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# Development and validation of a risk-prediction model for immune-related adverse events in patients with non-small-cell lung cancer receiving PD-1/PD-L1 inhibitors

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Lung cancer remains the leading cause of cancer deaths worldwide and is the most common cancer in males. Immune-checkpoint inhibitors (ICIs) that target programmed cell death protein-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) have achieved impressive efficacy in the treatment of non-small-cell lung cancer (NSCLC) (Pardoll, 2012; Champiat et al., 2016; Gao et al., 2022). Although ICIs are usually well tolerated, they are often accompanied by immune-related adverse events (irAEs) (Doroshow et al., 2019). Non-specific activation of the immune system produces off-target immune and inflammatory responses that can affect virtually any organ or system (O'Kane et al., 2017; Puzanov et al., 2017). Compared with adverse events caused by chemotherapy, irAEs are often characterized by delayed onset and prolonged duration and can occur in any organ at any stage of treatment, including after cessation of treatment (Puzanov et al., 2017; von Itzstein et al., 2020). They range from rash, pneumonitis, hypothyroidism, enterocolitis, and autoimmune hepatitis to cardiovascular, hematological, renal, neurological, and ophthalmic irAEs (Nishino et al., 2016; Kumar et al., 2017; Song et al., 2020). Hence, we conducted a retrospective study to identify validated factors that could predict the magnitude of the risk of irAEs in patients receiving PD-1/PD-L1 inhibitors; our approach was to analyze the correlation between the clinical characteristics of patients at the start of treatment and relevant indicators such as hematological indices and the risk of developing irAEs. Then, we developed an economical, practical, rapid, and simple model to assess the risk of irAEs in patients receiving ICI treatment, as early as possible.

A total of 357 patients with NSCLC who received PD-1/PD-L1 inhibitors were included in our study. Their characteristics are given in Table S1. The training dataset for construction of the irAE risk-prediction model consisted of 214 patients, while the remaining 143 were used to validate it. The median age was 65 years, males accounted for 293 cases (82.1%), and the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was 0 or 1 in 271 patients (75.9%); 79 patients (22.1%) had grade≥2 irAEs. A total of 92 cases (25.8%) were stage III, and 265 cases (74.2%) were stage IV at the time of diagnosis. A total of 110 (30.8%) patients were treated with PD-1/PD-L1 inhibitors as monotherapy, 187 (52.4%) patients were treated with first-line therapy, and 199 (55.7%) had distant metastases from the tumor. There were 45 patients (21.0%) with irAEs in the training set and 34 (23.8%) with irAEs in the validation set.

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Among the 79 (22.1%) patients with irAEs, the median time between the first PD-1/PD-L1 inhibitor and the onset of irAEs was 115 d. According to Cox regression analysis (Table 1), high age ($P$=0.002), high body

**Table 1 Univariate and multivariate Cox analyses of immune-related adverse events (irAEs)**

| Variable | Cut off value | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Age | ≥65 years | 2.791 (1.449–5.377) | 0.002 | 2.702 (1.374–5.314) | 0.008 |
| Gender | | | | | |
| Female | | 1 (Reference) | | | |
| Male | | 1.595 (0.569–4.473) | 0.375 | | |
| BMI | ≥23.74 kg/m$^2$ | 2.791 (1.499–5.198) | 0.001 | 2.223 (1.168–4.234) | 0.004 |
| Clinical stage | | | | | |
| III | | 1 (Reference) | | | |
| IV | | 1.065 (0.145–7.802) | 0.950 | | |
| Pathological type | | | | | |
| Adenocarcinoma | | 1 (Reference) | | | |
| Squamous-cell carcinoma | | 1.042 (0.572–1.899) | 0.892 | | |
| Therapy medicine | | | | | |
| Monotherapy | | 1 (Reference) | | | |
| Combination therapy | | 1.036 (0.557–1.928) | 0.911 | | |
| ECOG | | | | | |
| 0 | | 1 (Reference) | | | |
| 1 | | 1.308 (0.651–2.626) | 0.450 | | |
| 2 | | 2.016 (0.923–4.402) | 0.078 | | |
| 3 | | 1.116 (0.147–8.476) | 0.916 | | |
| Treatment line | | | | | |
| 1 | | 1 (Reference) | | | |
| 2 | | 1.289 (0.657–2.530) | 0.460 | | |
| 3 | | 1.563 (0.683–3.579) | 0.290 | | |
| 4 | | 0.671 (0.090–5.023) | 0.698 | | |
| Laboratory testing | | | | | |
| ALC | ≥1.06×10$^9$ L$^{-1}$ | 0.700 (0.383–1.278) | 0.245 | | |
| AMC | ≥0.45×10$^9$ L$^{-1}$ | 1.702 (0.903–3.206) | 0.100 | | |
| ANC | ≥6.38×10$^9$ L$^{-1}$ | 0.477 (0.201–1.128) | 0.092 | | |
| AEC | ≥0.11×10$^9$ L$^{-1}$ | 0.678 (0.374–1.228) | 0.200 | | |
| LDH | ≥260.00 U/L | 1.844 (0.927–3.668) | 0.081 | | |
| CRP | ≥19.00 mg/L | 0.599 (0.309–1.161) | 0.129 | | |
| NSE | ≥20.43 ng/μL | 0.242 (0.075–0.780) | 0.192 | | |
| SCC | ≥0.65 ng/μL | 2.422 (0.746–7.862) | 0.141 | | |
| ProGRP | ≥38.45 pg/μL | 2.211 (0.874–5.593) | 0.094 | | |
| CYFRA21-1 | ≥2.73 μg/L | 0.395 (0.200–0.782) | 0.647 | | |
| CA125 | ≥22.00 U/mL | 1.548 (0.816–2.939) | 0.181 | | |
| CEA | ≥1.83 ng/mL | 1.362 (0.767–2.421) | 0.292 | | |
| NLR | ≥5.22 | 0.494 (0.236–1.032) | 0.061 | | |
| LMR | ≥4.65 | 0.872 (0.691–1.100) | 0.249 | | |
| dNLR | ≥2.54 | 0.850 (0.667–1.083) | 0.189 | | |
| SII | ≥872.72 | 0.330 (0.168–0.650) | 0.001 | 0.281 (0.098–0.811) | 0.004 |
| PLR | ≥171.97 | 0.506 (0.279–0.919) | 0.025 | 0.635 (0.166–2.429) | 0.507 |
| PNI | ≥48.00 | 1.930 (1.088–3.423) | 0.025 | 1.500 (0.749–3.002) | 0.252 |

HR: hazard ratio; CI: confidence interval; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; ALC: absolute lymphocyte count; AMC: absolute monocyte count; ANC: absolute neutrophil count; AEC: absolute eosinophils count; LDH: lactate dehydrogenase; CRP: C-reactive protein; NSE: nerve-specific enolase; SCC: squamous cell carcinoma; ProGRP: pro-gastrin-releasing peptide; CYFRA21-1: cytokeratin 19 fragment 21-1; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; dNLR: derive neutrophil-to-lymphocyte ratio; SII: systemic immune-inflammation index; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.

mass index (BMI) ($P$=0.001), low systemic immune-inflammation index (SII) ($P$=0.001), high prognostic nutritional index (PNI) ($P$=0.025), and low platelet-to-lymphocyte ratio (PLR) ($P$=0.025) were associated with greater occurrence of irAEs (grade≥2).

Multifactorial Cox analysis confirmed that high BMI (hazard ratio (HR)=2.4955, 95% confidence interval (CI): 1.3416–4.6418, $P$=0.004), high age (HR=2.3908, 95% CI: 1.2556–4.5525, $P$=0.008), and low SII (HR=0.3694, 95% CI: 0.1862–0.7329, $P$=0.004) were independent predictors of the occurrence of grade≥2 irAEs (Table 1). We developed a risk-prediction model for irAEs based on the three independent predictors mentioned above (SII<872.71, age≥65 years, and BMI≥23.74 kg/m$^2$) (Fig. 1a). Patients were risk-stratified according to the irAE risk-prediction model. Of the 214 patients in the training set, 90 (42.0%) were in the high-risk group and 124 (57.9%) in the low-risk group, with a significant difference in the occurrence of grade≥2 irAEs between the two groups ($P$<0.001). Of the 143 patients in the validation set, 55 (38.5%) were in the high-risk group and 88 (61.5%) in the low-risk group, and there was also a significant difference in the occurrence of grade≥2 irAEs between the two groups ($P$<0.001; Figs. 1b and 1c).

We used the area under the receiver operating characteristic (ROC) curve (AUC) to assess the discriminatory performance of the irAE risk-prediction model. Good discriminative ability was verified for both the training and validation sets (Figs. 2a and 2b). In the

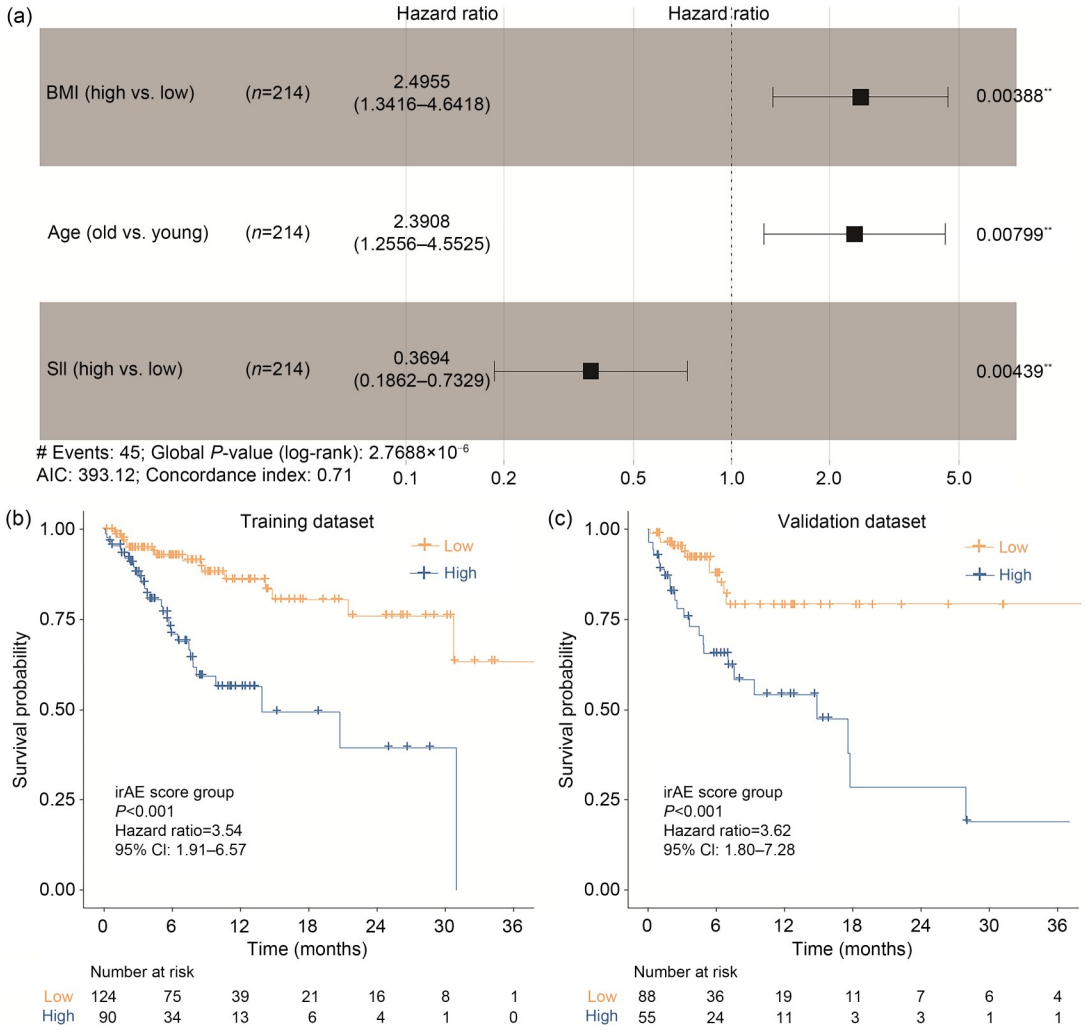


**Fig. 1 Multifactorial analysis of immune-related adverse events (irAEs) (a) and Kaplan-Meier curves for occurrence of irAEs in a population (training dataset (b) and validation dataset (c)) stratified according to the irAE risk-prediction model. BMI: body mass index; SII: systemic immune-inflammation index; AIC: Akaike information criterion; CI: confidence interval. ** $P$<0.01.**

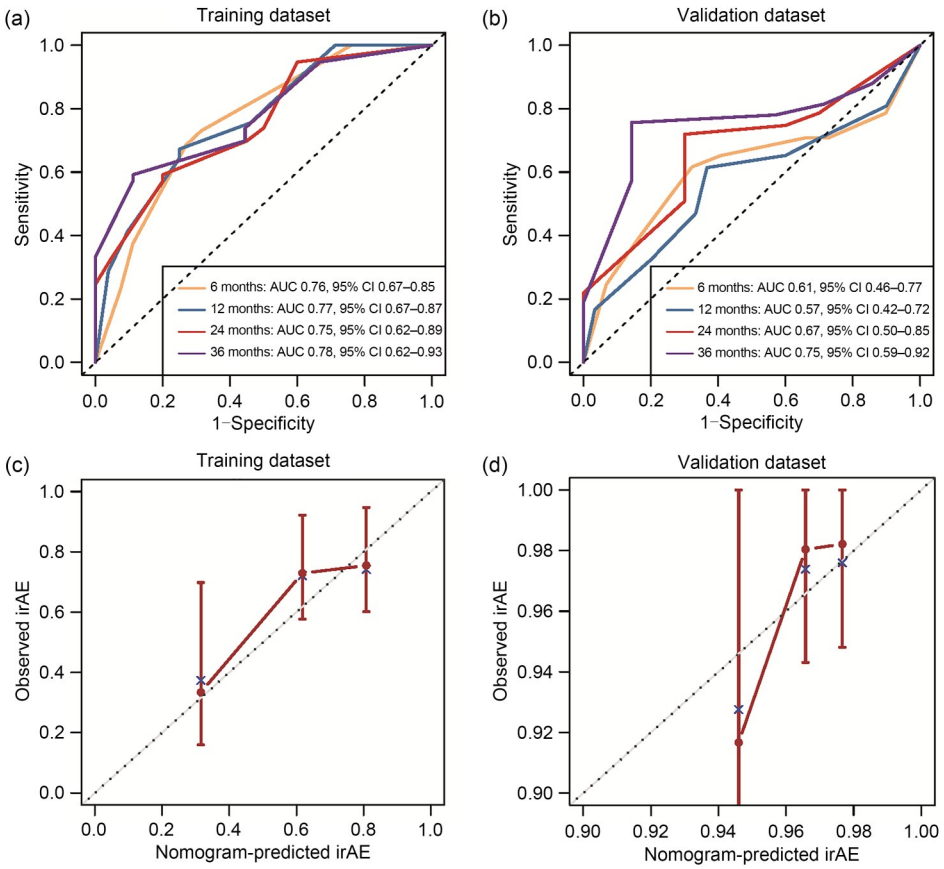


**Fig. 2 Receiver operating characteristic (ROC) analyses and calibration curves. (a, b) ROC curves of immune-related adverse event (irAE) predictions in the training (a) and validation (b) datasets; (c, d) Calibration plots for the training (c) and testing (d) datasets. AUC: area under curve; CI: confidence interval.**

training data set: 6-month AUC 0.76, 95% CI 0.67–0.85; 12-month AUC 0.77, 95% CI 0.67–0.87; 24-month AUC 0.75, 95% CI 0.62–0.89; 36-month AUC 0.78, 95% CI 0.62–0.93. In the validation data set: 6-month AUC 0.61, 95% CI 0.46–0.77; 12-month AUC 0.57, 95% CI 0.42–0.72; 24-month AUC 0.67, 95% CI 0.5–0.85; 36-month AUC 0.75, 95% CI 0.59–0.92. In addition, calibration plots of the irAE risk-prediction model showed that actual clinical outcomes correlated closely with predicted outcomes (Figs. 2c and 2d).

Seventy-nine patients (22.1%) in the entire study population experienced at least one irAE (grade≥2). Sixty (75.9%) of them were male. The specific distribution of irAEs is shown in Table 2. The most common were immune-associated pneumonitis ($n$=38, 10.6%), skin disease ($n$=26, 7.2%), and immune-associated hepatitis ($n$=15, 4.2%). Of the irAEs exhibited in different organ types, those in the endocrine system resulted in relatively long median progression-free survival (mPFS) (14.53 months) and median overall survival (mOS)

**Table 2 Frequency and long-term prognosis of different types of immune-related adverse events (irAEs)**

| Variable | Frequency (number (percentage)) | mPFS (months) | mOS (months) |
|---|---|---|---|
| Grade of irAE | | | |
| Non-≥2 | 278 (77.9%) | 6.30 | 11.30 |
| ≥2 | 79 (22.1%) | 8.90 | 13.13 |
| Type of irAE | | | |
| Skin disease | 26 (7.2%) | 9.67 | 14.77 |
| Enteritis | 3 (0.8%) | 1.60 | 14.57 |
| Nephritis | 5 (1.4%) | 4.33 | 14.13 |
| Pneumonitis | 38 (10.6%) | 8.27 | 13.00 |
| Neurotoxicity | 1 (0.2%) | 16.77 | 16.77 |
| Endocrine toxicities | 8 (2.2%) | 14.53 | 21.40 |
| Hepatitis | 15 (4.2%) | 8.53 | 11.27 |
| Blood disorders | 1 (0.2%) | 1.97 | 3.63 |

When more than one type of irAE occurred in a patient, the incidence is reported by the number of irAE types. mPFS: median progression-free survival; mOS: median overall survival.

(21.4 months); this excludes neurotoxicity, which occurred in only one patient.

The median follow-up time for the total population was 11.8 months, and the maximum follow-up duration was 60.8 months. According to the univariate Cox regression analysis, the occurrence of grade≥2 irAEs in the study population was significantly associated with better PFS ($P$=0.006) and better OS ($P$=0.002) (Figs. 3a and 3b). PFS ($P$=0.003) and OS ($P$=0.001) were statistically significantly different in patients with grade 2 irAEs compared to those with non-≥2 irAEs; however, PFS ($P$=0.551) and OS ($P$=0.680) were not statistically different in patients with severe irAEs (grade≥3) compared to those with non-≥2 irAEs (Figs. 3c and 3d).

We performed a subgroup analysis of the 357 patients for key clinical parameters such as therapeutic agents, clinical tumor node metastasis classification (TNM) stage, treatment route, and surgical history, and found that the predictive power of the irAE risk-prediction model was very stable across subgroups (Table S2). In addition, the Kaplan-Meier curve shows that the irAE risk-prediction model could not predict the PFS, but could predict OS (Figs. 4a and 4b). High risk as predicted by the model was strongly associated with longer OS ($P$<0.001).

In summary, we identified the predictors and constructed an irAE risk-prediction model to help clinicians identify NSCLC patients receiving PD-1/PD-L1 inhibitors who would be at risk of developing early irAEs; this would permit more proactive and effective management of irAEs. The investigational biomarkers currently are available as predictors and diagnostics of irAEs such as cell, hormone, tissue, antibody, and microbe, all of which are at an early stage of exploration and therefore have many limitations in true clinical application. For example, they are expensive, difficult to obtain, and have a small scope of application (von

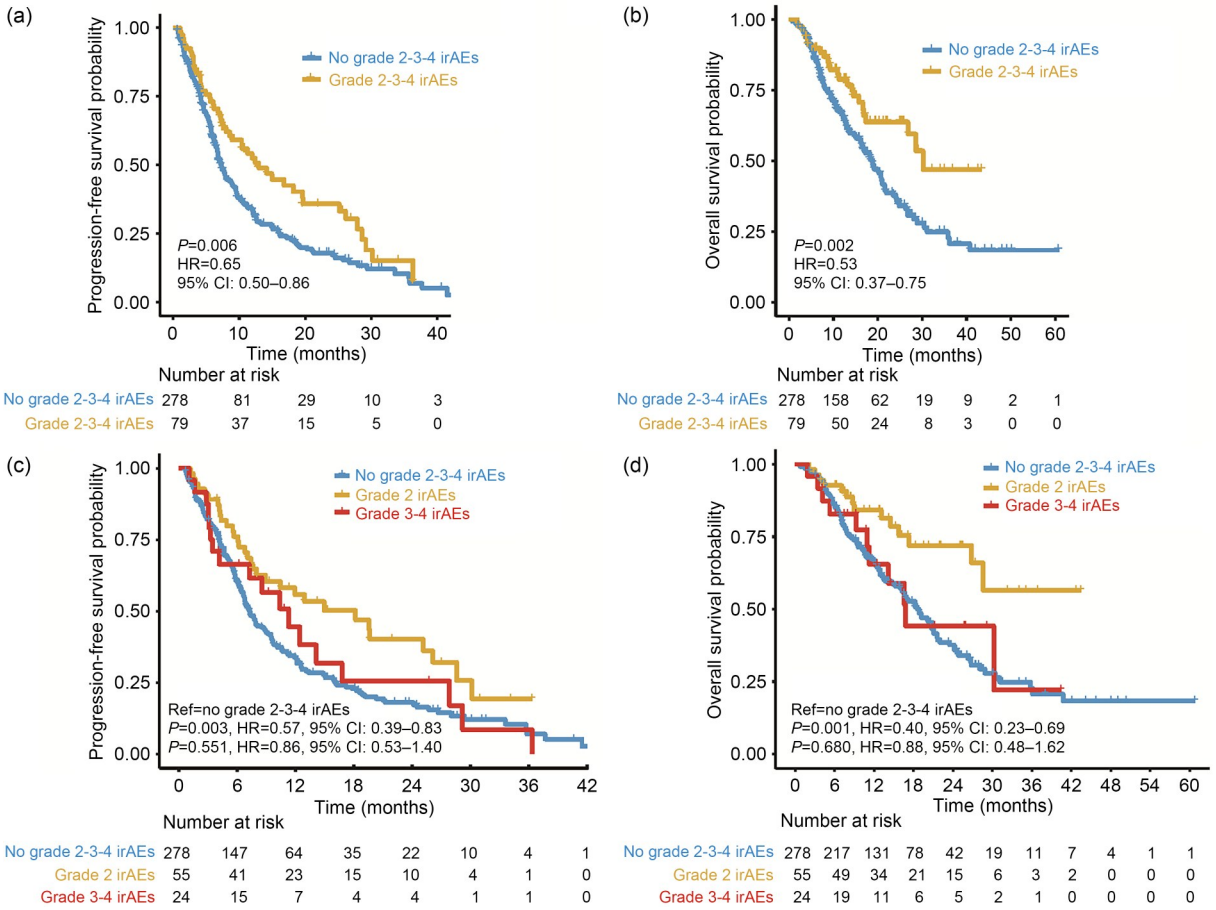


**Fig. 3 Progression-free survival (PFS) (a, c) and overall survival (OS) (b, d) for each immune-related adverse event (irAE) population (grade≥2). PFS (a) and OS (b) in patients with grade 2 irAEs and non-≥grade 2 irAEs; PFS (c) and OS (d) in different grades of irAEs. HR: hazard ratio; CI: confidence interval.**

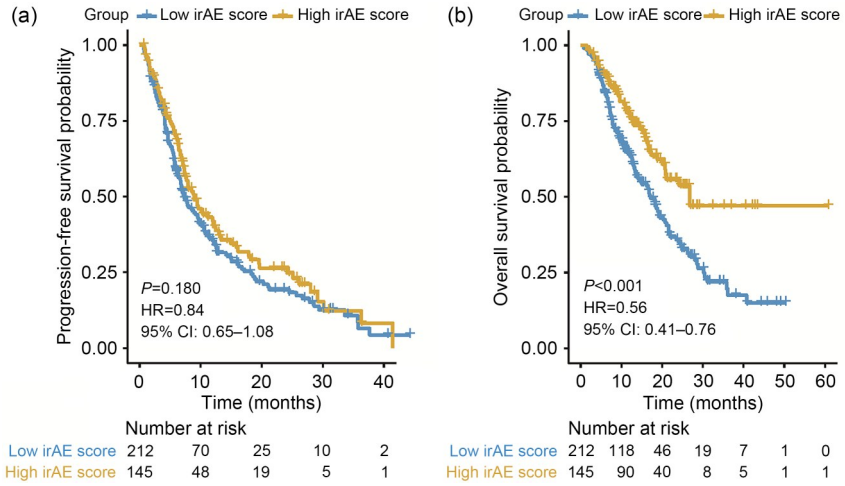


**Fig. 4 Kaplan-Meier curves of progression-free survival (PFS) (a) and overall survival (OS) (b) in high-risk and low-risk populations according to the immune-related adverse event (irAE) risk-prediction model.**

Itzstein et al., 2020). This risk-prediction model does not require additional tests or invasive examinations, and has the advantages of being fast, economical, and practical.

We identified three predictors: BMI, SII, and age. BMI is a common indicator for assessing body fat (Deurenberg et al., 1998), and some studies have found that high levels of body fat can play a key role in the induction of toxicity in cancer patients during treatment by affecting the body's metabolic and inflammatory profile (Georgiadis et al., 1995; Mirsoian and Murphy, 2015). One study evaluated 1700 patients with advanced cancer and found that overweight and obese patients had higher rates of skin, endocrine, gastrointestinal, liver, and other irAEs compared with normal-weight patients (Cortellini et al., 2020). A high BMI may lead to pharmacokinetic changes that affect the absorption, distribution, metabolism, and excretion of ICIs, leading to an increased risk of irAEs after administration (Daly et al., 2017). In fact, a positive association between higher BMI and clinical outcomes has been found in cancer patients treated with ICIs (Cortellini et al., 2019, 2020; Eun et al., 2019). Regarding the relationship between higher BMI, irAE occurrence, and better survival outcomes, Cortellini et al. (2020) suggested that this may be the basis for an "immunogenic phenotype." This is consistent with our findings, which demonstrate that baseline BMI can be used as a biomarker for the development of irAEs and explain the efficacy of this risk-prediction model in predicting survival (Huang et al., 2022).

The SII is calculated based on neutrophil ($N$), platelet ($P$), and lymphocyte ($L$) counts: SII=$N\times P/L$. It works rapidly and has been widely used to predict outcomes for clinical treatment of cancer since it was first proposed (Hu et al., 2014). There are three possible mechanisms that have been considered to date. The first is that neutrophils promote tumor angiogenesis and adhesion of circulating tumor cells by secreting cytokines and chemokines, causing distant metastasis. The next possibility is that tumor cells activate platelets through direct contact and secretion of soluble factors, causing platelets to bind to tumor cells; this would allow the latter to evade the body's immune agents such as natural killer (NK) cells, and promote tumor spread and metastasis. Finally, lymphocytes may mediate adaptive immune responses, inhibit malignant cell proliferation, and decrease tumor progression (Mantovani et al., 2008; Dvorak, 2015; Li, 2016). In a prospective study of 87 patients with NSCLC and 26 healthy donors, Zamora et al. (2021) found that circulating leukocyte–platelet complexes, which cause inflammation and autoimmune disease, were effective predictors of the occurrence of irAEs. Another study retrospectively analyzed 102 patients with advanced NSCLC and found that lower neutrophil-to-lymphocyte ratio (NLR) was an independent predictor of the development of irAEs (Peng et al., 2020). Biswas et al. (2020) compared two different chemotherapy regimens, namely pemetrexed+cisplatin (PEM) and etoposide+cisplatin (ETO), in combination with radiation therapy for stage III non-squamous NSCLC, and demonstrated that lower baseline SII levels were associated with improved survival in lung cancer. SII combines both NLR and platelet count and has the advantages of reproducibility,

convenience, non-invasiveness, and low cost. Although this is the first study to find that low SII is an independent predictor of the occurrence of irAEs in NSCLC patients, these previous studies are congruent with our conclusions.

There is no reported link between PD-1/PD-L1 inhibitors and age-related irAEs in NSCLC. However, there is a consensus that immune-cell subsets and overall immune function decline with age, and this is called "immune aging" (Castelo-Branco and Soveral, 2014). Notably, Kugel et al. (2018) analyzed 538 melanoma patients, constructed a mouse model of melanoma, and found that patients over 60 years of age responded more effectively to anti-PD-1 and that the likelihood of an anti-PD-1 response increased with age. This may be because older melanoma patients have fewer regulatory T cells than cluster of differentiation 8-positive ($CD8^+$) T cells in tumor deposits (Pawelec, 2018). Our results show that irAEs are more likely to occur in older patients than in younger patients. Kugel et al. (2018) also found that the immune microenvironment was more suppressed in the tumors of younger mice, which may explain our finding.

Lymphocytes are one of the most sensitive cell subgroups to radiotherapy, but we did not find a significant difference in lymphocyte counts between the radiotherapy and non-radiotherapy groups, possibly because the interval between radiotherapy and immunotherapy was longer than one month (Wang et al., 2021).

Our results show that the occurrence of irAEs (grade≥2) is associated with a better long-term prognosis. Baseline peripheral blood SII<872.71, age≥65 years, and BMI≥23.74 kg/$m^2$ were independent predictors of the occurrence of irAEs, and we constructed a risk-prediction model for irAEs based on this, which successfully identified groups with a greater risk of developing irAEs. Moreover, the high-risk groups had better OS. These results need to be validated by further prospective studies. Our study also has certain limitations: first, the limited number of patients we studied and the retrospective nature of the data make the results subject to potential information bias. In addition, patients had to be alive at the time of the first irAE to be classified in the irAE group, which may have led to temporal bias (Maillet et al., 2020). Moreover, we did not analyze some important biomarkers such as PD-L1 and tumor mutation burden because of data limitations. Finally, we only considered patients with grade≥2 irAEs because retrospective collection of grade 1 irAEs could have caused significant information bias and because of the large heterogeneity in clinicians' reporting of grade 1 irAEs.

## Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

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## Author contributions

Conception and design: Jun ZHANG and Xinyou XIE. Financial support: Jun ZHANG. Provision of study materials: Qing QIU, Enguo CHEN, Hanliang JIANG, and Longfei JI. Collection and assembly of data: all authors. Data analysis and interpretation: Qing QIU, Yuzhen GAO, and Chenghao WU. Manuscript writing: Qing QIU, Guangwei DAI, and Wenxiao TANG. Manuscript supervised: Jun ZHANG, Xinyou XIE, and Yuzhen GAO. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

## Compliance with ethics guidelines

Qing QIU, Chenghao WU, Wenxiao TANG, Longfei JI, Guangwei DAI, Yuzhen GAO, Enguo CHEN, Hanliang JIANG, Xinyou XIE and Jun ZHANG declare that they have no conflicts of interest for this work.

This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China (No. 2019 Scientific Research Ethics (20190211-55)).

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**Supplementary information**

Tables S1 and S2; Materials and methods