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Immune Checkpoint Inhibitor Score Predicts Survival Benefit of Immunotherapy in Patients with Non-small Cell Lung Cancer

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Abstract

Background: The use of immune checkpoint inhibitors (ICIs) in patients with advanced lung cancer is increasing. Despite ongoing studies to predict the efficacy of ICIs, its use in clinical practice remains difficult. Thus, we aimed to discover a predictive marker by analyzing blood cell characteristics and developing a scoring system for patients treated with ICIs.

Methods: This was a prospective multicenter study in patients with advanced non-small cell lung cancer (NSCLC) who received ICIs as second-line treatment from June 2021 to November 2022. Blood cell parameters in routine blood samples were evaluated using an automated hematology analyzer. Immune checkpoint inhibitor score (IChIS) was calculated as the sum of neutrophil count score and immature granulocyte score.

Results: A total of 143 patients from four institutions were included. The treatment response was as follows: partial response, 8.4%; stable disease, 37.1%; and progressive disease, 44.8%. Median progression-free survival and overall survival after ICI treatment was 3.0 and 8.3 months, respectively. Median progression-free survival in patients with an IChIS of 0 was 4.0 months, which was significantly longer than 1.9 months in patients with an IChIS of 1 and 1.0 month in those with an IChIS of 2 (p=0.001). The median overall survival in patients with an IChIS of 0 was 10.2 months, which was significantly longer than 6.8 and 1.8 months in patients with an IChIS of 1 and 2, respectively (p<0.001).

Conclusion: Baseline IChIS could be a potential biomarker for predicting survival benefit of immunotherapy in NSCLC.

Keywords: Immune Checkpoint Inhibitor; Biomarker; Lung Cancer

Introduction

The development of immune checkpoint inhibitors (ICIs) has significant shifted the paradigm in lung cancer treatment, demonstrating a survival benefit[1]. The use of ICIs has increased not only in advanced lung cancer but also in the early stages[2]. As such, almost all lung cancer patients now receive ICI treatment. When

ICIs were first developed, a favorable efficacy of ICIs and survival benefit was expected for patients with advanced lung cancer. However, such effects were observed only in a very small percentage of patients, with the majority experiencing primary or acquired resistance[3]. Thus, predicting a favorable and long-lasting efficacy is difficult because durable responses are only observed in a few individuals. Currently, the selection of ICI drugs is based on the expression of tumor programmed death-ligand 1 (PD-L1)[4]. However, the actual predictive accuracy based on PD-L1 expression remains low[5]. Hence, a clinically applicable biomarker for predicting the efficacy of ICIs is lacking.

In lung cancer immunotherapy research, various biomarkers are under investigation, with an extensive focus on host-related biomarkers[6]. Circulating immune cells, which reflect systemic inflammation, and not just immune cells within the tumor microenvironment (TME), are known to play a significant role in determining the efficacy of ICIs[7]. Commonly known markers such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have shown significant differences in progression-free survival (PFS) and overall survival (OS) in various cancer types upon ICI treatment[8,9]. Neutrophils, which are closely associated with immune system regulation in cancer patients, are being considered as a potential biomarker[10]. The heterogeneity of the neutrophil population is related to both pro- and antitumor characteristics, and immature neutrophils are known to be associated with cancer progression[11,12]. ICIs bind to the programmed cell death protein 1 (PD-1) receptor or PD-L1, allowing activated T cells to combat tumor cells by inhibiting the binding of the PD-1 ligand on tumor cells to PL-L1 on immune cells[13]. Therefore, lymphocytes also play a crucial role in cancer immunotherapy[14]. Circulating neutrophils, as well as neutrophils in the TME, are important for the prognosis in patients with lung cancer treated with ICIs[15]. The NLR, as a ratio of circulating immune blood cells, is a simple representative laboratory parameter that helps predict the prognosis of ICI treatment in patients with lung cancer[8]. However, variations in cut-off values across studies limit its clinical application[8,16].

An intensive care infection score (ICIS) was developed by Sysmex (Kobe, Japan) as a novel marker for prediction of infection and its severity in patients with sepsis[17,18]. In these studies, the complete blood count (CBC) is determined using an automated hematology analyzer and a score based on various indicators is calculated to determine the likelihood of sepsis. ICIS includes parameters that consider not only the neutrophil and immature granulocyte (IG) counts but also the characteristics of neutrophils and lymphocytes[17]. Thus, ICIS enables evaluation of indicators beyond those that can be observed in the actual CBC results. To date, there have been no studies conducted using ICIS in patients with malignancy or non-infectious diseases other than infectious diseases such as sepsis or pneumonia. We hypothesized that since blood neutrophil count and NLR are well known as prognostic factors for ICI treatment, the ICIS index, which reflects not only neutrophil and IG counts but also neutrophil and lymphocyte characteristics, may be helpful to predict treatment response and prognosis in patients treated with ICIs.

In this study, we aimed to investigate the role of ICIS parameters, determined using an automated hematology analyzer, and develop a new scoring system for predicting the prognosis of ICI treatment in non-small cell lung cancer (NSCLC) patients.

Materials and Methods

1. Patients and treatment

This prospective multicenter study included patients with advanced NSCLC who were treated with PD-1/PD-L1 inhibitors as a second-line treatment at Chungnam National University Hospital (CNUH) (Daejeon, Korea), Asan Medical Center (AMC) (Seoul, Korea), Chonnam National University Hwasun Hospital (CNUHH) (Hwasun, Korea), or Pusan National University Yangsan Hospital (PNUYH) (Yangsan, Korea) from June 2021 to November 2022. Patients were intravenously administered nivolumab (3 mg/kg of body weight, every 2 weeks), pembrolizumab (200 mg, every 3 weeks), or atezolizumab (1,200 mg, every 3 weeks) as a second-line treatment. Treatment was continued until the patient experienced serious adverse effects (AEs), had confirmed investigator-assessed disease progression, or withdrew their consent. Peripheral blood was collected from the patients before treatment (day 0) and at the first response evaluation after receiving the PD-1/PD-L1 inhibitor.

2. Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of each participating institution (2020-10-077 at CNUH, 2021-0705 at AMC, CNUHH-2021-042 at CNUHH, and 05-2021-065 at PNUYH). All patients were required to provide written informed consent before participating in this study.

Table 1. Baseline characteristics and efficacy outcomes in all patients (n=143)

Variable	Value
Age, yr	67.7±7.7
Sex	
Male	120 (83.9)
Female	23 (16.1)
Smoking status	
Never	30 (21.0)
Former/Current	109 (76.2)
Unknown	4 (2.8)
ECOG performance	
1	124 (86.7)
2	16 (11.2)
3	3 (2.1)
Disease stage at diagnosis	
IA	2 (1.4)
IB	4 (2.8)
IIA	3 (2.1)
IIB	6 (4.2)
IIIA	13 (9.1)
IIIB	11 (7.7)
IIIC	9 (6.3)
IVA	36 (25.2)
IVB	57 (39.7)
Histology	
Squamous cell carcinoma	59 (41.3)
Adenocarcinoma	70 (49.0)
NSCLC NOS	8 (5.6)
Other	6 (4.2)
PD-L1 expression*	
No (TPS <1%)	52 (36.4)
Low (TPS 1%–49%)	39 (27.3)
High (TPS ≥50%)	51 (35.7)
Agent	
Nivolumab	9 (6.3)
Pembrolizumab	45 (31.5)
Atezolizumab	89 (52.2)
Response to treatment	
PR	12 (8.4)
SD	53 (37.1)
PD	64 (44.8)
Not evaluable	14 (9.8)
Immune-related AE	
No	57 (39.9)
Yes	86 (60.1)

Values are presented as mean±standard deviation or number (%).
*The classification of subgroups according to PD-L1 expression was based on the results of the 22C3 pharmDx assay, and patients without 22C3 pharmDx assay results were classified based on the SP263 assay.
ECOG: Eastern Cooperative Oncology Group; NSCLC NOS: non-small cell lung cancer no otherwise specified; PD-L1: programmed death-ligand 1; TPS: tumor proportion score; PR: partial response; SD: stable disease; PD: progressive disease; AE: adverse events.

3. PD-L1 expression

The expression of PD-L1 was assessed using qualitative immunohistochemical (IHC) staining with the *in vitro* diagnostic PD-L1 IHC 22C3 pharmDx test (Agilent Technologies, Santa Clara, CA, USA) on a Dako Autostainer (Dako, Carpinteria, CA, USA) and PD-L1 IHC SP263 test on the Ventana BenchMark platform (Ventana Medical Systems, Tucson, AZ, USA). The percentage of immunoreactive tumor cells was quantified according to the manufacturer's recommendations. Cancer cells were considered positive when any cell membrane staining was present, and exclusively cytoplasmic immunoreactions were ignored. Staining of immune cells was also disregarded. The expression of PD-L1 was determined based on the percentage of viable tumor cells showing partial or complete membrane staining (tumor proportion score [TPS])[19]. Three categories of PD-L1 expression were designed according to TPS cut-offs of 1% and 50%: no (<1%), low (1%–49%), and high (≥50%) PD-L1 expression. The classification of subgroups according to PD-L1 expression was based on the results of the 22C3 pharmDx assay, and patients without 22C3 pharmDx assay results were classified based on the SP263 assay.

4. ICIS

For the ICIS measurement, blood was collected from enrolled patients in a K3EDTA tube (Greiner Bio-One, Kremsmünster, Austria) before ICI treatment. ICIS parameters were measured on a modified fluorescence flow hematology analyzer with fully automated gating (Sysmex)[20]. Samples from CNUHH were sent to CNUH for analysis, and three institutions, CNUH, AMC, and PNUYH, used the same XN-series hematology analyzer. The ICIS comprises five blood cell-derived parameters

that characterize the innate immune response. The five parameters include the mean fluorescence intensity of mature (segmented) neutrophils (NEUT-SFL), difference in hemoglobin concentration between newly formed and mature red blood cells (Delta-He), total segmented neutrophil count (#NEUT), antibody secreting lymphocytes (#ASL), and accurate IG count (#IG), as previously described[17]. Each parameter is evaluated using a standard routine method and can be measured within 1 minute, without sample preparation, on a modified fluorescence flow hematology analyzer with fully automated gating (Sysmex)[17]. We used the previously reported cut-off values for each parameter (Supplementary Table S1). The previously reported ICIS score calculation method is divided into 1, 2, and 4 points according to the cut-off representing the best area under the curve, 85% specificity, and 95% specificity for each of the five parameters. The total ICIS score ranges from a minimum of 0 to a maximum up to 20 points (Supplementary Table S2).

5. Treatment response, adverse events, and survival analysis

The response was assessed with computed tomography every three cycles for patients treated with pembrolizumab or atezolizumab, and every four cycles for those treated with nivolumab. The response was assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Immune-related AEs (irAEs) were defined as dysimmune toxicities caused by immune system imbalance; these toxicities mainly involved the skin, gut, liver, endocrine glands, or lungs, but could affect any tissue. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. PFS was defined as the time from the date of the first ICI treatment to the date of documented progression or death from any cause. OS was measured from the date of the first ICI treatment to the date of death or the last day of follow-up.

6. Statistical analysis

The chi-square test and independent t-test were used to analyze differences in the clinicopathological data of the patients. Survival was estimated using the Kaplan-Meier method, and survival rates were compared using the log-rank test. Multivariate analysis of the independent prognostic factors for survival was performed using the Cox proportional hazard regression model with a 95% confidence interval (CI). A $p<0.05$ was considered statistically significant. The SPSS program version 22 (IBM Co., Armonk, NY, USA) was used for all statistical analyses.

Results

1. Patient baseline characteristics

A total of 143 patients were enrolled in the study—37 at CNUH, 48 at AMC, 41 at CNUHH, and 17 at PNUYH. The baseline characteristics and efficacy outcomes of ICI treatment are summarized in Table 1. Most patients were male and former or current smokers. The major histological types were adenocarcinoma (49.0%) and squamous cell carcinoma (41.3%). The stage at diagnosis varied, but most patients had stage III or IV NSCLC, and all had recurred or advanced state before ICI treat-

Figure 1. Progression-free survival (PFS) and overall survival (OS) curve in total patients. (A) The median PFS in total patients was 89 days (95% confidence interval [CI], 56.3 to 121.7). (B) The median OS in total patients was 250 days (95% CI, 197.4 to 302.6).

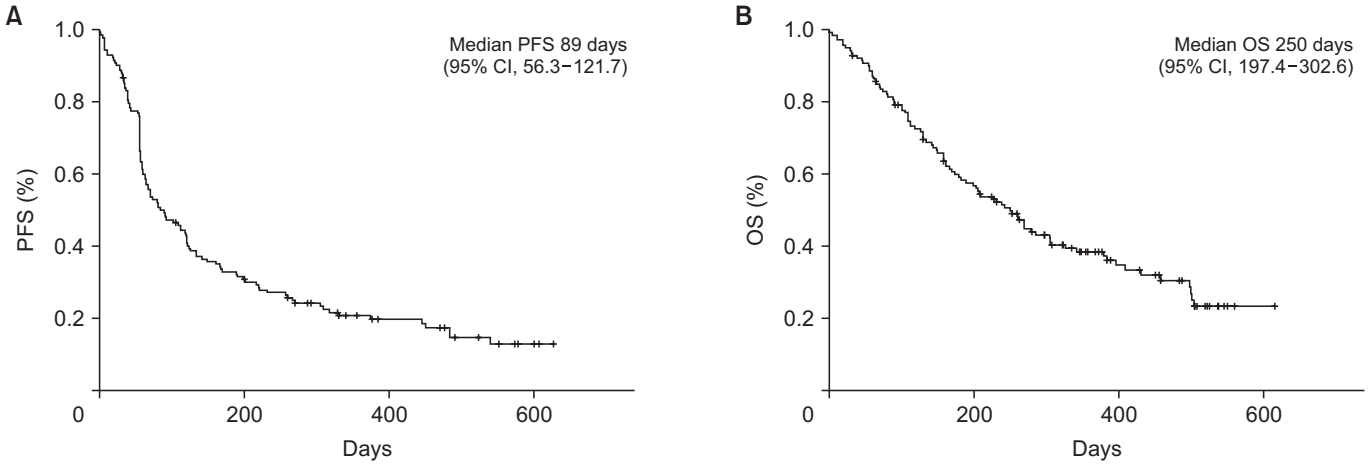

Figure 2. Distribution of intensive care infection score (ICIS) and progression-free survival (PFS) according to ICIS in the total population. (A) ICIS values ranged from 0 to 9 points in all the patients. (B) The median PFS in patients with ICIS 0 was 134 days, which was significantly longer than 67 days in patients with ICIS ≥1 (p=0.005).

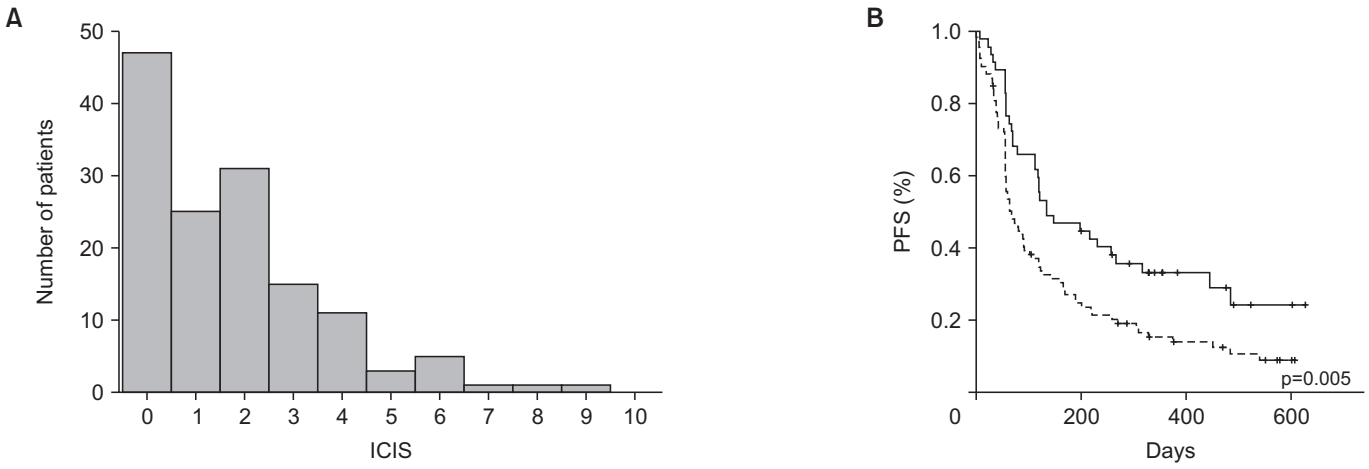

Figure 3. Progression-free survival (PFS) according to intensive care infection score parameters. PFS according to (A) fluorescence intensity of mature (segmented) neutrophils (NEUT-SFL), (B) total segmented neutrophil count (#NEUT), (C) accurate immature granulocyte count (#IG), (D) antibody secreting lymphocytes (#ASL), and (E) hemoglobin concentration between newly formed and mature red blood cells (Delta-He).

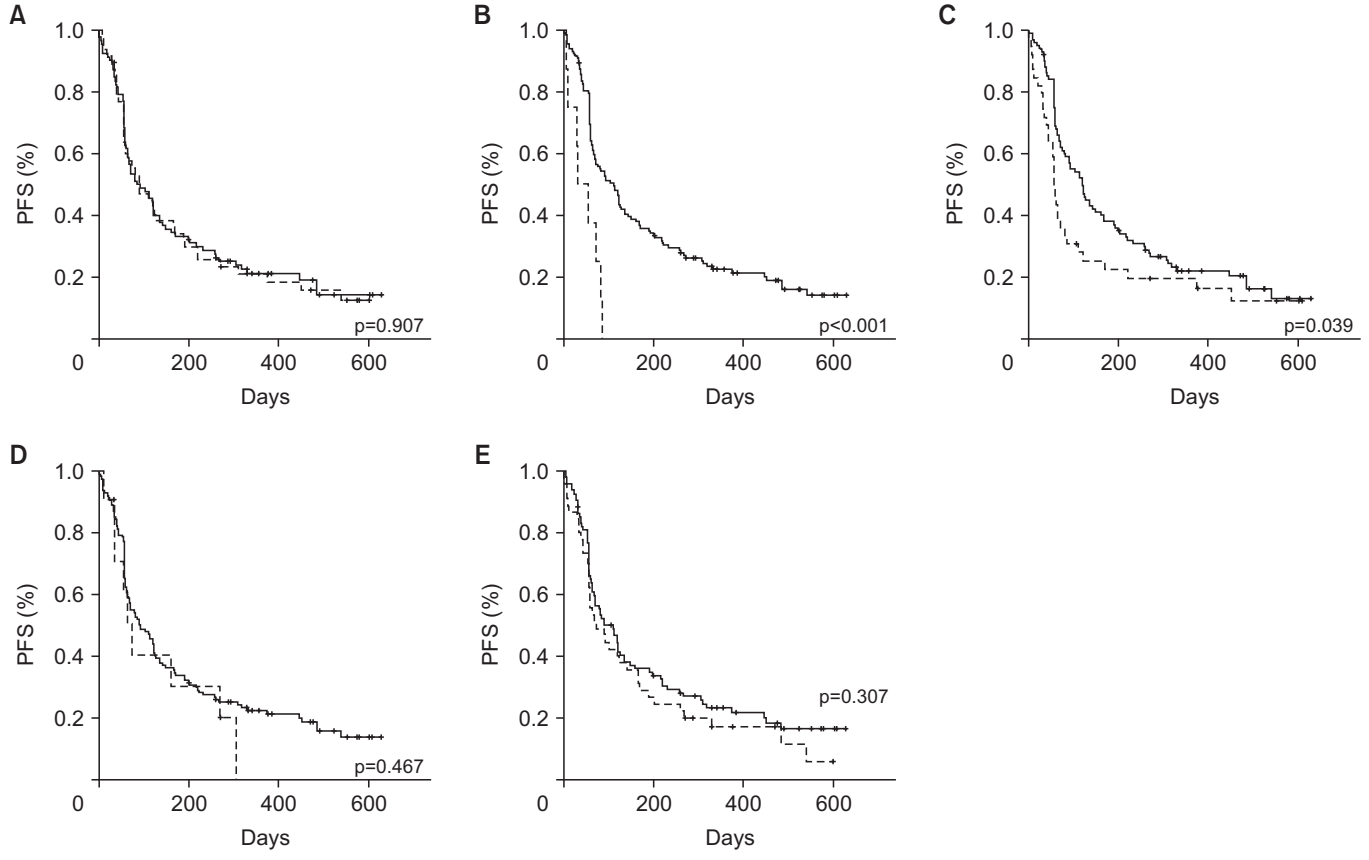

Table 2. Immune checkpoint inhibitor score

Parameter	Cut-off value*	Score
A. NEUT#, cells/μL	>9,000	1
	≤9,000	0
B. Immature granulocyte#, cells/μL	>80	1
	≤80	0
ICHIS=A score+B score		0–2

*The cut-off value was set equal to the previously reported cut-off for the intensive care infection score, which was determined to be the best area under the curve value in sepsis patients.
NEUT#: total segmented neutrophil count; ICHIS: immune checkpoint inhibitor score.

Table 3. Univariate and multivariate analysis for progression-free survival

Variable	Median (95% CI), day	Univariate (p-value)	Multivariate (p-value, HR)
Age, yr		0.787	
<70	81 (36.9–125.1)		
≥70	89 (40.2–137.8)		
Gender		0.090	
Male	84 (41.5–126.5)		
Female	89 (48.3–129.7)		
Smoking status		0.814	
Never	91 (49.4–132.6)		
Former or current	73 (37.1–108.9)		
ECOG		0.210	
0–1	102 (66.0–138.0)		
≥2	63 (45.5–80.5)		
Histology		0.516	
SqCC	67 (54.1–80.0)		
Non-SqCC	92 (62.5–121.5)		
PD-L1 expression		<0.001	0.279
No (TPS <1%)	58 (46.2–69.8)		
Low (TPS 1%–49%)	64 (43.0–85.0)		
High (TPS ≥50%)	167 (0.0–346.5)		
Agent		<0.001	0.414
Nivolumab	190 (67.3–312.7)		
Pembrolizumab	169 (0.0–410.5)		
Atezolizumab	60 (52.8–67.2)		
ICHIS		0.001	0.011
0	120 (85.8–154.2)		
1	58 (49.8–66.2)		HR, 1.239 (0.780–1.968)
2	30 (0.0–64.6)		HR, 3.213 (0.493–6.912)

CI: confidence interval; HR: hazard ratio; ECOG: Eastern Cooperative Oncology Group; SqCC: squamous cell carcinoma; PD-L1: programmed death-ligand 1; TPS: tumor proportion score; ICHIS: immune checkpoint inhibitor score.

ment. A total of 36.4% (52/143) of the patients had no expression of PD-L1, 27.3% (39/143) had low expression, and 35.7% (51/143) had high expression. Among the different ICIs, 6.3% (9/143) patients received nivolumab, 31.5% (45/143) received pembrolizumab, and 52.2% (89/143) received atezolizumab.

2. Treatment outcome and survival analysis

The objective response rate to ICI treatment was 8.4% (12/143) and the disease control rate was 45.5% (65/143). All grade irAEs occurred in 60.1% of the patients. The median PFS after ICI treatment in total patients was 89 days (95% CI, 56.3 to 121.7) (Figure 1A). The median OS after ICI treatment in total patients was 250 days (95% CI, 197.4 to 302.6) (Figure 1B).

3. ICIS and immune checkpoint inhibitor score

The distribution of ICIS among the patient population is shown in Figure 2A. ICIS values ranged from 0 to 9 points. PFS showed a significant difference when divided based on the median value of 1 (134 days vs. 67 days, p=0.005) (Figure 2B). To determine which of the five parameters included in ICIS affect PFS for ICI treatment, PFS analysis was performed according to the score for each parameter (Figure 3). A significant difference in PFS depending on the total segmented neutrophil count (109 days vs. 30 days, p<0.001) (Figure 3B) and accurate IG count (120 days vs. 56 days, p=0.039) (Figure 3C) was noted. However, no significant difference in PFS depending on the mean fluorescence intensity of mature (segmented) neutrophils, difference in hemoglobin concentration between newly formed and mature red blood cells, and antibody secreting lymphocytes score was observed (Figure 3A, D, E). Based on these results, we defined immune checkpoint inhibitor score (IChIS) as the sum of the scores of two meaningful parameters using the cut-off value, as previously reported for ICIS (Table 2).

4. Survival analysis according to IChIS

In univariate analysis, PD-L1 expression on tumor cells, type of agent, and IChIS were associated with a longer PFS (Table 3). In multivariate analysis using the Cox regression model, IChIS was the only significant independent factor associated with PFS. The median PFS after ICI treatment in patients with IChIS 0 was 120 days (95% CI, 85.8 to 154.2), which was significantly longer than that in patients with IChIS 1 (58 days; 95% CI, 49.8 to 66.2) and IChIS 2 (30 days; 95% CI, 0.0 to 64.6) (Figure 4A). In univariate analysis, Eastern Cooperative Oncology Group (ECOG) performance status, type of agent, and IChIS were associated with a longer OS (Table 4). In multivariate analysis using the Cox regression model, ECOG performance status and IChIS were the significant independent variables associated with OS. The median OS after ICI treatment was 305 days (95% CI, 203.1 to 406.9) in patients with IChIS 0 and 203 days (95% CI, 68.2 to 337.8) in those with IChIS 1, which were significantly longer than 54 days (95% CI, 0.0 to 126.1) in patients with IChIS 2 (p<0.001) (Figure 4B).

Discussion

This is the first report on a scoring system for predicting the prognosis of ICI treatment based on blood cell parameters, evaluated using an automated hematology

Figure 4. Multivariate Cox's proportional hazards regression model for progression-free survival (PFS) and overall survival (OS) according to Immune checkpoint inhibitor score (IChIS). (A) PFS according to IChIS in all patients (n=140). (B) OS according to IChIS in all patients (n=140). mPFS: medianPFS; mOS: medianOS.

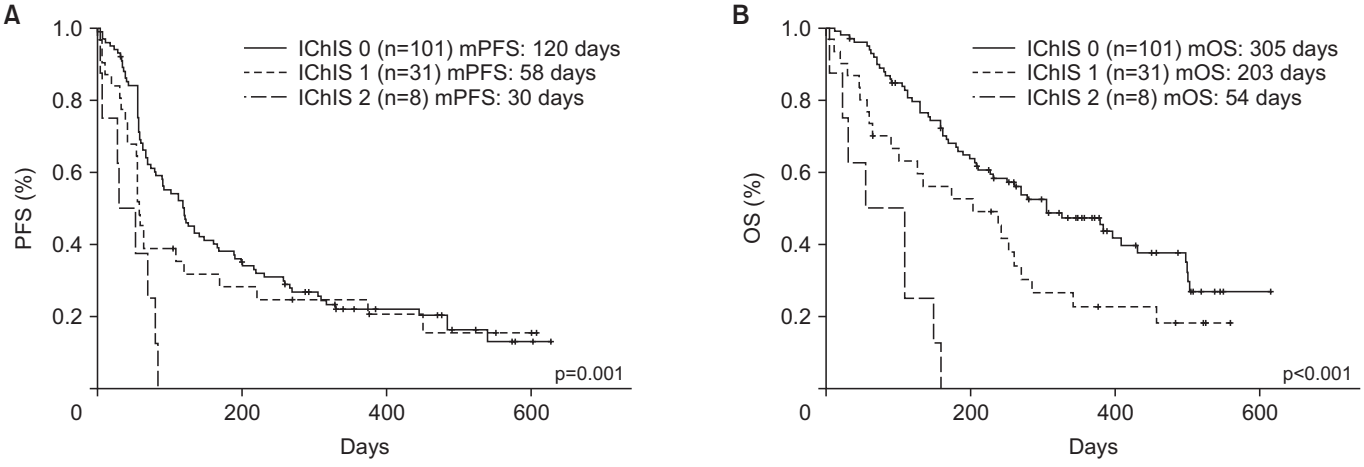

Table 4. Univariate and multivariate analysis for overall survival

Variable	Median (95% CI), day	Univariate (p-value)	Multivariate (p-value, HR)
Age, yr		0.933	
<70	252 (184.3–319.7)		
≥70	242 (150.6–333.4)		
Gender		0.479	
Male	250 (187.2–312.8)		
Female	260 (137.5–382.5)		
Smoking status		0.845	
Never	285 (172.0–398.0)		
Former or current	250 (195.6–304.4)		
ECOG		0.007	0.009
0–1	269 (219.6–318.4)		
≥2	126 (85.5–166.5)		HR, 2.112 (1.205–3.702)
Histology		0.606	
SqCC	260 (217.6–302.4)		
Non-SqCC	207 (114.0–300.0)		
PD-L1 expression		0.084	
No (TPS <1%)	198 (132.6–263.4)		
Low (TPS 1%–49%)	285 (155.6–414.4)		
High (TPS ≥50%)	305 (75.0–535.0)		
Agent		0.023	0.106
Nivolumab	383 (0.0–898.6)		
Pembrolizumab	379 (10.0–615.0)		
Atezolizumab	210 (149.6–270.3)		
IChIS		<0.001	<0.001
0	305 (203.1–406.9)		
1	203 (68.2–337.8)		HR, 1.476 (0.896–2.431)
2	54 (0.0–126.1)		HR, 6.108 (2.766–13.487)

CI: confidence interval; HR: hazard ratio; ECOG: Eastern Cooperative Oncology Group; SqCC: squamous cell carcinoma; PD-L1: programmed death-ligand 1; TPS: tumor proportion score; IChIS: immune checkpoint inhibitor score.

analyzer, that considers not only cell count but also the characteristics of cells.

The development of ICIs marked a significant paradigm shift in the treatment landscape for NSCLC[21]. However, despite notable advancements, a substantial proportion of patients continues to experience ICI resistance[22]. Moreover, the predictive value of PD-L1 expression on tumor cells, which is a widely used marker, is not sufficient to conclusively determine the treatment efficacy[23]. Patients with high PD-L1 expression have the option of receiving either ICI monotherapy or a combination of ICI and cytotoxic chemotherapy[24]. Because a favorable response to ICI treatment is not universal among patients with high PD-L1 expression[25], identifying patients who would benefit from combination treatment remains challenging. Understanding the factors influencing ICI treatment response and prognosis is pivotal in the current era of expanding combination therapies. The ability to predict poor outcomes with ICI monotherapy would prompt consideration for alternative combinations, which emphasizes the need for precise patient stratification.

Systemic inflammation may be crucial in influencing the effectiveness and prognosis of ICI treatment[26]. In NSCLC, multiple markers of systemic inflammation, which can be detected in peripheral blood, correlate with outcomes of immunotherapy[27]. The NLR, calculated by dividing absolute neutrophil counts (ANCs) by

lymphocyte counts, and the derived NLR, calculated as ANC/(white blood cell [WBC]–ANC), have been the first easy-to-use parameters correlating with the outcome of immunotherapy[28,29]. PLR and lymphocyte-to-monocyte ratio have also emerged as prognostic indicators[30,31]. Among these, the NLR, which is easily determined using CBC, has garnered substantial attention as a predictive factor for the outcomes of immunotherapy[32]. A high NLR has been consistently reported as a poor prognostic factor in patients treated with ICI[33]. However, the interpretation of NLR remains challenging considering the ambiguity surrounding whether the poor prognosis is attributable to elevated neutrophil levels or diminished lymphocyte counts. The variability in reported cut-off values further complicates the clinical applicability of NLR as a prognostic marker[16].

Neutrophils account for 50% to 70% of circulating leukocytes in humans, and play a well-established role in host defense[34]. They are also key effector cells in the interaction of the adaptive immune system with different cell populations[35]. In recent years, the relevance of neutrophils in the immune response against cancer has been highlighted, although their roles are not completely understood[11]. Pro- and antitumor activities of neutrophils depend on the tissue and context[11,36]. Tumor-associated neutrophils predict poor OS in many cancer types[37]. A high neutrophil count in peripheral blood was shown to be an independent prognostic factor for poor survival in patients with unresectable advanced NSCLC[38]. The diversity of circulating neutrophils with regard to maturation, tumor cytotoxicity, and immunosuppression has been reported in advanced cancer[35]. IG is a newly identified marker of inflammation that is not well known to most clinicians[39]. IG is an indicator of increased myeloid cell production in conditions such as bone marrow activation and infection. It is a useful marker in infectious diseases such as acute pyelonephritis and acute appendicitis because it can be measured with an automatic analyzer along with CBC; however, its role in lung cancer has not yet been clearly identified[40]. The significance of this study is that we created a scoring system using not only the neutrophil count but also the IG count, which can be easily measured using an automated hematology analyzer and applied it to patients with NSCLC who were treated with ICIs.

This study has some limitations. First, despite it being a multicenter study, the number of patients was not enough to come to a definitive conclusion, and IChIS was not validated in an independent validation cohort. Thus, our results must be further validated in larger cohorts. Second, because only patients receiving ICI monotherapy were enrolled in this study, additional research is also needed for patients receiving ICI–chemo combination treatments. Third, other inflammatory markers such as WBC and C-reactive protein were not investigated in this study. In the future, the correlation analysis between IChIS and other inflammatory markers is necessary.

IChIS can be easily determined with a small volume of blood using an automated hematology analyzer. We found that lower baseline IChIS was associated with significantly longer PFS and OS in patients with NSCLC treated with ICIs. In conclusion, baseline IChIS could be a potential biomarker for predicting survival benefit of immunotherapy in NSCLC.

Authors' Contributions

Conceptualization: Kang DH, Lee JE. Methodology: Choi CM, Park CK, Oh IJ, Kim YC, Yoon SH. Validation: Kang DH, Kim Y, Lee JE. Formal analysis: Kang DH, Kim Y, Lee JE. Data curation: Choi CM, Park CK, Oh IJ, Kim YC, Yoon SH. Writing - original draft preparation: Kang DH, Lee JE. Writing - review and editing: Choi CM, Park CK, Oh IJ, Kim YC, Yoon SH, Kim Y. Approval of final manuscript: all authors.

Conflicts of Interest

In-Jae Oh is an editor of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Intensive care infection score parameters and cut-off value.

Supplementary Table S2. Intensive care infection score calculation.

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