# Prognostic Value of Bone Marrow Metabolism on Pretreatment $^{18}$F-FDG PET/CT in Patients with Metastatic Melanoma Treated with Anti-PD-1 Therapy

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Our purpose was to investigate the prognostic value of $^{18}$F-FDG PET/CT parameters in melanoma patients before beginning therapy with antibodies to the programmed cell death 1 receptor (anti-PD-1). **Methods:** Imaging parameters including $SUV_{max}$, metabolic tumor volume, and the ratio of bone marrow to liver $SUV_{mean}$ (BLR) were measured from baseline PET/CT in 92 patients before the start of anti-PD-1 therapy. The association with survival and imaging parameters combined with clinical factors was evaluated. Clinical and laboratory data were compared between the high-BLR group (>median) and the low-BLR group (≤median). **Results:** Multivariate analyses demonstrated that BLR was an independent prognostic factor for progression-free and overall survival ($P = 0.017$ and $P = 0.011$, respectively). The high-BLR group had higher white blood cell counts and neutrophil counts and a higher level of C-reactive protein than the low-BLR group ($P < 0.05$). **Conclusion:** Patients with a high BLR were associated with poor progression-free and overall survival, potentially explained by evidence of systemic inflammation known to be associated with immunosuppression.

**Key Words**: $^{18}$F-FDG; PET/CT; bone marrow uptake; immunotherapy; melanoma

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Metabolic tumor volume (MTV) and the glucose metabolism of normal tissues associated with immunity on $^{18}$F-FDG PET/CT before and during immune checkpoint inhibitor therapy have been explored as predictors of therapeutic efficacy (*1–4*). The link between $^{18}$F-FDG uptake by immune-mediating tissues, such as the bone marrow (BM) and spleen, and poor cancer outcomes is hypothesized to be explained by generalized inflammation (*5*,*6*).

We hypothesized that imaging parameters, including physiologic uptake in hematopoietic tissues on baseline PET/CT, combined with known clinical prognostic factors for melanoma may be more accurate than clinical factors alone in predicting the therapeutic efficacy and prognosis of melanoma patients treated with antibodies to the programmed cell death 1 receptor (anti-PD-1).

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## MATERIALS AND METHODS

### Patients

Ninety-two melanoma patients who received anti-PD-1 therapy (pembrolizumab or nivolumab) as first-line immunotherapy between April 2012 and June 2019 were enrolled in this retrospective study. The Institutional Review Board approved this study and waived the requirement for obtaining written informed consent.

### $^{18}$F-FDG PET/CT Protocol and Data Analysis

Approximately 1 h after intravenous injection of $^{18}$F-FDG, PET/CT images from the vertex to the toes were acquired per the standard-of-care protocol at our institution using a Discovery 600, 690, 710, or MI scanner (GE Healthcare). $SUV_{max}$, $SUV_{mean}$, MTV, and total lesion glycolysis with an SUV of at least 2.5 were measured for all $^{18}$F-FDG–avid lesions.

Liver and spleen $SUV_{mean}$ were measured by drawing a spheric volume of interest in the center of an area of nondiseased right hepatic lobe (3 cm; Fig. 1A) and spleen (2 cm; Fig. 1C), respectively. For the BM, spheric 1.5-cm volumes of interest were placed within the center of nondiseased L1–L4 vertebral bodies (Fig. 1B), and an average $SUV_{mean}$ was calculated for the lumbar vertebral bodies. Then, the BM-to-liver ratio (BLR) and spleen-to-liver ratio were calculated by dividing the BM $SUV_{mean}$ by the liver $SUV_{mean}$ and the spleen $SUV_{mean}$ by the liver $SUV_{mean}$, respectively (*1*,*7*,*8*).

### Comparison of Clinical Characteristics and Imaging Parameters of Patients with High and Low BLR

To clarify the clinical characteristics of patients with increased BM uptake, patients were classified into a high-BLR group (>median) and a low-BLR group (≤median), and physical data, laboratory data, and imaging parameters were compared between the 2 groups.

### Statistical Analysis

Values were compared between groups using the Mann–Whitney *U* test. Progression-free survival (PFS) was assessed from the start date of immunotherapy to disease progression based on immune-related RECIST (*9*). Overall survival (OS) was assessed from the start date of immunotherapy to death or last follow-up. Cutoffs for age and imaging parameters were set on median values. The patients' cohort was divided into separate groups based on the following parameters: age, sex, primary site, BRAF mutation status, presence of brain metastasis, serum lactate dehydrogenase (LDH) level, and imaging parameters. Factors identified as being significant in the log-rank test ($P < 0.05$) were entered into a multivariate Cox proportional-hazards model. Kaplan–Meier curves were generated for subgroups. The method of Holm was used to adjust the *P* values for multiple comparisons. Spearman rank correlation coefficients were calculated to assess the

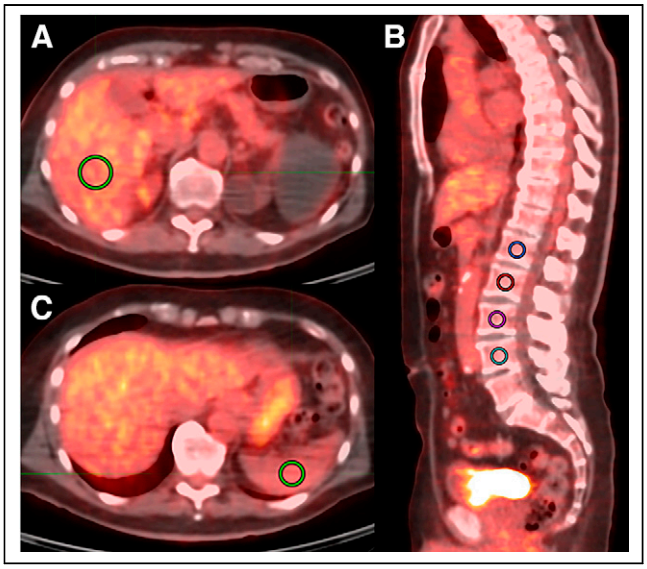


**FIGURE 1.** Illustration of placement of volume of interest in liver (A), L1–L4 vertebral bodies (B), and spleen (C).

relationships between continuous variables. *P* values of less than 0.05 were considered statistically significant.

## RESULTS

### Relationship of $^{18}$F-FDG PET Parameters to PFS and OS

Patient characteristics are summarized in Table 1. After the median follow-up of 18.2 mo, 53 patients had disease progression, and 32 of them died. Median PFS and OS were 11.6 mo (95% CI, 7.1–28.3 mo) and more than 60 mo, respectively. Multivariate analysis based on the results of univariate analysis (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org) demonstrated that BLR and BRAF mutation were independent prognostic factors for PFS ($P = 0.017$ and 0.018, respectively), and BLR, BRAF mutation, and LDH elevation were independent prognostic factors for OS ($P = 0.011$, 0.0078, and 0.013, respectively) (Table 2). Figure 2 shows Kaplan–Meier curves generated for subgroups based on variables significant in multivariate analysis for PFS and OS. The median PFS of the high-BLR (>0.78) group was 8.6 mo (95% CI, 3.0–42.5 mo), significantly shorter than that of the low-BLR group (28.3 mo; 95% CI, 7.7–54.9 mo) ($P = 0.027$). Similarly, the median OS of the high-BLR group was 28.0 mo (95% CI, 17.2–28.7 mo), significantly shorter than that of the low-BLR group (>60 mo) ($P = 0.019$).

### Combining BLR and Clinical Factors

Combining BLR and independent clinical factors (BRAF mutation and LDH elevation) provided further patient stratification. The population was stratified into 3 risk categories: low risk (low BLR and favorable clinical risk factors), intermediate risk (low BLR and unfavorable clinical risk factors or high BLR and favorable clinical risk factors), and high risk (high BLR and unfavorable clinical risk factors). The OS of the high-risk group was significantly worse than that of any other risk group (Fig. 3), and this combined approach to risk stratification differentiated patients according to survival better than BLR or the set of clinical parameters alone. The median OS of patients with a high BLR was 28.0 mo, whereas in patients with a

**TABLE 1**
Patient Characteristics

| Characteristic | Data |
|---|---|
| Patients | 92 |
| Race | |
| White | 79 (85.9%) |
| Hispanic | 8 (8.7%) |
| Asian | 3 (3.3%) |
| Other | 2 (2.2%) |
| Age (y) | 69 (55–76) |
| Male | 55 (59.8%) |
| Primary site | |
| Skin | 74 (80.4%) |
| Other or unknown | 18 (19.6%) |
| BRAF V600 mutation | 24/91 (26.4%) |
| Brain metastasis | 26/91 (28.6%) |
| LDH level > normal | 15/92 (16.3%) |
| Immune checkpoint inhibitors | |
| Pembrolizumab (anti-PD-1 therapy) | 72 |
| Nivolumab (anti-PD-1 therapy) | 9 |
| Nivolumab and ipilimumab (anti-CTLA-4 therapy) | 10 |
| Nivolumab and relatlimab (anti-LAG-3 therapy) | 1 |
| Intervals (d) | |
| Baseline PET to therapy initiation | 33.5 (18–50) |
| Baseline PET and laboratory test | 22 (9–34.3) |

Qualitative data are number and percentage; continuous data are median and interquartile range.

**TABLE 2**
Results of Multivariate Analyses for Predicting PFS and OS

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| Variable | Hazard ratio | 95% CI | *P* | Hazard ratio | 95% CI | *P* |
| High BLR (>0.78) | 2.07 | 1.14–3.77 | 0.017 | 2.85 | 1.28–6.39 | 0.011 |
| BRAF mutation | 2.06 | 1.13–3.75 | 0.018 | 2.71 | 1.30–5.65 | 0.0078 |
| Brain metastasis | 1.85 | 0.99–3.45 | 0.053 | 2.09 | 0.99–4.43 | 0.054 |
| Elevated LDH | 2.00 | 0.90–4.42 | 0.085 | 3.31 | 1.29–8.46 | 0.013 |

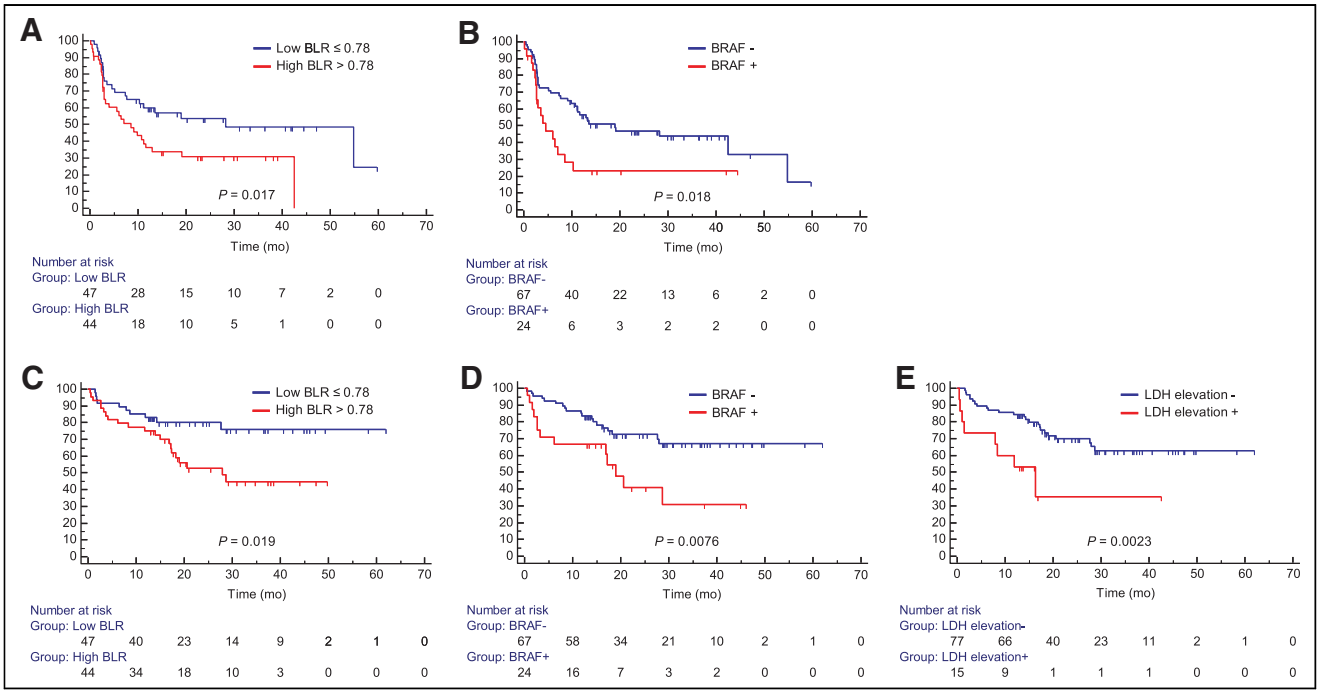


**FIGURE 2.** Kaplan–Meier curves for PFS (A and B) and OS (C–E) divided into 2 groups based on factors identified as being significant in multivariate analysis.

high BLR together with BRAF mutation or LDH elevation, OS was 16.9 and 1.0 mo, respectively.

### Comparison of Clinical Characteristics and Imaging Parameters of Patients with High and Low BLR

The high-BLR group had higher white blood cell, neutrophil, and red blood cell counts; a higher CRP level; a higher MTV; and lower levels of hemoglobin and albumin than the low-BLR group ($P < 0.05$) (Supplemental Table 2). Neutrophil count had the strongest correlation with BLR ($\rho = 0.40$, $P = 0.0002$) among laboratory data, and MTV correlated weakly with BLR ($\rho = 0.34$, $P = 0.0011$) (Supplemental Table 3).

## DISCUSSION

BLR on baseline $^{18}$F-FDG PET showed a significant inverse correlation with PFS and OS in melanoma patients treated with anti-PD-1 therapy. Like previously published studies showing a relationship between laboratory markers of inflammation and BM metabolism (*7*,*10*), we found a significantly positive correlation between $^{18}$F-FDG uptake in the BM and neutrophil count ($\rho = 0.40$) (*11*). This correlation could potentially be explained by the predominance of neutrophils in the BM, the high rates of granulopoiesis required to maintain the neutrophil population, and the preference of neutrophils to use glycolysis for energy production (*11*,*12*). A weak positive correlation between BLR and tumor burden (MTV, $\rho = 0.34$) was also found. An accumulation of inflammatory factors leads to immunosuppression, which is associated with cancer progression and poor outcomes (*5*). In melanoma, BM-derived cells play a key role in tumor progression, neovascularization, and priming of metastasis (*13*,*14*), potentially explaining the negative relationship between BM hypermetabolism and clinical outcomes observed in our study.

By combining information on BRAF and LDH elevation with BLR, we could extract a very poorly prognostic high-risk group with a median OS of 16.9 and 1.0 mo, respectively. We believe that this combination of predictive factors could allow the

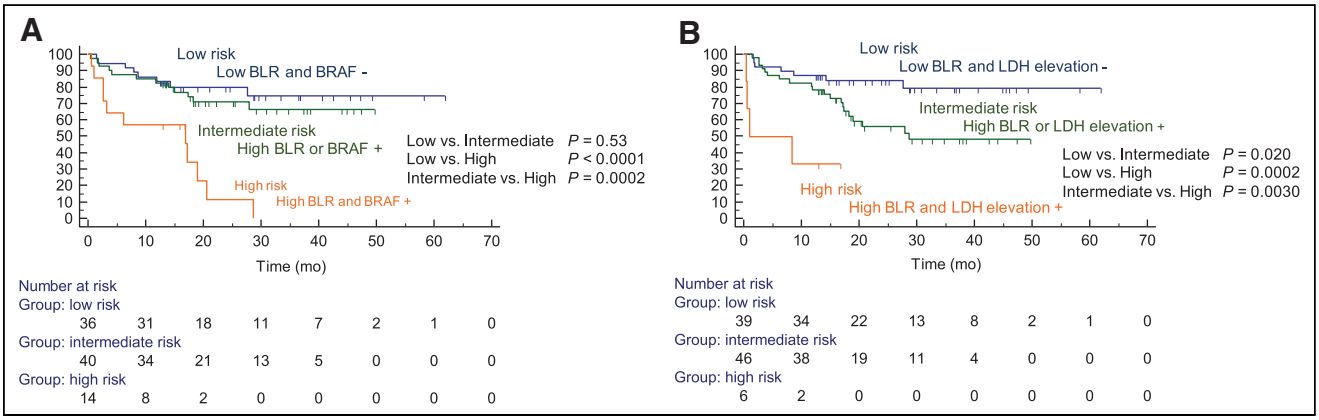


**FIGURE 3.** Kaplan–Meier curves for OS in 3 risk groups stratified according to BLR combined with BRAF mutation (A) or LDH elevation (B).

identification of high-risk patients who are not expected to benefit from anti-PD-1 therapy before treatment, allowing rapid selection of a potentially more efficacious treatment, such as novel therapies targeting cancer-related inflammation (*15*).

A recent retrospective study of 55 melanoma patients before treatment with anti-PD-1 reported the utility of BLR for predicting outcomes (*3*). The difference between the current study and this previous one is that we analyzed a larger number of patients ($n$ = 92) and included patients with brain metastasis. Brain metastasis is not less frequent in patients with advanced melanoma who receive immunotherapy (*16*); in fact, 28.6% of our patients had brain metastasis before immunotherapy. Therefore, we determined that patients with brain metastasis should be included in the search for imaging biomarkers useful for predicting the response to, and the prognosis after, immunotherapy based on real-world clinical scenarios. However, there was a recent report contradicting our finding that melanoma patients who responded to immunotherapy had significantly higher $^{18}$F-FDG uptake in the BM (BM $SUV_{mean}$ normalized by blood-pool activity) than did nonresponders (*17*).

Our study had several limitations. First, it was retrospective. In addition, the use of different PET scanners could have resulted in variability in SUV measurements of the MTV. However, the estimation of BM metabolism was assessed by standardizing values with liver background, allowing for harmonization of the PET features and potential generalizability of our model.

## CONCLUSION

Increased metabolism in the BM was associated with poor PFS and OS, potentially explained by evidence of systemic inflammation known to be associated with immunosuppression.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

**KEY POINTS**

**QUESTION:** Is pretreatment $^{18}$F-FDG uptake in the BM useful in the prognostic evaluation of advanced melanoma patients treated with anti-PD-1 therapy?

**PERTINENT FINDINGS:** Univariate and multivariate analyses revealed that BLR was an independent prognostic factor for PFS and OS ($P$ = 0.017 and 0.011, respectively). Patients with high BLR uptake (>median) tended to have systemic inflammation, known to be associated with immunosuppression.

**IMPLICATIONS FOR PATIENT CARE:** BLR may be a helpful imaging biomarker to select patients with advanced melanoma for immune-modulating therapies

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