Scientific Reports

https://doi.org/10.1038/s41598-026-46185-7

Article in Press

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Received: 25 March 2025

Accepted: 24 March 2026

Published online: 03 April 2026

Cite this article as: Takada S., Nasu I., Uozumi R. *et al.* Association of immune-related adverse events with survival in patients receiving immune checkpoint inhibitor plus chemotherapy for lung cancer. *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-46185-7

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Association of immune-related adverse events with survival in patients receiving immune checkpoint inhibitor plus chemotherapy for lung cancer

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Abstract

The association of immune-related adverse events (irAEs) and baseline peripheral blood count ratios with the effectiveness of immune checkpoint inhibitor (ICI) plus chemotherapy in patients with non-small cell lung cancer (NSCLC) remains unclear. This multicenter, retrospective study analyzed data from 191 patients treated with pembrolizumab or atezolizumab plus chemotherapy as first-line therapy across five hospitals in Japan between December 2018 and March 2021. Progression-free survival (PFS) and overall survival (OS) were assessed in relation to irAEs within a 6-week landmark analysis and baseline peripheral blood count ratios using Cox proportional hazards models. IrAEs occurred in 70 patients (36.6%) and showed no substantial association with survival (PFS: hazard ratio [HR]=1.04, 95% confidence interval [CI]=0.70–1.53; OS: HR=0.82, 95% CI=0.49–1.34). Conversely, baseline peripheral blood count ratios were considerably linked to survival. A higher neutrophil-to-lymphocyte ratio correlated with reduced PFS (adjusted HR=1.62, 95% CI=1.10–2.40) and OS (adjusted HR=2.50, 95% CI=1.53–4.09), with similar trends for the lymphocyte-to-monocyte and platelet-to-lymphocyte ratios. Collectively, these findings suggest that although irAEs were not predictive of survival, baseline blood count ratios can serve as prognostic biomarkers in patients with NSCLC receiving chemoimmunotherapy.

Keywords: pembrolizumab; atezolizumab; immune checkpoint inhibitors; immune-related adverse events; non-small cell lung cancer

Introduction

Cancer remains a major global health concern, with approximately one in three individuals in Japan estimated to experience the disease. Lung cancer (LC) is particularly prevalent and deadly, responsible for approximately 1.8 million deaths annually, as reported by Global Cancer Statistics 2022[1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all LC cases, and many patients with NSCLC are diagnosed with stage IV, with a 5-year survival rate of <20%[2]. It comprises two major histological subtypes, including adenocarcinoma (approximately 40–50% of cases) and squamous cell carcinoma (approximately 20–30% of cases). Advancements in technology and increased awareness of regular physical examinations have substantially improved LC diagnosis and management. Platinum chemotherapy remains a key treatment option for patients with driver-gene-negative advanced NSCLC. Recent progress in molecular immunology has enabled the approval of immune checkpoint inhibitors (ICI), which target programmed cell death protein 1 (PD-1), programmed cell death protein ligand 1, or cytotoxic T-lymphocyte antigen-4. Furthermore, the combination of ICI with platinum chemotherapy has emerged as the standard first-line treatment for patients with driver-gene-negative advanced NSCLC[3,4]. Notably, previous studies have observed a correlation between ICI efficacy and the occurrence of immune-related adverse events (irAEs), with patients who experience skin- or endocrine-related irAEs demonstrating better survival than those who do not[5-7]. This observed association suggests that the occurrence of irAEs reflects immune system activation, thereby enhancing the antitumor immune response. However, this correlation does not establish a causal relationship between irAEs and prognosis.

Several baseline peripheral blood count ratios, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), have been associated with survival prognosis. Previous studies have demonstrated that patients with a higher NLR, lower LMR, or higher PLR exhibit poorer survival outcomes than those without these characteristics[8-12]. This association suggests that systemic inflammation and immunological status are linked to the prognosis of various solid tumors. Compared with irAEs, these routinely available baseline peripheral blood inflammatory markers may provide direct evidence of causation. Although inflammatory markers have been investigated in the context of ICI monotherapy, only a few studies have elucidated the relationship between these baseline peripheral blood parameters and treatment efficacy in chemoimmunotherapy. Similarly, no reports have examined the incidence of irAEs and treatment efficacy in the context of ICI plus chemotherapy.

Therefore, this study aimed to clarify the relationship between the incidence of irAEs and clinical benefits in patients with driver-gene-negative advanced NSCLC treated with ICI plus chemotherapy. We also examined the connection between treatment outcomes and baseline peripheral blood count ratios.

Methods

Study design

We conducted a multicenter, retrospective, observational, case-control study across five hospitals in Japan. These include the National Hospital Organization Hokkaido Cancer Center, Nagoya City University Hospital, Showa University Hospital, Gifu University Hospital, and Keio University Hospital. Patient data were initially extracted from electronic medical records. These data were double-checked by two researchers, entered into the electronic case report form at each institution, and consolidated at the Keio University Faculty of Pharmacy. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[13] and adopted methodologies from previous studies[14-16].

Patients aged ≥20 years with advanced LC and consecutive patients receiving ICIs (pembrolizumab or atezolizumab) combined with platinum chemotherapy as a first-line treatment between December 2018 and March 2021 were included in this study. Clinical follow-up schedules were tailored daily by attending physicians based on efficacy and toxicity profiles.

The exclusion criteria were (i) refusal to consent to the use of medical records for research purposes; (ii) insufficient patient data; (iii) active double cancer or autoimmune disease; (iv) history of tuberculosis or interstitial pneumonia; (v) participation in clinical trials involving investigational drugs; (vi) diagnoses other than NSCLC; and (vii) treatment discontinuation within the first 6 weeks after ICI initiation due to death, transfer to another hospital, progressive disease (PD), or adverse events. To mitigate lead-time bias, a 6- and 4-week landmark analysis was performed, including patients with disease control who remained alive 6 and 4 weeks after ICI initiation[5,6].

Data collection

Patient information was anonymized and managed without identifiers. The collected data included age, sex, chemotherapy regimen, the Eastern Cooperative Oncology Group performance status (ECOG PS), and baseline peripheral blood count ratios (NLR, LMR, and PLR). NLR, LMR, and PLR were calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, LMR by dividing the absolute lymphocyte count by the absolute monocyte count, and PLR by dividing the platelet count by the absolute lymphocyte count. Additional data included the date of progression or death from the time of ICI initiation and the incidence of irAEs. The date of PD was defined as the first incidence of progression based on computed tomography using the Response Evaluation Criteria in Solid Tumors version 1.1[17], or clinical progression as determined by the attending physician. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0[18]. The study's follow-up period concluded on September 30, 2021.

Endpoints

The primary endpoint was to evaluate the association between the occurrence of any irAEs and survival after chemoimmunotherapy.

Secondary endpoints included the evaluation of skin-related irAEs and baseline peripheral blood count ratios (NLR, LMR, and PLR). Progression-free survival (PFS) was defined as the interval from the ICI plus chemotherapy initiation to the date of PD or all-cause mortality. Overall survival (OS) was defined as the time from ICI plus chemotherapy initiation to all-cause mortality. Patients without PD and those who were alive at the end of the follow-up period were censored for PFS and OS on the date of their last follow-up, respectively.

Statistical analysis

Baseline patient characteristics were summarized as median (interquartile range [IQR]) and proportions for continuous and categorical variables, respectively. PFS and OS were estimated using the Kaplan–Meier method and compared using a log-rank test. An initial analysis assessed the association between irAEs and survival, with an additional focus on skin-related irAEs, as highlighted in previous research[5]. A secondary analysis examined the associations between baseline peripheral blood count ratios (NLR, LMR, and PLR) and survival outcomes. Time-dependent receiver operating characteristic (ROC) curve analyses and Youden's index were employed to determine optimal NLR, LMR, and PLR cutoff values predictive of OS. The area under the ROC curve (AUC) was used to evaluate predictive ability. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Primary analyses incorporated a multivariable Cox proportional hazards model, adjusting for covariates such as age (per 10-year increase) and ECOG PS (2 vs. 0–1). Follow-up time was calculated using the reverse Kaplan–Meier estimate[19]. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics for Windows, version 29.0.2.0 (IBM Corp., Armonk, NY, USA). All *P*-values were two-sided, with the significance level set at 0.05.

Ethics statement

The study protocol was approved by the Ethics Committees of the National Hospital Organization Hokkaido Cancer Center (approval number: 03-15), Nagoya City University Hospital (approval number: 60-21-0074), Showa University Hospital (approval number: 3503), Gifu University Hospital (approval number: 2021-0188), Keio University Hospital (approval number: 20210049), and Keio University Faculty of Pharmacy (approval number: 231004-1). This study adhered to the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health 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. The requirement for written or oral informed consent was waived by the Ethics Committees of the participating institutions due to the retrospective nature of this study. Consequently, patients were provided with an opt-out option via the official website of each institution.

Use of an LLM Statement

ChatGPT-4 was used to improve readability and language during the preparation of this manuscript. All authors reviewed and edited the content as necessary and take full responsibility for the final content of this publication.

Results

Patient characteristics

Fig. 1 shows the patient flowchart. A total of 191 patients were evaluated, with 70 (36.6%) experiencing any irAEs. **Table 1** presents the patient characteristics. The median age of the patients was 68 (IQR=61–73) years. Approximately 90% of patients had an ECOG PS of 0–1. The most common regimen of ICI plus platinum chemotherapy was pembrolizumab + carboplatin + pemetrexed, administered to 90 (47.1%) patients.

Endpoints

The median follow-up time, PFS, and OS were 1.6 (95% CI=1.5–1.8), 0.7 (95% CI=0.6–1.0), and 2.2 (95% CI, 1.9–not estimable) years, respectively. As shown in **Fig 2**, the presence of any irAEs was not significantly associated with PFS or OS in a 6-week landmark (HR=1.04; 95% CI=0.70–1.53; $P = 0.83$ and HR=0.82; 95% CI=0.49–1.34; $P = 0.45$, respectively). Similarly, skin-related irAEs showed no significant relationship with PFS or OS in a 6-week landmark (HR=0.93; 95% CI=0.56–1.47; $P = 0.77$ and HR=0.63; 95% CI=0.29–1.21; $P = 0.20$, respectively). The presence of any irAEs were not significantly associated with PFS or OS in a 4-week landmark (HR=0.95; 95% CI=0.64–1.39; *P* = 0.81 and HR=0.97; 95% CI=0.62–1.49; *P* = 0.88, respectively). Similarly, skin-related irAEs showed no significant relationship with PFS or OS in a 4-week landmark (HR=0.87; 95% CI=0.52–1.38; *P* = 0.58 and HR=0.63; 95% CI=0.32–1.13; *P* = 0.15, respectively).

Fig. 3 shows the time-dependent AUC of NLR, LMR, and PLR, which remained higher than 0.6 over time. Time-dependent ROC curve analyses identified optimal NLR, LMR, and PLR cutoff values predictive of OS (**Fig. 4**). The AUCs for NLR were 0.719, 0.667, and 0.607 at 1, 1.5, and 2 years post-ICI initiation, respectively, with optimal cutoff values of 4.4, 3.2, and 4.8, respectively. For LMR, the AUCs were 0.761, 0.712, and 0.657 at 1, 1.5, and 2 years, respectively, with optimal cutoff values of 2.4, 3.1, and 3.1, respectively. The AUCs for PLR were 0.687, 0.627, and 0.649 at 1, 1.5, and 2 years, respectively, with optimal cutoff values of 235, 235, and 287, respectively. Clinical relevance led to the selection of 1-year cutoff values for subsequent analyses.

As shown in **Fig. 5**, NLR >4.4 was significantly associated with reduced PFS and OS (HR=1.69; 95% CI=1.16–2.45; *P* = 0.006 and HR=2.52; 95% CI=1.58–4.01; *P* < 0.001, respectively). LMR <2.4 and PLR >235 were negatively associated with survival (LMR: HR=1.73, 95% CI=1.19–2.52, *P* = 0.004 for PFS; HR=2.96, 95% CI=1.84–4.76, *P* < 0.001 for OS; PLR: HR=1.59, 95% CI=1.09–2.31, *P* = 0.015 for PFS; HR=2.34, 95% CI=1.46–3.75, *P* < 0.001 for OS).

In a multivariable Cox proportional hazards model (**Table 2**), NLR >4.4 was significantly associated with reduced PFS and OS (adjusted

HR=1.62; 95% CI=1.10–2.40; $P = 0.015$ and adjusted HR=2.50; 95% CI=1.53–4.09; $P < 0.001$, respectively). Similar associations were observed for LMR <2.4 and PLR >235 (LMR: adjusted HR=1.79, 95% CI=1.21–2.65, $P = 0.004$ for PFS; adjusted HR=3.22, 95% CI=1.95–5.33, $P < 0.001$ for OS; PLR: adjusted HR=1.51, 95% CI=1.02–2.24, $P = 0.040$ for PFS; adjusted HR=2.22, 95% CI=1.35–3.67, $P = 0.002$ for OS).

Discussion

This study investigated the association between irAEs and treatment efficacy and assessed the role of baseline peripheral blood inflammatory markers (NLR, LMR, and PLR) in patients with driver-gene-negative advanced NSCLC receiving ICI plus platinum chemotherapy. The results indicated that the occurrence of irAEs, including skin-related irAEs, within 6 weeks of treatment initiation was not considerably associated with PFS or OS. Conversely, elevated NLR, reduced LMR, and increased PLR were correlated with poorer survival outcomes. To the best of our knowledge, this is the first study to report that irAEs were not associated with survival outcomes, whereas baseline peripheral blood count ratios were predictive of survival in Japanese patients with driver-gene-negative advanced NSCLC receiving chemoimmunotherapy in a real-world setting.

The lack of a relationship between irAEs and survival outcomes in this study could be due to the balancing effect of ICI plus platinum chemotherapy compared with ICI monotherapy. Although previous studies on immunotherapy have linked irAEs to favorable treatment outcomes, platinum chemotherapy may induce distinct immune and inflammatory responses, potentially diminishing the correlation observed with ICI monotherapy. The longer OS may be due to the appropriate management of irAEs and ratio of subsequent therapies. Yokoo et al.[20] reported that irAEs did not affect OS in patients with extensive disease SCLC treated with ICI plus platinum agents. Similarly, Bi et al.[21] reported that irAEs did not affect OS in patients with SCLC. However, since SCLC differs from the present study population, these findings cannot be directly extrapolated and should be interpreted cautiously until further reports on NSCLC become available. Previous studies on ICI monotherapy usually involved second-line or later-line treatments, whereas immunotherapy is known to exert a carry-over effect[22], which may help explain the results observed in this study. Although irAEs may reflect patient immune reactivity, which can vary considerably, baseline peripheral blood inflammatory markers (such as NLR, LMR, and PLR) are directly measurable at treatment initiation and may better capture systemic inflammatory states that more consistently influence patient outcomes. Previous studies on patients with NSCLC treated with ICIs have evaluated the impact of these inflammatory markers on survival, showing that higher NLR and PLR and lower LMR are associated with poorer survival. Meta-analyses by Jin et al.[23] (reported on 23 papers and 2,068 patients), Li et al.[24] (17 papers, 2,106 patients), and Zhang et al.[25] (21 papers, 1,845 patients) have similarly reported that high NLR and PLR are associated with lower survival rates in patients with LC treated with ICIs. These findings align with our results in the setting of combination therapy, further supporting the intriguing reports from these previous studies.

ICI monotherapy has been reported to differ from ICI plus platinum chemotherapy. Prior studies have consistently demonstrated that antibiotic use before ICI treatment adversely affects the efficacy of monotherapy across various cancer types[26-28]. However, Tamura et al.[29] and a European retrospective study by Cortellini et al.[30] suggested that antibiotics did not affect the efficacy of chemoimmunotherapy in patients with advanced NSCLC. Although the underlying mechanism remains unclear, platinum chemotherapy may counteract the negative effects of antibiotic-induced dysbiosis. These findings align with the lack of an association between irAEs and survival in the present study of ICI plus chemotherapy.

Our findings align with prior research highlighting the prognostic role of NLR, LMR, and PLR in patients with NSCLC treated with ICI monotherapy[31-34]. These studies have demonstrated that elevated NLR and PLR, alongside reduced LMR, are associated with poor prognosis across various solid tumors, supporting their use as markers of systemic inflammation and immune suppression. Compared with irAEs, these markers provide measurable baseline data that can more reliably guide patient prognosis and therapeutic strategies in combination therapies. However, the lack of a substantial association between irAEs and outcomes in the present study differs from findings of research on ICI monotherapy, underscoring the need for a more nuanced understanding of how chemotherapy modulates immune responses in NSCLC.

This study had several strengths. First, the multicenter design, which involved five hospitals in Japan, allowed for the generalization of findings to similar populations in clinical settings. Second, the focus on ICI plus platinum agents reflects the current standard first-line treatment for patients with driver-gene-negative advanced NSCLC. Finally, the use of a 6-week landmark analysis minimized lead-time bias arising from the time-dependent occurrence of irAEs, and the application of time-dependent ROC curve analyses clarified the relationships between NLR, LMR, and PLR and survival outcomes. We utilized both 4- and 6-week landmarks, corresponding to the completion of the first and second cycles of platinum-based chemotherapy, respectively. Although landmark analysis inevitably excludes patients with relatively poor prognoses who experience early progression or death, the consistent lack of substantial association between irAEs and survival at both time points suggests that the exclusion of early progressors does not solely drive our findings. Together, these factors strengthen the robustness of the findings and represent novel aspects of this study.

However, some limitations of this study should also be described. First, the retrospective observational design is inherently subject to bias and relies on the accuracy of electronic health record data. Importantly, the multivariable analysis adjusted only for age and ECOG PS. Potential confounders—such as programmed cell death receptor-ligand-1 expression status, tumor burden, histology, comorbidities, and the use of corticosteroids or antibiotics—were not included due to data unavailability or sample size limitations. These factors could influence both the development of irAEs and survival outcomes. Although these unmeasured confounders are unlikely to completely overturn the lack of a strong association observed between irAEs and survival outcomes in the chemoimmunotherapy setting, residual confounding cannot be excluded. Second, the relatively small sample size may have affected statistical power. Particularly, all irAEs were grouped in the primary analysis. Given that the prognostic impact of irAEs varies by organ system (e.g., endocrine vs. pulmonary), this approach may have obscured organ-specific associations. Therefore, future studies with larger cohorts are needed to investigate the impact of specific irAE subtypes. Third, the use of baseline peripheral blood inflammatory markers without incorporating their variations over time during treatment limited the comprehensive evaluation of systemic inflammation. Fourth, while we employed a landmark analysis to handle immortal time bias, this approach inherently excludes patients who experienced early progression or death before the landmark point, potentially introducing selection bias. Landmarking treats irAE status as fixed at the cutoff point. Consequently, patients who experienced irAEs after the 6-week mark were classified into the non-irAE group. This misclassification could dilute the potential survival benefit of irAEs, biasing the results toward the null. Although a time-dependent Cox proportional hazards model would be more rigorous in addressing this issue, we prioritized landmark analysis to facilitate comparison with previous studies. Therefore, the lack of a substantial association observed in this study should be cautiously interpreted, as the potential positive effect of late-onset irAEs may have been underestimated. Finally, this study was conducted as a discovery cohort and lacked a validation cohort, which could have strengthened the findings.

These findings highlight the potential utility of NLR, LMR, and PLR as prognostic— although not necessarily predictive—markers in this population. Prognostic markers may inform risk stratification; however, they do not necessarily guide treatment selection. Therefore, incorporating these biomarkers into patient assessments could support the development of personalized treatment strategies. Future research, including prospective studies and validation across diverse treatment settings, remains essential to further evaluate and optimize the clinical application of these inflammatory biomarkers to improve patient outcomes.

Conclusions

In our analysis, the occurrence of irAEs was not substantially associated with improved survival in Japanese patients with driver-gene-negative advanced NSCLC treated with ICI plus chemotherapy, whereas baseline peripheral blood count ratios were predictive of survival outcomes. The impact of irAEs may differ between ICI monotherapy and combination therapy with platinum chemotherapy. While these findings may be applicable to the broader Japanese population, future validation studies in both Asian and Western populations are warranted.

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Acknowledgments

We extend our gratitude to all patients and multidisciplinary team staff at the National Hospital Organization Hokkaido Cancer Center, Nagoya City University Hospital, Showa University Hospital, Gifu University Hospital, and Keio University Hospital for their participation in this study. We also thank Prof. Kazunori Kimura, Prof. Tadanori Sasaki, and the Effectiveness of Platinum Chemotherapy and Immune Checkpoint

Inhibitors by Concomitant Use (EPIC) investigators for their valuable support. Additionally, we are grateful to Editage (www.editage.com) for the English language editing.

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Data analysis and interpretation: R.U. and H.K.

Manuscript writing: S.T., I.N., and H.K.

Final approval of manuscript: All authors.

Funding

This research was supported in part by the Research Foundation for Pharmaceutical Sciences in Japan and the JSPS KAKENHI (grant numbers 20H04147 to R.U. and 22K06776 to H.K.). The funders had no role in the study's design, data collection, analysis, interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

Competing Interests

I.N. reports employment with Flatiron Health, Inc., an independent member of the Roche group, and stock ownership in Roche. R.U. has consulting/advisory relationships with Eisai, Sawai Pharmaceutical, SBI

Pharmaceuticals, Daiichi Sankyo, Statcom, and EPS Corporation and has received honoraria from Janssen Pharmaceutical, SAS Institute Japan, and Nippon Kayaku outside the submitted work. H.I. received personal fees from Astellas, AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Nippon Kayaku, Ohara, Sawai, Taiho, and Yakult outside the submitted work. S.O. received research funding from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Pfizer, MSD, Sanofi, Taiho, and Takeda and lecture fees from AstraZeneca, Chugai, MSD, and Takeda outside the submitted work. S.K. received honoraria fees from AstraZeneca, Chugai, Taiho, Korin, Daiichi Sankyo, Bristol-Myers Squibb, MSD, and Amgen outside the submitted work. H.K. received research funding from Eli Lilly outside the submitted work. The remaining authors declare no competing or financial interests.

Data Availability Statement

The data underlying this article cannot be shared publicly to protect the privacy of the individuals who participated in this study. The data will be shared upon a reasonable request to the corresponding author.

Figure legends

Fig. 1 Patient flowchart.

Fig. 2 Kaplan–Meier survival curves according to the absence or presence of any irAEs (**a** and **b**) or skin-related irAEs (**c** and **d**).

(a) PFS, (**b**) OS, (**c**) PFS, and (**d**) OS.

Blue lines represent the absence of irAEs or skin-related irAEs, while red lines represent their presence.

Abbreviations: irAEs, immune-related adverse events; PFS, progression-free survival; OS, overall survival.

Fig. 3 Time-dependent AUC for NLR **(a)**, LMR (**b**), and PLR (**c**).

Abbreviations: AUC, area under the curve; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio.

Fig. 4 Time-dependent ROC curve analyses for determining optimal cutoff values for NLR (**a**), LMR (**b**), and PLR (**c**) to predict OS at 1, 1.5, and 2 years.

Abbreviations: ROC, receiver operating characteristic; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio; OS, overall survival.

Fig. 5 Kaplan–Meier survival curves according to baseline peripheral blood count ratios of NLR (**a** and **b**), LMR (**c** and **d**), and PLR (**e** and **f**).

(**a**) PFS, (**b**) OS, (**c**) PFS, (**d**) OS, (**e**) PFS, and (**f**) OS.

Blue and red lines represent NLR >4.4 and NLR ≤4.4, respectively.

Blue and red lines represent LMR <2.4 and LMR ≥2.4, respectively.

Blue and red lines represent PLR >235 and PLR ≤235, respectively.

Abbreviations: PFS, progression-free survival; OS, overall survival; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio.

Table 1 Patient characteristics.

	With irAEs (N=70)	**Without irAEs (N=121)**
Age (years), median (IQR)	70 (62–74)	68 (61–72)
Sex, *n* (%)		
Male	47 (67.1)	91 (75.2)
Female	23 (32.9)	30 (24.8)
ECOG PS, *n* (%)		
0	27 (38.6)	61 (50.4)
1	34 (48.6)	49 (40.5)
2	4 (5.7)	6 (5.0)
Unknown	5 (7.1)	5 (4.1)
ICI + platinum chemotherapy, *n* (%)		
Pembrolizumab + carboplatin + pemetrexed	34 (52.9)	56 (46.3)
Pembrolizumab + carboplatin + nab-paclitaxel	19 (27.1)	30 (24.8)
Pembrolizumab + cisplatin + pemetrexed	4 (5.7)	11 (9.1)
Pembrolizumab + carboplatin + paclitaxel	0 (0)	1 (0.8)
Atezolizumab + carboplatin + paclitaxel ± bevacizumab	8 (11.4)	9 (7.4)
Atezolizumab + carboplatin + nab-paclitaxel	5 (7.1)	10 (8.3)

Atezolizumab + carboplatin + paclitaxel	0 (0)	2 (1.7)
Atezolizumab + carboplatin + pemetrexed	0 (0)	1 (0.8)
Atezolizumab + cisplatin + pemetrexed	0 (0)	1 (0.8)
Baseline peripheral blood count, median (IQR)		
Absolute neutrophil count	4730 (3379–6832)	4873 (3843–6545)
Absolute lymphocyte count	1370 (899–1786)	1320 (889–1785)
Platelet count	290000 (196500–370000)	275000 (235000–346000)
Absolute monocyte count	481 (368–700)	497 (353–657)
Baseline peripheral blood count ratios		
NLR, median (IQR)	3.66 (2.51–5.48)	3.88 (2.59–6.15)
PLR, median (IQR)	214.5 (136.3–336.2)	208.5 (150.0–308.5)
LMR, median (IQR)	2.55 (1.60–3.92)	2.58 (1.75–3.92)
Grade		
1	41 (58.6)	-
2	23 (32.9)	-
3	4 (5.7)	-
4	2 (2.9)	-

Abbreviations: IQR, interquartile range; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group performance status.

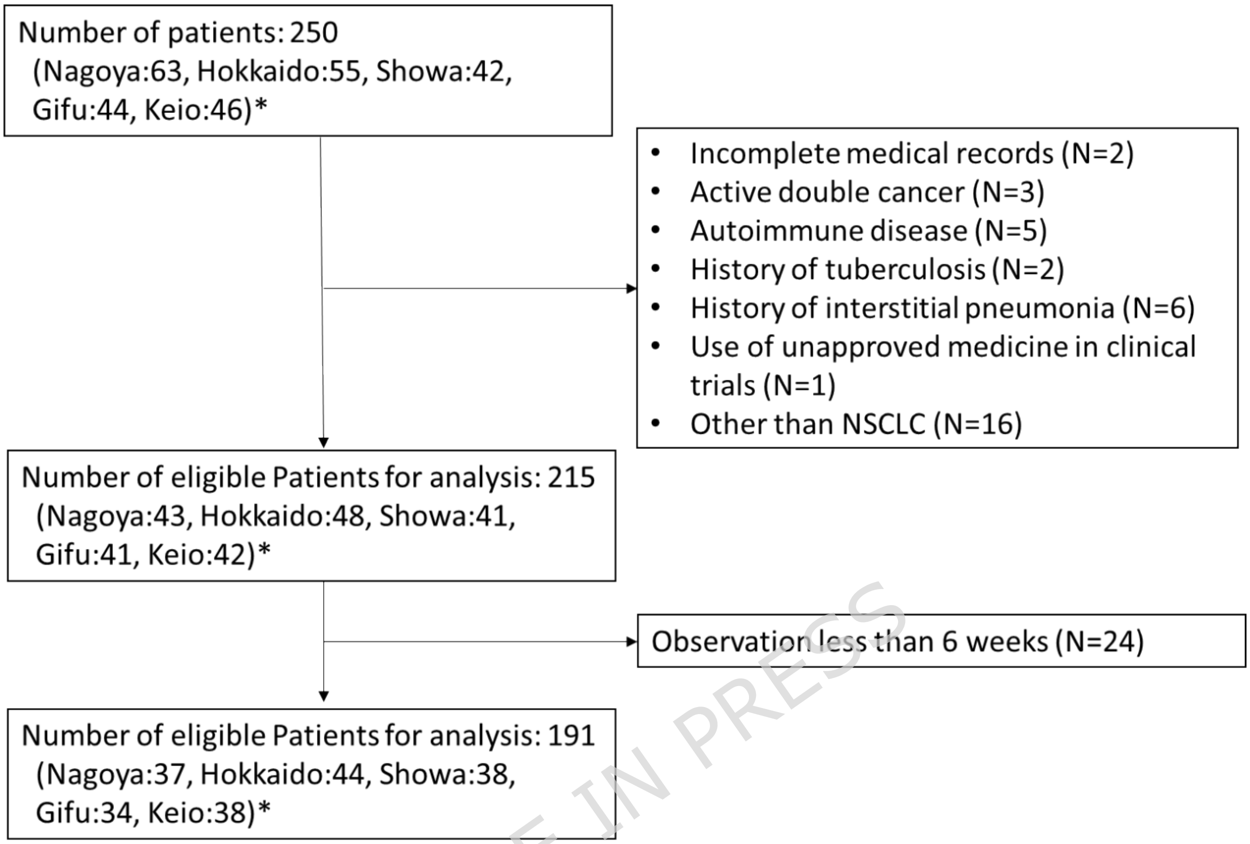
Table 2 Multivariable Cox proportional hazards model for PFS and OS.

	Adjusted HR (95% CI)	*P*-value
PFS		
NLR >4.4	1.62 (1.10–2.40)	0.015
LMR <2.4	1.79 (1.21–2.65)	0.004
PLR >235	1.51 (1.02–2.24)	0.040
OS		
NLR >4.4	2.50 (1.53–4.09)	<0.001
LMR <2.4	3.22 (1.95–5.33)	<0.001
PLR >235	2.22 (1.35–3.67)	0.002

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PLR, platelet-lymphocyte ratio.

The multivariate Cox proportional hazards model included age (per 10-year increase) and ECOG PS (2 vs. 0–1) as covariates.

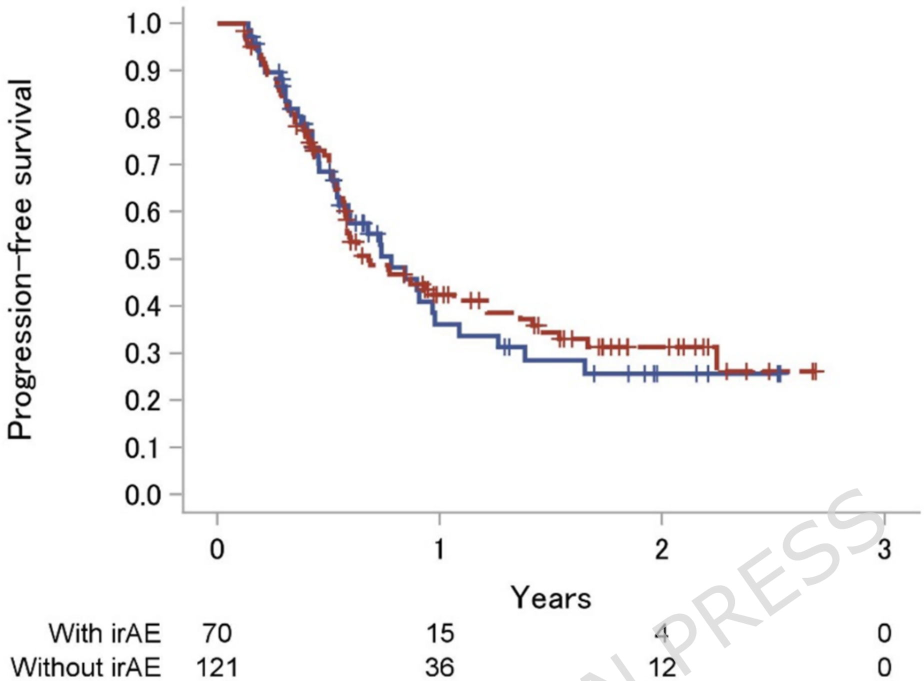
Fig. 1



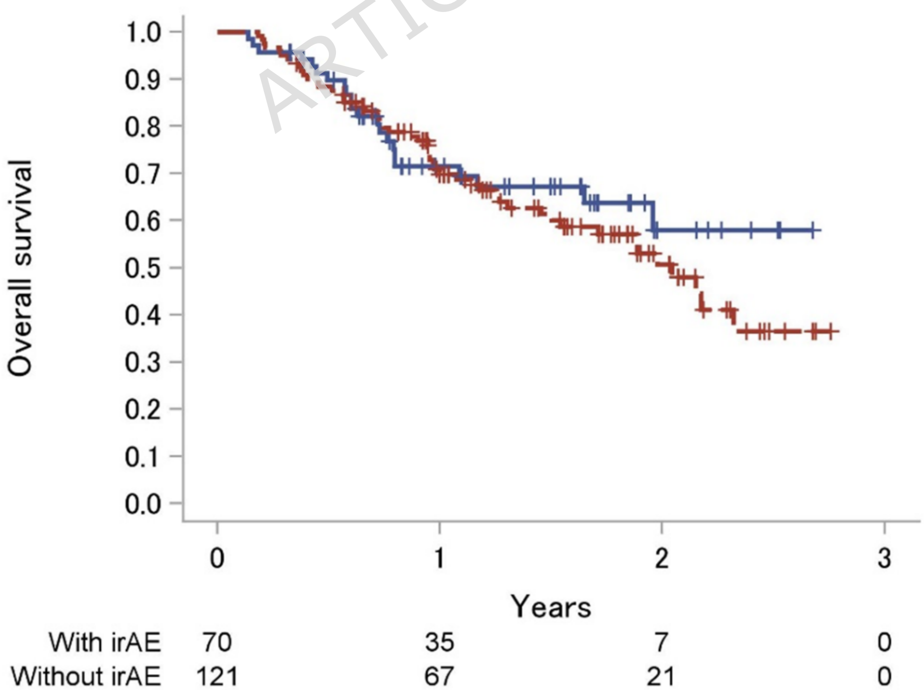
*Nagoya: Nagoya City University Hospital
Hokkaido: National Hospital Organization Hokkaido Cancer Center
Showa: Showa University Hospital
Gifu: Gifu University Hospital
Keio: Keio University Hospital

Fig. 2

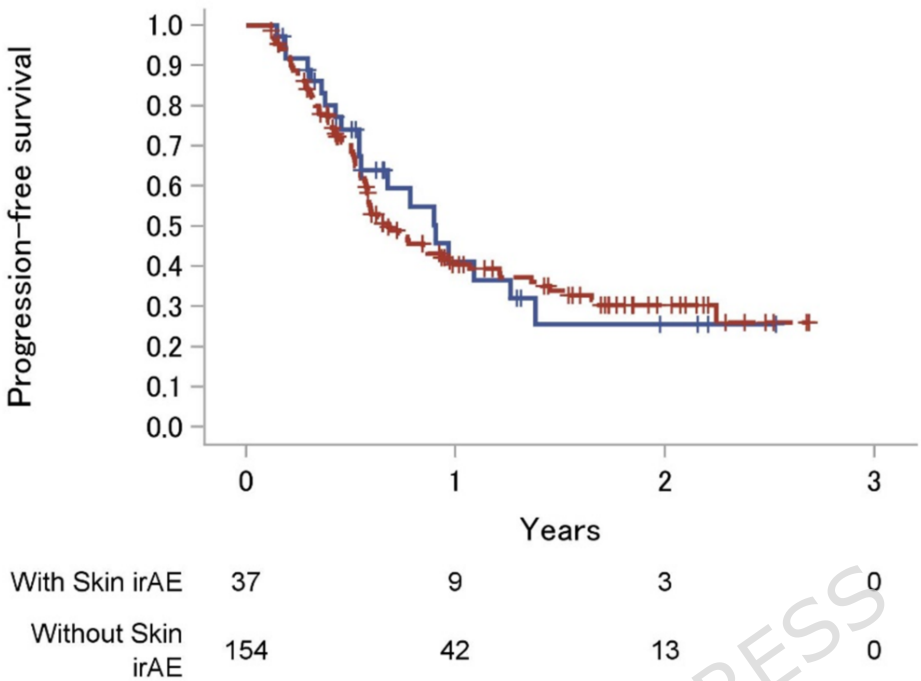
(A)


Progression−free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
Years
With irAE 70 15 4 0
Without irAE 121 36 12 0

(B)

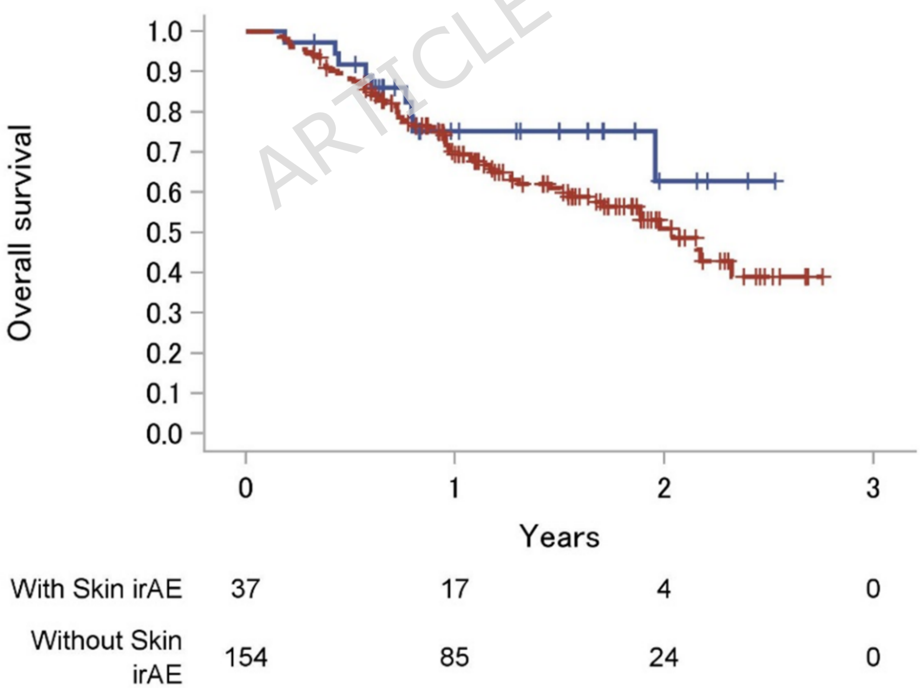

Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
Years
With irAE 70 35 7 0
Without irAE 121 67 21 0

(C)



1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Progression-free survival
0
1
2
3
Years
With Skin irAE
37
9
3
0
Without Skin irAE
154
42
13
0

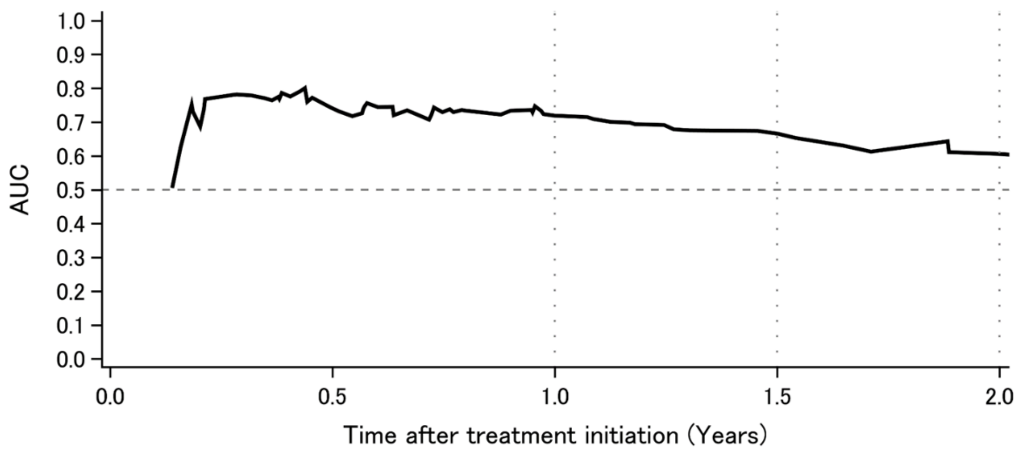
(D)



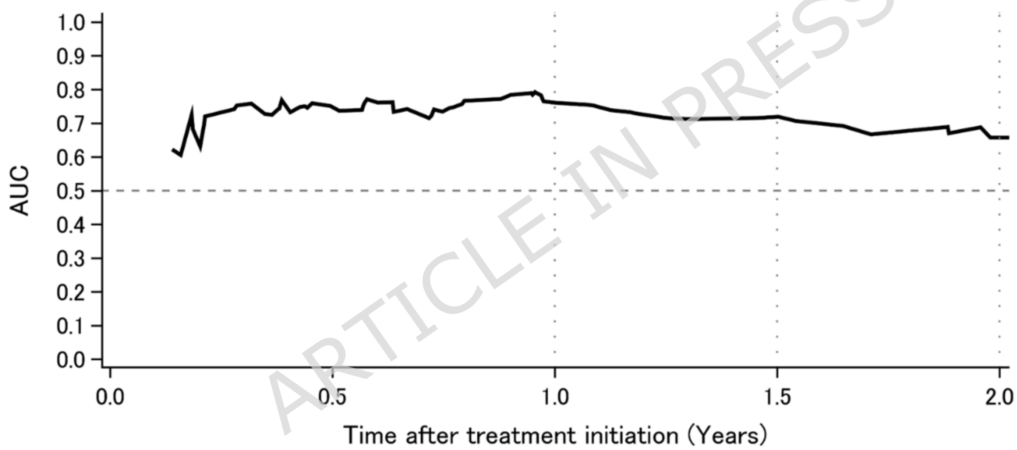
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Overall survival
0
1
2
3
Years
With Skin irAE
37
17
4
0
Without Skin irAE
154
85
24
0

Fig. 3

(A)


AUC
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
Time after treatment initiation (Years)

(B)


AUC
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
Time after treatment initiation (Years)

(C)

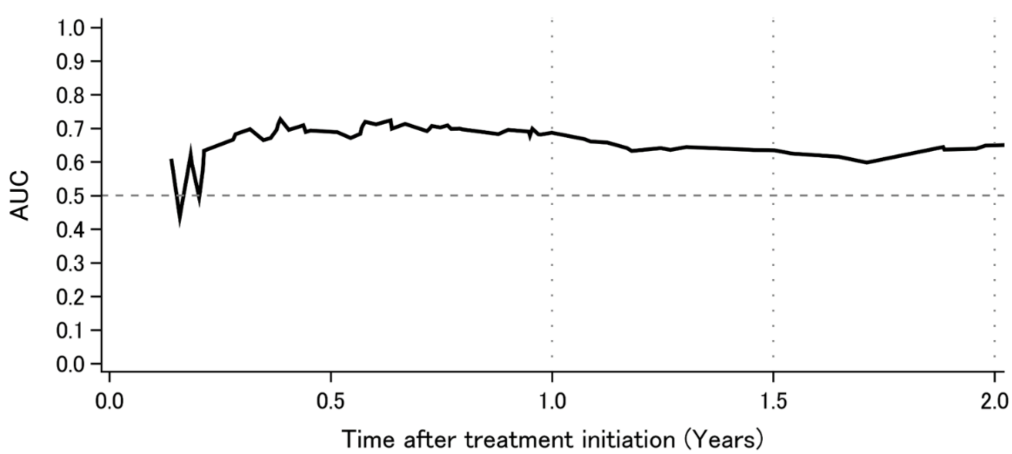
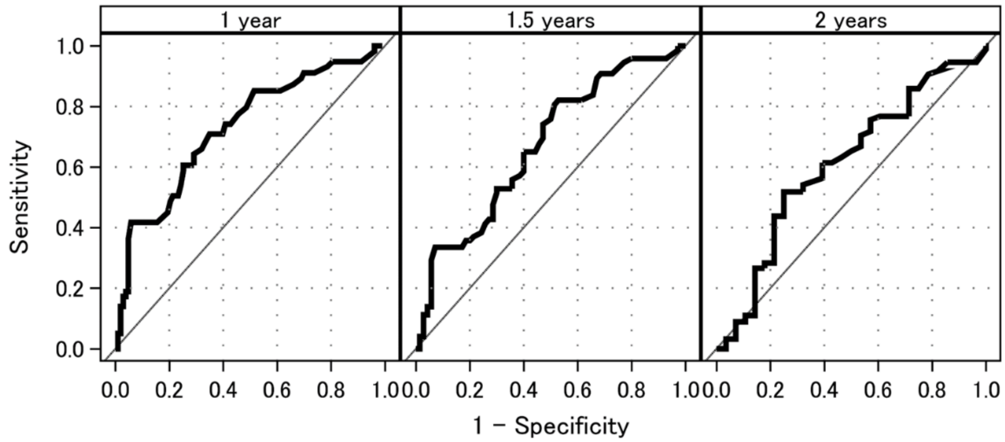
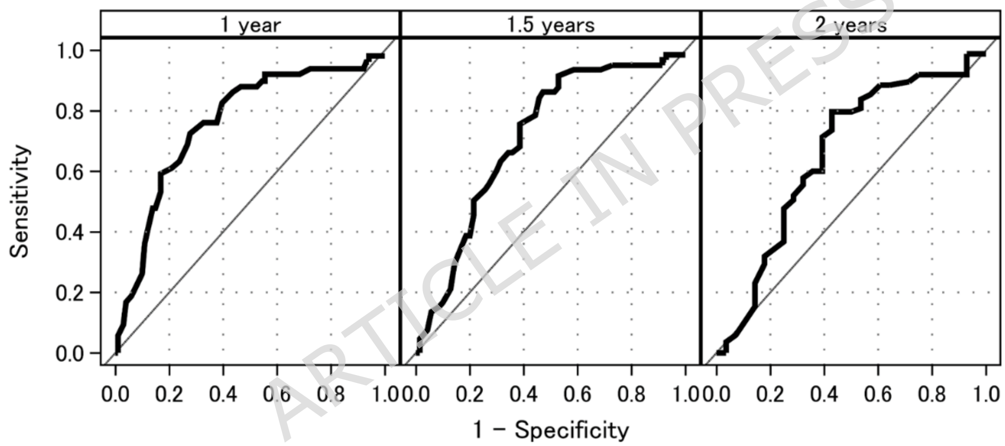

AUC
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
Time after treatment initiation (Years)

Fig. 4

(A)


1 year
1.5 years
2 years
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 − Specificity

(B)


1 year
1.5 years
2 years
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 − Specificity

(C)

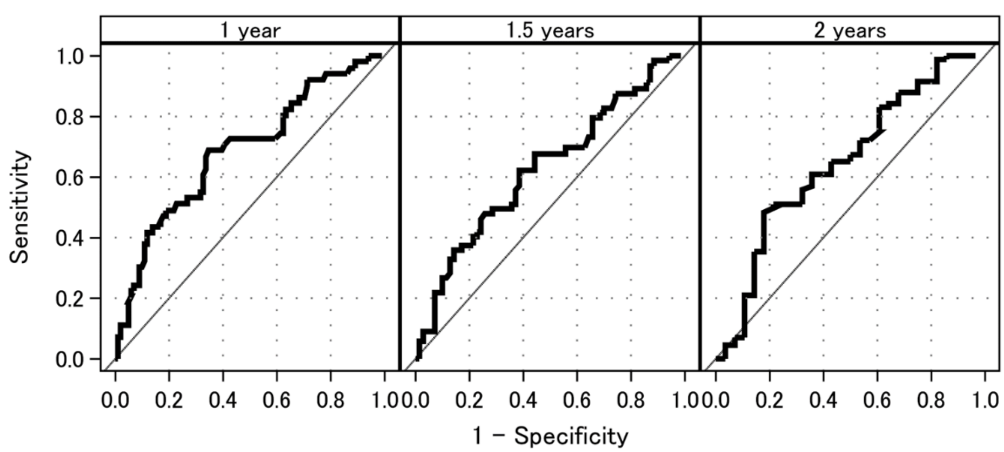
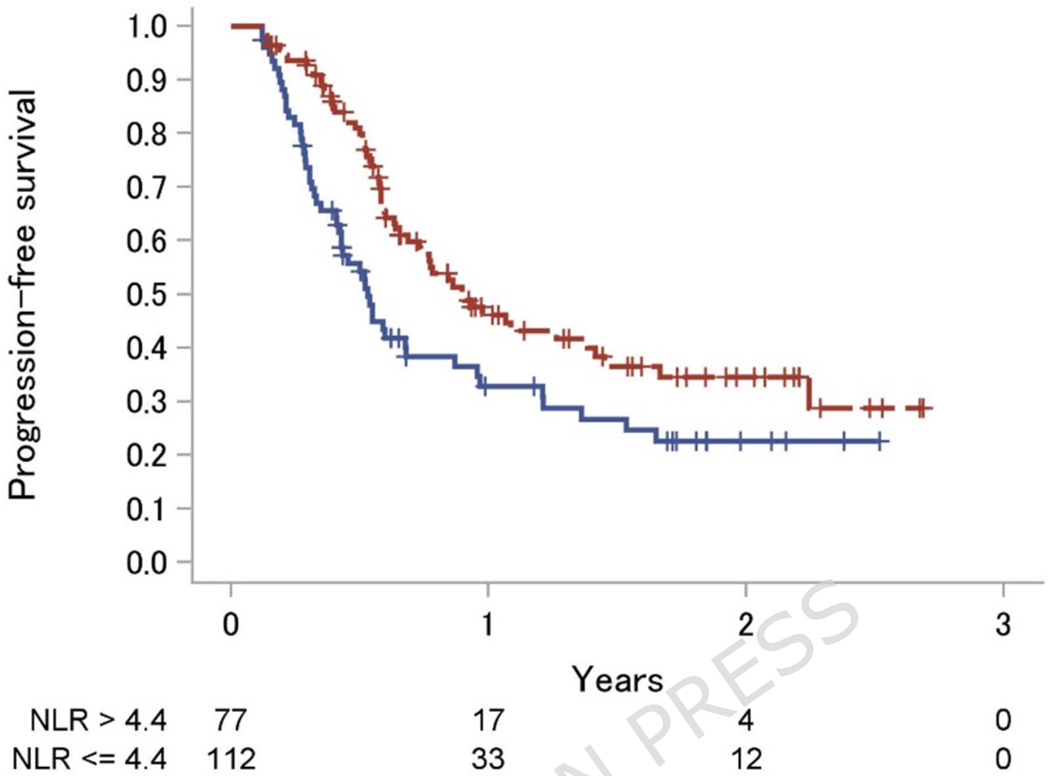
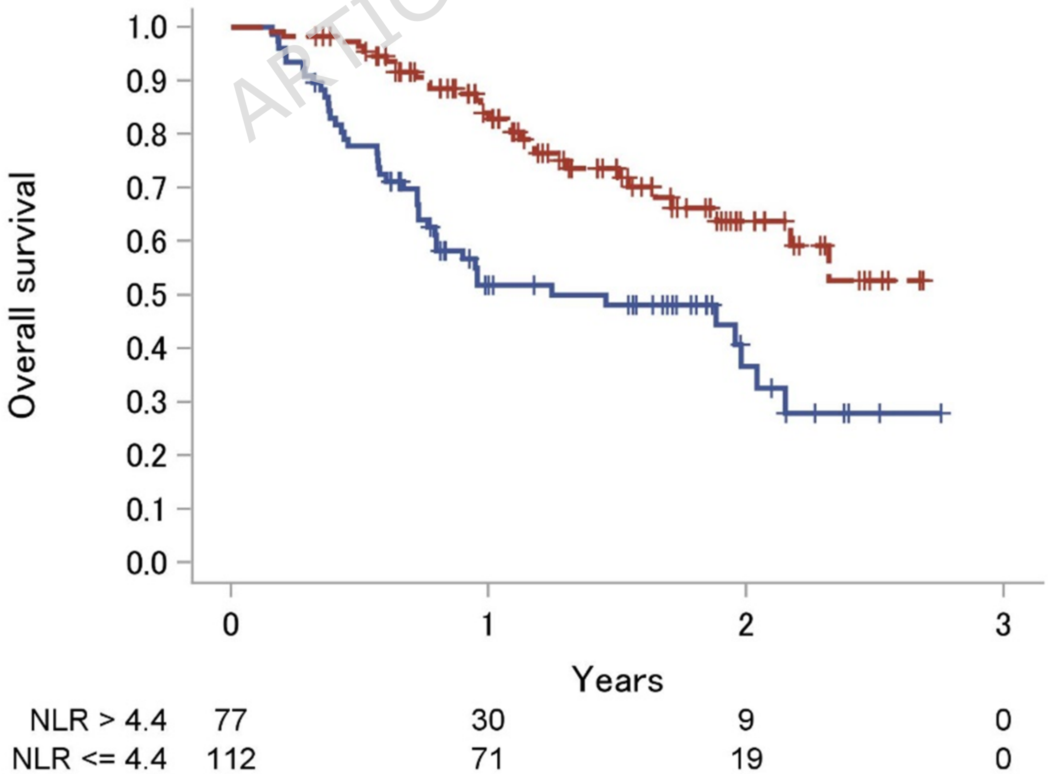

1 year
1.5 years
2 years
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 − Specificity

Fig. 5

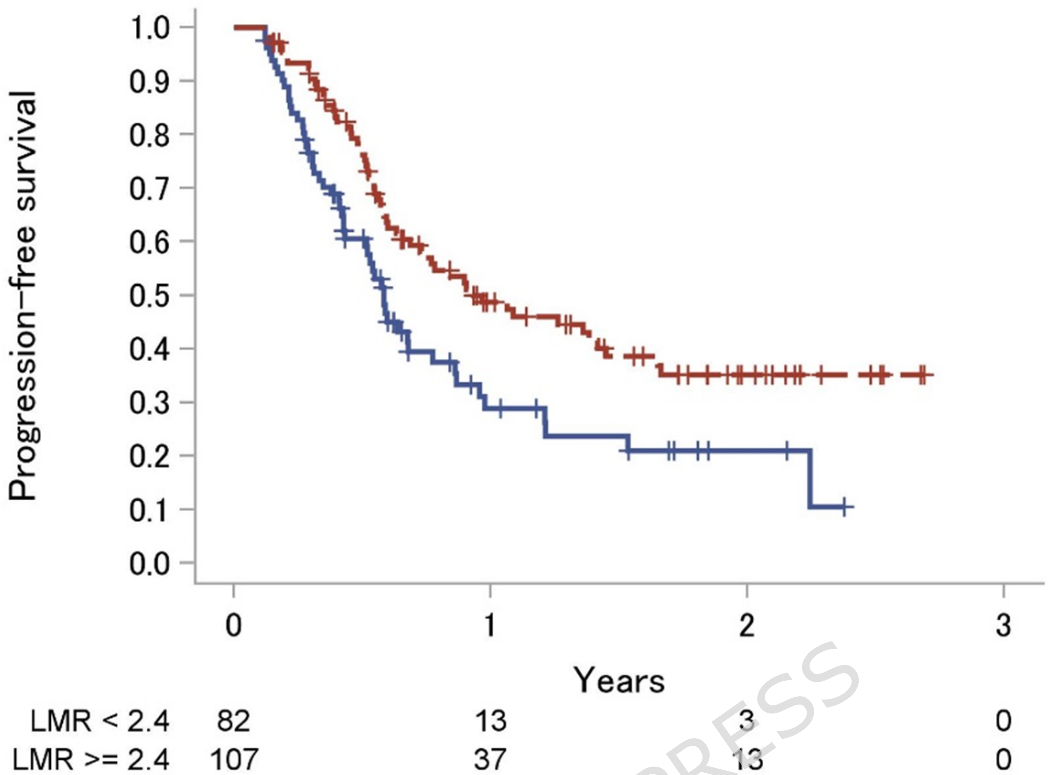
(A)


Progression−free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
Years
NLR > 4.4 77 17 4 0
NLR <= 4.4 112 33 12 0

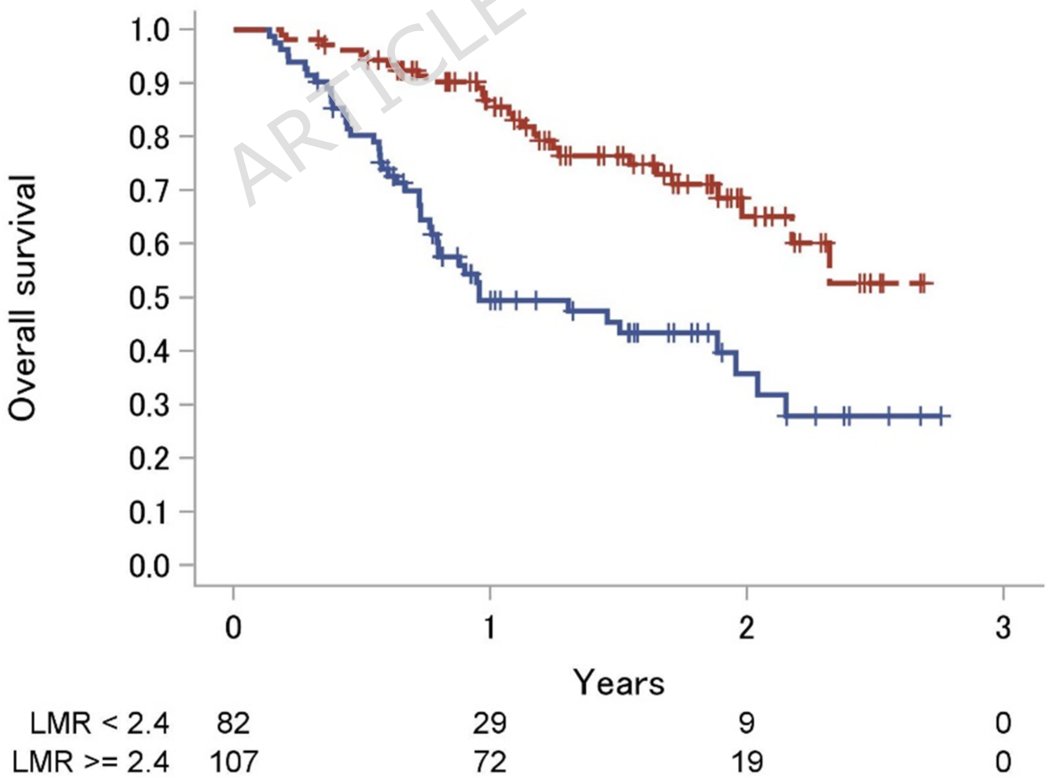
(B)


Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
Years
NLR > 4.4 77 30 9 0
NLR <= 4.4 112 71 19 0

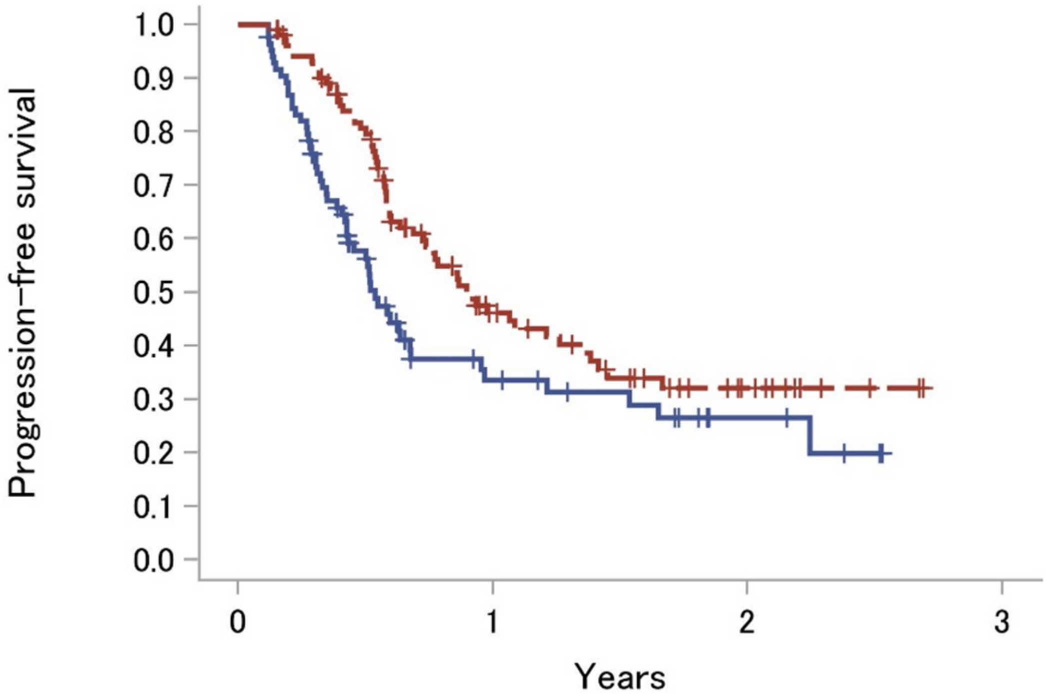
(C)


Progression-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
Years
LMR < 2.4 82 13 3 0
LMR >= 2.4 107 37 13 0

(D)

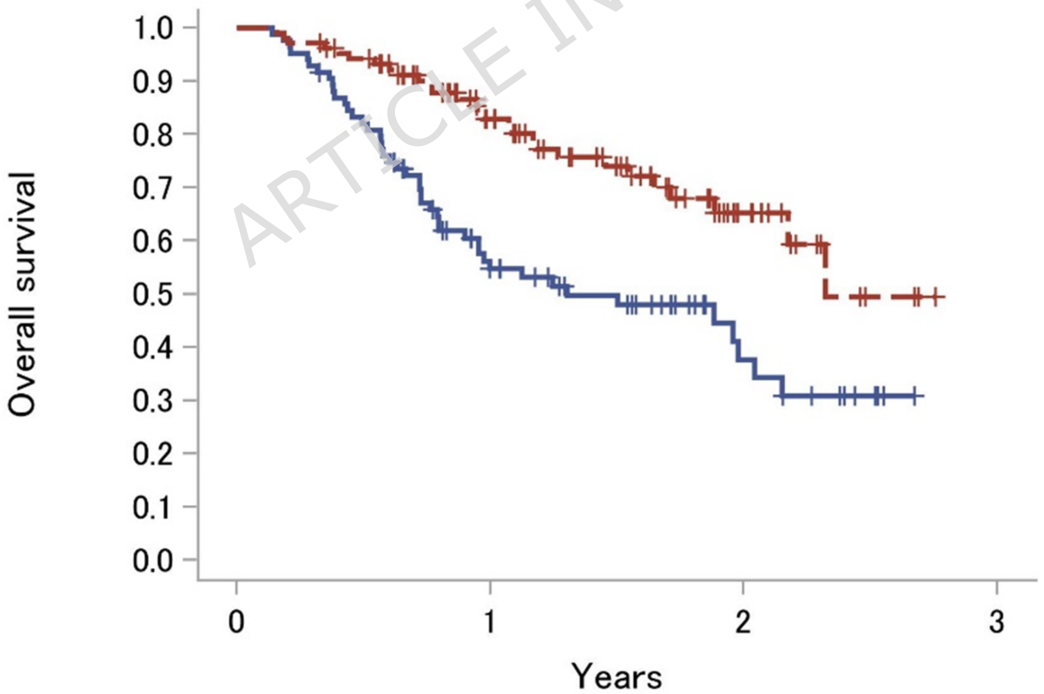

Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
Years
LMR < 2.4 82 29 9 0
LMR >= 2.4 107 72 19 0

(E)



	0	1	2	3
PLR > 235	84	17	5	0
PLR <= 235	104	33	11	0

(F)



	0	1	2	3
PLR > 235	84	37	11	0
PLR <= 235	104	64	17	0