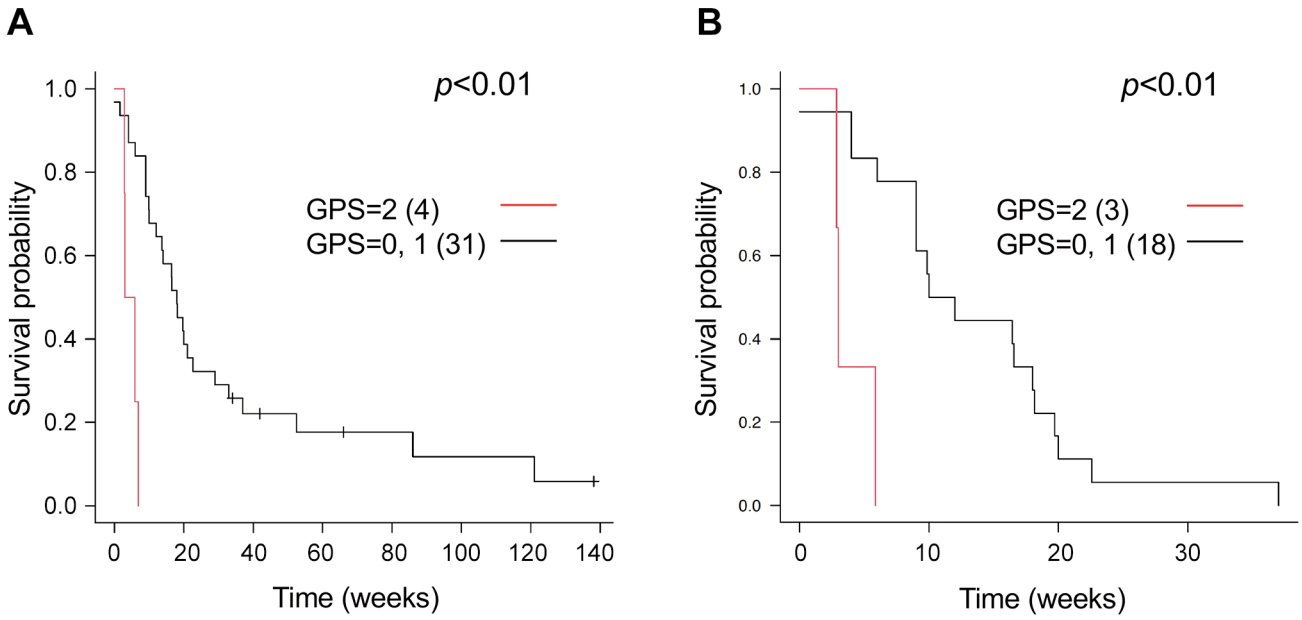

Figure 2. *Comparison of the time to treatment failure of initial therapy between patients with Glasgow prognostic score (GPS) 0/1 and GPS 2. (A) All patients [GPS 2 (n=4) vs. GPS 0/1 (n=31)]. (B) Patients receiving chemotherapy as first-line treatment for metastatic breast cancer [GPS 2 (n=3) vs. GPS 0/1 (n=18)].*

Table III. *Adverse events (grade ≥2) due to chemotherapy.*

Adverse events	GPS score 0/1 (n=18) n (%)	GPS score 2 (n=3) n (%)	*p*-Value
Hematologic adverse events	12 (66.7)	2 (66.7)	1.00
Non-hematologic adverse events	13 (72.2)	1 (33.3)	0.247
Fatigue	3	0	
Anorexia	1	0	
Peripheral neuropathy	8	0	
Increased ALT	2	0	
Arthralgia	2	0	
Nausea	3	1	
Sepsis	1	0	
Edema	2	0	
Diarrhea	2	0	
Myalgia	1	0	
Febrile neutropenia	0	1	

ALT, Alanine aminotransferase.

Table IV. *Reasons for discontinuation of initial chemotherapy in patients receiving chemotherapy as first-line treatment.*

Adverse events	GPS score 0/1 (n=18) n (%)	GPS score 2 (n=3) n (%)	*p*-Value
Progressive disease	12 (66.7)	0	0.526
Other than progressive disease	6 (33.3)	3 (100)	
Adverse events	8	2	
Unknown	4	0	
Bone fracture	1	0	
Decreased ADL	1	0	
Dementia	0	1	

ADL, Activities of daily living.

independent predictive marker. Since the GPS is a simple marker that can be assessed from routine laboratory test results, it is recommended that all cancer patients be routinely screened for the risk or presence of inflammation and malnutrition to predict survival, treatment response, and QOL. Further studies are needed to determine whether anti-inflammatory or nutritional interventions after the diagnosis or the initiation of treatment are useful for improving outcomes.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

K.Y., Y.K.: Data interpretation. K.Y.: Paper writing. K.Y., S.M., A.S., S.O., H.S., Y.K.: Critical revision of the article, writing, review, and editing. K.Y., S.M., A.S., S.O., H.S., Y.K.: final approval.

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