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RISK FACTORS AND PROGNOSTIC IMPACT OF SERIOUS IMMUNE-RELATED ADVERSE EVENTS INDUCED BY NIVOLUMAB PLUS IPILIMUMAB COMBINATION THERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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ABSTRACT – *Objective:* Immune checkpoint inhibitor (ICI) combination therapy has higher efficacy than ICI monotherapy but is associated with a high grade 3 or 4 immune-related adverse event (irAE) incidence. Since ICI treatment is performed in outpatient settings, irAE monitoring is challenging. We elucidated risk factors for early irAE detection and prevention.

Patients and Methods: We retrospectively investigated factors related to irAE severity and their impact on survival in patients with non-small cell lung cancer (NSCLC) receiving nivolumab plus ipilimumab at our center from January 2020 to December 2022.

Results: Baseline platelet count and platelet-to-lymphocyte ratio (PLR) were higher in the grade 3 or higher group than in the grade 2 or lower group (median, 314 × 10^3/μL and 288 vs. 227 × 10^3/μL and 150; p = 0.035 and 0.010, respectively). irAE grade and number of multisystem irAEs were positively correlated; 83% of patients in the grade 3 or higher group had multisystem irAEs. Using a PLR cutoff of 204 (determined using receiver operating characteristic curves), all patients with grade 3 or higher irAEs were in the PLR ≥ 204 group, representing 66.7% of patients. Severe irAE presence was associated with prolonged overall survival (OS) (p = 0.081). Progression-free survival and OS were longer in patients with multisystem irAEs than in those without (p = 0.004 and 0.016, respectively).

Conclusions: Multisystem irAEs are associated with a better prognosis in patients with NSCLC receiving nivolumab plus ipilimumab. Determining platelet count and PLR immediately before this regimen may help predict the occurrence of severe irAEs.

KEYWORDS: Immune-related adverse event, Ipilimumab, Nivolumab, Overall survival, Risk factor.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) enhance immunity tumors by reactivating T cells *via* binding to inhibitory receptors or their ligands, which are immune checkpoint molecules[1]. Recently, the efficacy of ICI combination therapy has garnered attention owing to the synergistic effects from drug agents *via* different pathways compared to conventional chemotherapy or ICI monotherapy, and its use is increas-

ing for a variety of cancer types[2]. Although ICIs enhance immune function against tumors, they may cause characteristic side effects known as immune-related adverse events (irAEs), which result from excessive immune responses in normal tissues. irAEs occur in all organs of the body, including the skin and gastrointestinal, endocrine, and nervous systems, and can be severe enough to warrant treatment discontinuation and death[3,4]. The incidence of grade 3 and 4 irAEs has been shown to be higher with ICI combination therapy than with ICI monotherapy[2,5]. Furthermore, as ICI treatment is usually performed in an outpatient setting, it is difficult for healthcare professionals to always monitor the occurrence of irAEs, making it difficult to respond immediately to their occurrence. Given this, it is worthwhile to elucidate risk factors that facilitate early detection and prevention of irAEs, ensuring immediate healthcare intervention and patient safety.

The gut microbiota has been shown to be strongly associated with the development of cardiovascular disease risk factors such as arteriosclerosis, inflammation, obesity, and insulin resistance[6]. It has also been suggested that the diversity and composition of the gut microbiota are associated with increases or decreases in platelet count, an inflammatory parameter[7]. In addition, the composition of the gut microbiota and specific microbial species have been shown to affect the effectiveness of ICIs[8,9], and T cell involvement has also been reported[10]. Furthermore, intestinal microbiota variation has been correlated with the development of immune-related diarrhea in patients with lung cancer treated with anti-programmed cell death 1 (PD-1) antibodies, and the occurrence of grade 3 or higher irAEs has been associated with gut microbiota characteristics in patients receiving combined ICI therapy targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1[11,12].

Recently, inflammatory parameters based on blood components, such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), have been linked to the occurrence and severity of irAEs following nivolumab or pembrolizumab monotherapy in patients with non-small cell lung cancer (NSCLC)[13,14]. PLR and NLR have also been reported to be associated with the occurrence and severity of irAEs in patients with gastric, colorectal, and renal cancers treated with anti-PD-1 antibody monotherapy[15,16]. However, PLR and NLR have not been examined as risk factors for irAEs in ICI combination therapy, which has recently been shown to be effective.

The occurrence of irAEs during ICI treatment is associated with prolonged progression-free survival (PFS) and overall survival (OS)[17,18]. However, only a few studies have been conducted on PFS and OS in ICI combination therapy, and the effect of irAE severity on PFS and OS has been rarely reported to date[19,20]. Here, we explored factors associated with irAE severity and their impact on survival in patients with NSCLC treated with the nivolumab plus ipilimumab combination.

PATIENTS AND METHODS

Patients

We retrospectively collected data from 20 patients with NSCLC who received chemotherapy-free nivolumab plus ipilimumab combination therapy as outpatient treatment at the Osaka International Cancer Institute between January 2020 and May 2022. Patients were discharged after a short hospital stay (mean, 7 days) for monitoring of adverse events and subsequently treated as outpatients. Patients with a diagnosed or suspected infection at treatment initiation, a history of autoimmune disease, those receiving steroids or antibiotics at treatment initiation, those who had received radiation therapy prior to treatment initiation (excluding irradiation of metastatic sites), and those without blood test data obtained immediately before treatment initiation (within 1 week) were excluded. The observation period lasted until the nivolumab plus ipilimumab combination therapy was discontinued, death occurred, or the end of the study period (December 2022). The standard dose of the nivolumab plus ipilimumab combination therapy was 360 mg/body and 1 mg/kg, respectively, every 4 weeks.

Baseline data collected included patient sex, age, smoking index calculated from smoking history, Eastern Cooperative Oncology Group performance status (PS; 0 indicating no symptoms and 1 indicating mild symptoms, on a scale from 0 to 5, with higher scores indicating greater disability), line of treatment (number of previous treatment regimens), cancer stage classification, histopathological diagnosis, programmed death ligand 1 (PD-L1) expression, presence or absence of proton pump inhibitor administration, white blood cell count, neutrophil count, lymphocyte count, platelet count, eosinophil count, basophil count, and drug administration history. Adverse events documented as irAEs in the medical records were evaluated according to the classification of irAEs in cancer immunotherapy guidelines[21]. The severity of irAEs was evaluated according to the Common Terminology Criteria for Adverse Events ver

5.0, in which grade 1 corresponds to mild adverse events, grade 2 to moderate adverse events, grade 3 to severe adverse events, grade 4 to life-threatening adverse events, and grade 5 to death resulting from adverse events. Multisystem irAEs were defined as irAEs involving more than one organ. NLR and PLR were calculated from blood test values measured immediately before nivolumab + ipilimumab administration. Each item was extracted from electronic medical records.

The study was approved by the ethics committees of Kobe Gakuin University (protocol number HEB22-04; August 30, 2022) and the Osaka International Cancer Center (protocol number 22039; June 9, 2022), and was conducted in accordance with the Ethical Guidelines for Medical and Biological Research involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare of Japan. Informed consent was waived due to the study's retrospective nature. Patient anonymity was ensured.

Statistical Analysis

For intergroup comparisons of patient background and each blood test value, the Mann-Whitney *U* test was used for quantitative data comparisons, Fisher's exact probability test was used for qualitative data comparisons between irAE severity, and Spearman's rank correlation matrix was used for correlation analysis. PFS and OS were assessed using the Kaplan-Meier method and compared with irAE severity or the presence and absence of multisystem irAEs using the log-rank test. Statistical significance was set at $p < 0.05$. A receiver operating characteristic (ROC) curve was used to determine the cutoff value for the relationship between PLR and irAE severity. All statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

Patient Characteristics

Of the 20 patients screened, 18 were included in the analysis after excluding 1 patient who had received radiation therapy prior to treatment initiation and 1 who was receiving steroids at treatment initiation. None of the included patients had a diagnosed or suspected infection, a history of autoimmune disease, or were receiving antibiotics at treatment initiation, and none had missing blood test data obtained immediately before treatment initiation.

Patient baseline characteristics are summarized in Table 1. Among the 18 patients, 6 had grade 3 or higher irAEs, 11 had grade 2 or lower irAEs, and 1 had no irAEs (Table 1). There were no significant differences in age, sex, ECOG PS, smoking history, smoking index, line of treatment, stage classification, histology, PD-L1 expression, proton pump inhibitor use, white blood cell count, neutrophil count, lymphocyte count, eosinophil count, basophil count, or NLR between the grade 2 or lower and grade 3 or higher groups. In contrast, platelet count and PLR were significantly higher in the grade 3 or higher group than in the grade 2 or lower group ($p = 0.035$ and $p = 0.010$, respectively). The median (range) treatment duration was 152 (20-499) days in the grade 2 or lower group and 151 (32-336) days in the grade 3 or higher group.

irAEs and Severity of irAEs Observed with Nivolumab plus Ipilimumab Combination Therapy

The irAEs that occurred during the observation period and their grade classifications are shown in Figure 1. Seventeen patients experienced irAEs, of whom 11 (64.7%) had multisystem irAEs. A total of 39 irAEs were recognized, comprising 19 grade 1 irAEs, 13 grade 2 irAEs, and 7 grade 3 irAEs. The most common type of irAE was skin lesions (13 patients), particularly grade 1. Grade 2 lung disorders were the second most common. Skin lesions included rash and/or pruritus, whereas lung disorders included interstitial pneumonia or dyspnea. Grade 3 irAEs were observed in nearly all adverse events. Among the 11 patients with multisystem irAEs, the most common were combined skin and lung disorders in 6 patients, followed by combined skin and gastrointestinal disorders in 4 patients. The relationship between multisystem irAEs and irAE severity is shown in Table 2. In the grade 3 or higher group, 83% of patients had multisystem irAEs. The rank correlation coefficient between the grade of irAEs and the number of irAEs in multiple organs was 0.538, indicating a significant positive correlation ($p < 0.05$) (Figure 2).

Table 1. Baseline characteristics of the patients.

	Grade 2 or lower (n = 12)	Grade 3 or higher (n = 6)	*p*-value
Sex (Male/Female)	11/1	4/2	0.245*
Age	77 (58-88)	76 (56-80)	0.452†
ECOG PS‡ (0-1/2)	10/2	5/0	1.000*
Smoking history (Yes/No)	10/2	4/2	0.569*
Smoking index	970 (0-3,300)	1,060 (0-1,920)	0.851†
Treatment line (1st/≥2nd)	11/1	5/1	1.000*
Stage (I-II/III-IV)	3/9	0/6	0.515*
Histologic type‡ (squamous cell carcinoma/adenocarcinoma)	8/2	3/2	0.560*
PD-L1‡ (<1% / 1-49%)	4/6	1/4	0.600*
Treated with PPI (Yes/No)	5/7	3/3	1.000*
White blood cells (10^3/μL)	7.30 (4.01-12.39)	6.38 (4.04-11.11)	0.607†
Neutrophils (10^3/μL)	4.92 (2.40-9.85)	5.06 (2.18-8.70)	0.888†
Lymphocytes (10^3/μL)	1.41 (0.71-2.57)	1.04 (0.60-1.57)	0.083†
Platelets (10^3/μL)	227 (132-320)	314 (248-446)	0.035†
Eosinophils (/μL)	129 (40-312)	115 (49-226)	1.000†
Basophils (/μL)	34.5 (5.5-76.9)	38.9 (12.8-55.6)	0.888†
NLR	3.18 (1.16-11.10)	5.39 (1.70-8.55)	0.281†
PLR	150 (98-415)	288 (204-677)	0.010†

Qualitative variables are expressed as the number of patients, continuous variables as median (range). ECOG PS: Eastern Cooperative Oncology Group performance status. PPI: proton pump inhibitor. NLR: neutrophil-to-lymphocyte ratio. PLR: platelet-to-lymphocyte ratio. *Fisher's exact test, †Mann-Whitney *U* Test, ‡Excluding unknown.

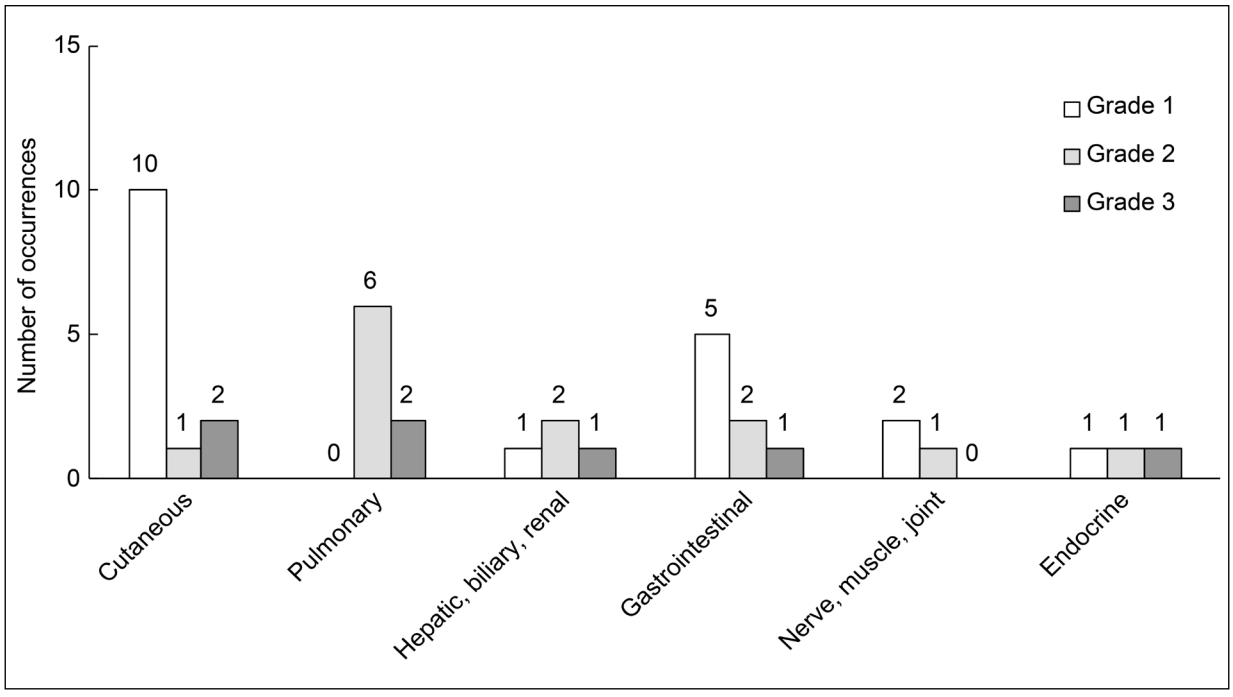

Figure 1. Nivolumab + ipilimumab combination therapy-induced immune-related adverse event (irAE) types and their severity (six types: one patient, five types: one patient, four types: one patient, three types: two patients, two types: six patients).

Table 2. Relationship between multisystem irAEs and severity.

	Grade 2 or lower (n = 12)	Grade 3 or higher (n = 6)
None	6 (50%)	1 (17%)
Multisystem irAEs	6 (50%)	5 (83%)

Each value represents the number of patients (percent).

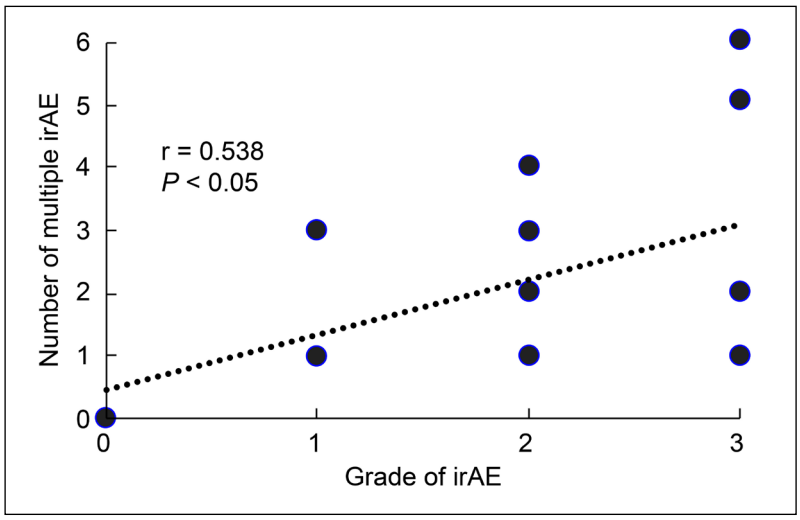

Figure 2. Relationship between the grade and number of immune-related adverse events (irAEs) in multiple organs.

Relationship between PLR and irAE Occurrence

The PLR cutoff value immediately before the start of nivolumab plus ipilimumab therapy in the presence or absence of serious irAEs was calculated to be 204 (sensitivity: 1.00, specificity: 0.25, area under the ROC curve: 0.889, $p < 0.001$) using ROC curve analysis (Supplementary Figure 1). When this PLR cutoff value was used to examine the relationship with irAE severity, only patients with a PLR < 204 had grade 2 or less irAEs, whereas those with a PLR ≥ 204 had grade 3 or higher irAEs, accounting for 66.7% of the study population (Figure 3).

Relationship between irAE Severity and Survival

There was no significant difference in PFS between the grade 3 or higher group and the grade 2 or lower group (Figure 4A). In contrast, the OS tended to be longer in the grade 3 or higher group than in the grade 2 or lower group (Figure 4B). Furthermore, PFS and OS were significantly longer in patients with multisystem irAEs than in those without (Figure 5A, B).

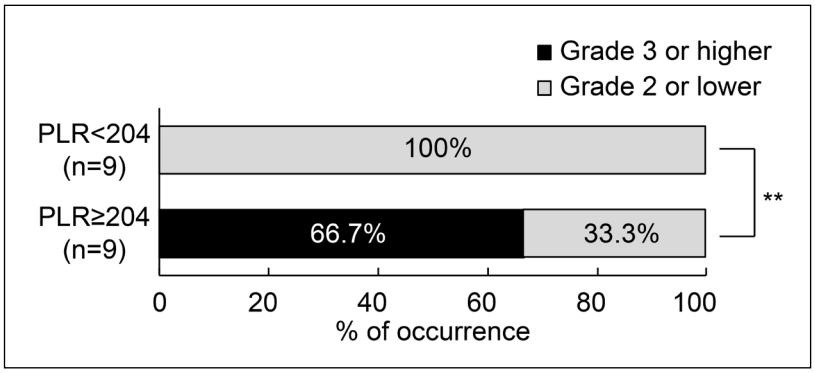

Figure 3. Relationship between platelet-to-lymphocyte ratio and severity of immune-related adverse events (irAEs) $^{**}p < 0.01$ (Fisher's exact test).

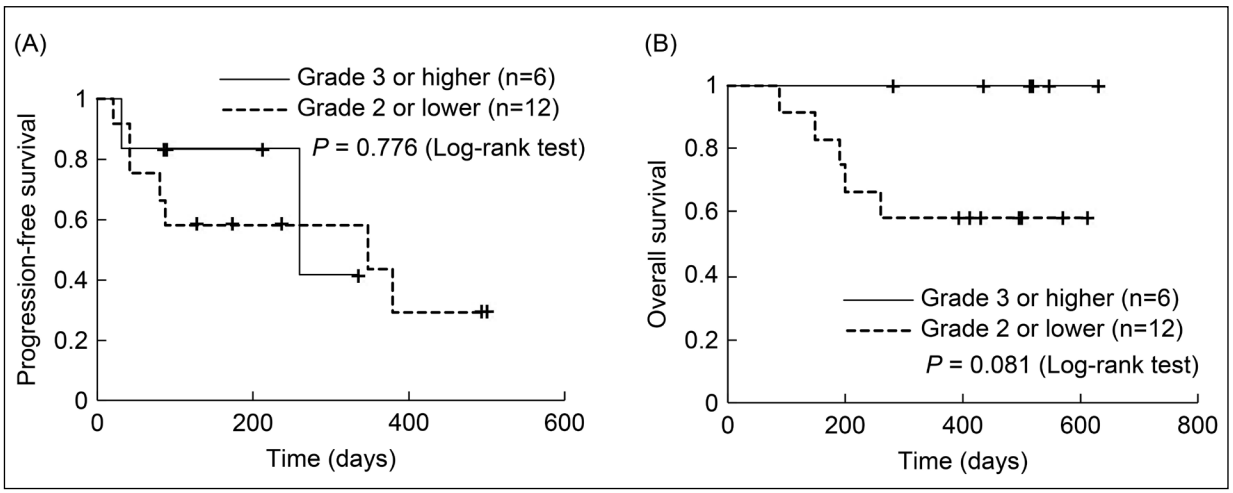

Figure 4. Kaplan-Meier curves for progression-free survival *(A)* and overall survival *(B)* based on immune-related adverse event (irAE) severity.

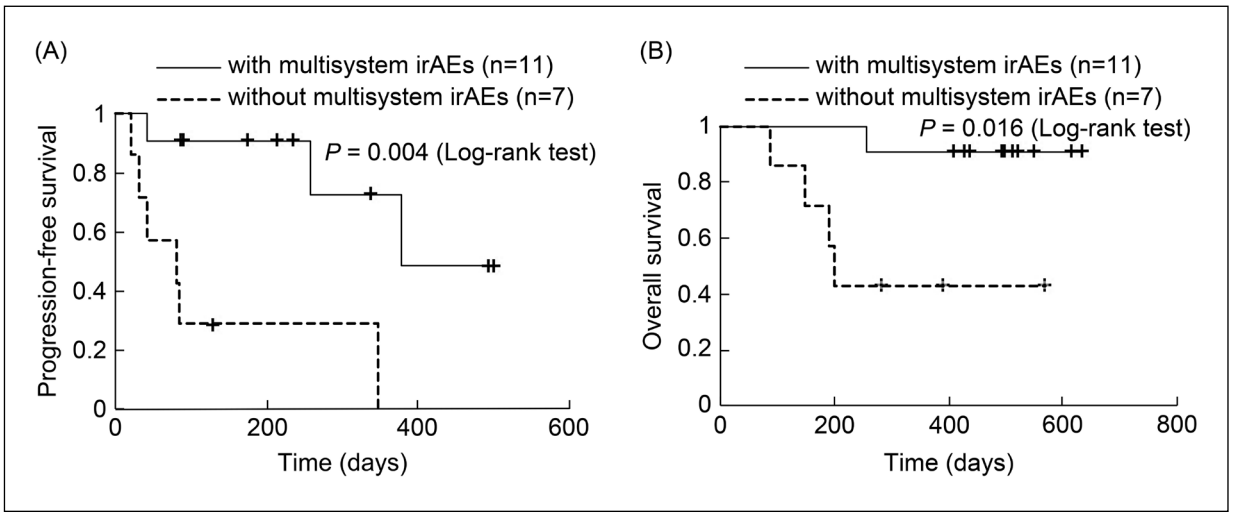

Figure 5. Kaplan-Meier curves for progression-free survival *(A)* and overall survival *(B)* based on multisystem immune-related adverse events (irAEs).

DISCUSSION

The management of irAEs that may lead to treatment discontinuation or death is important in ICI therapy. In this study, we explored factors associated with the severity of irAEs and their impact on survival in patients treated with nivolumab plus ipilimumab, which has been shown to have better efficacy but a higher incidence of high-grade irAEs than ICI monotherapy[2,5]. Herein, 33.3% of patients had grade 3 or higher irAEs. In a racially diverse clinical trial, the incidence of irAEs was 32.8% when nivolumab plus ipilimumab was administered to patients with NSCLC[2], similar to the incidence observed in the present study. The most frequent multiorgan irAEs observed in the present study were skin and lung disorders, followed by skin and gastrointestinal disorders.

Shankar et al[22] reported that the most common combination of irAEs in monotherapy with anti-PD-1/PD-L1 antibodies is pulmonary inflammation and thyroiditis, followed by hepatitis and thyroiditis, dermatitis and pulmonary inflammation, and dermatitis and thyroiditis. The most common irAE combination from combination therapy with an anti-CTLA-4 antibody or chemotherapy is diarrhea/colitis and dermatitis[22]. In addition, a high incidence of thyroiditis, an endocrine disorder, was observed in Shankar et al[22], in contrast to the results of the present investigation. Therefore, when used in combination with

ICI therapy, the concurrent occurrence of skin and lung disorders or skin and gastrointestinal disorders may be most frequent. A significant positive correlation between the grade of irAE and the number of irAEs across multiple organs, especially in the grade 3 or higher group, was observed in the current study, with 83% of patients having multisystem irAEs. Therefore, when multisystem irAEs are observed, preventing serious complications through close observation and prompt response is useful.

In this study, platelet counts and PLR at the start of ICI administration were significantly higher in the grade 3 or higher group than in the grade 2 or lower group. Similarly, in a study involving the first-line treatment of NSCLC with anti-PD-1/PD-L1 antibody monotherapy, including chemotherapy, significantly higher platelet counts and PLR at the start of ICI administration were reported in the irAE-positive group than in the irAE-negative group[23]. Cancer cells may utilize various mechanisms to affect platelet production and activation, and platelets are involved in cancer metastasis and immune escape[24,25]. Additionally, podoplanin, which is highly expressed in various malignant tumors, is involved in platelet aggregation and promotes cancer-related thrombosis and inflammatory thrombosis[26]. Platelets enhance the immune response of CD8-positive T cells, and CD8-positive T cell infiltration has been reported in tissues where irAEs occur[27-29]. Therefore, platelet counts may increase following the development of cancer, and the involvement of T cells in irAE expression may be speculated. PLR has been well-investigated as a biomarker for predicting efficacy and adverse effects. Therefore, we obtained a PLR cutoff value (204) from the ROC curve and examined the relationship between PLR ≥ 204 and irAE severity. There was a significant difference between a PLR ≥ 204 and a PLR < 204, with the former associated with all patients with grade 3 or higher irAEs. In Japan, the incidence of irAEs is significantly higher in patients with a PLR ≥ 191 than in those with a PLR < 191 following nivolumab monotherapy, and a PLR > 165 is significantly associated with an increased risk of irAEs during pembrolizumab monotherapy in patients with NSCLC[13,14]. In contrast, a study in the USA that included approximately 20% of patients treated with the combination of nivolumab and ipilimumab (mainly anti-PD-1/PD-L1 antibodies) reported that platelet counts and PLR were significantly lower in the irAE group that required hospitalization than in the other groups[30]. However, the study did not exclude steroid-treated patients or those with infections, nor did it report the incidence of irAEs. Similarly, studies in China[31] and Italy[32] have reported an association between low platelet counts and low PLR with serious irAEs in patients treated with pembrolizumab or nivolumab monotherapy with anti-PD-1 antibodies, and that patients treated with pembrolizumab, nivolumab, or atezolizumab monotherapy with a PLR < 180 have a higher incidence of irAEs than those with a PLR >180. Comparing the present findings with these reports is difficult because of differences in the irAEs observed and in patient backgrounds, such as patients receiving systemic steroids and those with infections not being excluded. Nevertheless, this is currently the only study on nivolumab plus ipilimumab combination therapy. Further studies with a larger number of patients are needed to validate our findings.

Because ICI treatment is usually performed in outpatient settings, monitoring and responding to irAE occurrence are difficult. Thus, elucidating risk factors for early detection and prevention of irAEs, ensuring immediate healthcare intervention, and protecting patient safety are important. In this study, there was no significant difference in PFS between the grade 2 or lower and grade 3 or higher groups; however, there was a trend toward prolonged OS in the grade 3 or higher group. A previous study[33] that included monotherapy as well as nivolumab + ipilimumab combination therapy reported that OS is significantly longer in patients with grade 3-4 irAEs than in other patients. In contrast, another study[19] reported no significant difference in PFS or OS across irAE severity levels in patients with NSCLC treated with nivolumab plus ipilimumab, including some patients treated with platinum drugs. As 83% of patients in the grade 3 or higher group had multisystem irAEs and there was a correlation between irAE severity and the number of multiorgan irAEs, we also compared survival with and without multisystem irAEs. Consequently, PFS and OS were significantly prolonged in the group with multiorgan irAEs. In patients with NSCLC treated with anti-PD-1/PD-L1 antibody monotherapy or in combination with an anti-CTLA-4 antibody or chemotherapy, those with multisystem irAEs show significantly prolonged PFS and OS[22]; the same has been reported in patients with hepatocellular carcinoma[34]. Additionally, many patients who develop irAEs have a favorable prognosis[17,18]. In this study, there was no significant difference in PFS between the grade 3 or higher and grade 2 or lower groups, but there was a significant difference in PFS between patients with and without multisystem irAEs. Therefore, the occurrence of certain systemic irAEs associated with ICI administration may have a favorable prognostic impact.

This was a single-center retrospective study with a limited population of 18 patients. Additionally, the median treatment duration was only 152 and 151 days in the grade 2 or lower and grade 3 or higher groups, respectively. Moreover, as patients started treatment between January 1, 2020, and May 31, 2022, some had an observation period of only 6 months, considering that the end date of the study period was December 31, 2022. Therefore, these findings should be interpreted with caution, and further studies are needed to increase the number of patients and extend the observation period.

The findings of this study suggest that multisystem irAEs are associated with better prognosis in patients with NSCLC treated with nivolumab plus ipilimumab combination therapy and that the determination of platelet count and PLR immediately before administration may be predictors of irAE severity. These laboratory parameters, routinely tested in patients undergoing cancer drug therapy, are inexpensive and convenient biomarkers. Therefore, we believe that monitoring focused on these factors will contribute to the early detection of and response to serious irAEs and improvement of prognosis.

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Authors' Contributions:
Akitoshi Tatsumi, Koki Nozawa, Yukio Kadokawa, and Mari Takagi conceived and designed the study. Akitoshi Tatsumi, Koki Nozawa, and Kana Funatomi acquired the data and analyzed the results. Akitoshi Tatsumi and Koki Nozawa wrote the manuscript. Yukio Kadokawa, Satoshi Hasegawa, Kenji Takeda, and Mari Takagi revised the manuscript. All authors reviewed the manuscript.

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Conflict of interest:
The authors declare that they have no conflict of interest to disclose.

Data Availability Statement:
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval:
The study was approved by the Ethics Committees of Kobe Gakuin University (protocol number HEB22-04; August 30, 2022) and the Osaka International Cancer Center (protocol number 22039; June 9, 2022), and was conducted in accordance with the Ethical Guidelines for Medical and Biological Research involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare of Japan and Declaration of Helsinki and its later amendments.

Informed Consent:
The requirement for informed consent was waived owing to the retrospective nature of the study. Patient anonymity was ensured.

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