Development and Validation of a Prediction Model for Thyroid Immune-Related Adverse Events in Lung Cancer Patients: Postprint

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Abstract

Background In recent years, immune checkpoint inhibitors (ICIs) have demonstrated significant efficacy in the treatment of lung cancer, but the immune-related adverse events (irAEs) they induce have also attracted widespread attention. Thyroid dysfunction, as the most common endocrine irAE, holds important clinical value for constructing a predictive model. Objective To construct a predictive model for thyroid irAEs in lung cancer patients after ICI therapy. Methods A total of 243 lung cancer patients who received ICI therapy at Hebei General Hospital from January 2020 to March 2024 were retrospectively enrolled as study subjects and randomly sampled at a 7:3 ratio into a training set (n=169) and a validation set (n=74). Based on thyroid function, the training set was divided into a thyroid irAE group (n=71) and a non-thyroid irAE group (n=98). General patient data and laboratory examination indicators were collected, and subgroup analysis was performed according to the Common Terminology Criteria for Adverse Events (CTCAE). Univariate analysis was used to screen variables, and multivariate Logistic regression analysis was employed to identify independent influencing factors of thyroid irAEs; variance inflation factor was used to assess multicollinearity among predictive factors. Based on the multivariate Logistic regression analysis results, a nomogram model for thyroid irAEs was constructed. The receiver operating characteristic (ROC) curve for predicting thyroid irAEs was plotted, and the area under the ROC curve (AUC) was calculated. Bootstrap resampling method was used for internal validation of the model, and model performance was evaluated through Hosmer-Lemeshow test, decision curve analysis (DCA), and clinical impact curve (CIC). Kaplan-Meier analysis was used to compare the cumulative incidence of thyroid irAEs across risk stratifications. Multivariate Logistic regression analysis was employed to analyze influencing factors of thyroid irAEs in patients with different CTCAE grades. Results Among the 169 lung cancer patients in the training set, 138 were male (81.66%) and 31 were female (18.34%); the median age was 66 years (60,

71). The thyroid irAE group comprised 71 cases (42.01%), and the non-thyroid irAE group comprised 98 cases (57.99%). Comparisons between the two groups in ICI treatment cycles, Ki-67, tumor size, and FT3 showed statistically significant differences (P<0.05). Multivariate Logistic regression analysis results showed that TSH, FT3, tumor size, Ki-67, and CYFRA21-1 were independent influencing factors for thyroid irAEs in lung cancer patients (P<0.05). A nomogram model was constructed using TSH, FT3, Ki-67, CYFRA21-1, and tumor size as predictive factors. The AUC of the nomogram model for diagnosing thyroid irAEs in lung cancer patients was 0.796, with a specificity of 0.827 and sensitivity of 0.634; the validation set AUC was 0.730, with a specificity of 0.810 and sensitivity of 0.562. Bootstrap internal validation yielded a C-index of 0.796 and an accuracy of 75%, indicating good discriminative ability of the model; Hosmer-Lemeshow test results showed good goodness-of-fit (P>0.05). The calibration curve showed good consistency between predicted probabilities and actual observed values for thyroid irAE occurrence; the DCA curve demonstrated that the model could provide good clinical net benefit within a probability range of 0-95%; the CIC curve indicated that as the model threshold increased, predicted thyroid irAE occurrence was consistent with actual diagnostic results, suggesting good clinical utility of the model. Based on the optimal probability threshold of the thyroid irAE prediction model (Pr value $\geq$ 0.474), the 243 lung cancer patients were divided into a high-risk group of 94 cases (38.68%) and a low-risk group of 149 cases (61.32%). Kaplan-Meier analysis results showed that the cumulative incidence of thyroid irAEs in the high-risk group was significantly higher than that in the low-risk group at the 6th treatment cycle (2 = 28.15, P<0.001), with the risk in the high-risk group being 2.63 times that of the low-risk group. Multivariate Logistic analysis results of influencing factors for thyroid irAEs across different CTCAE grades showed that FT3 and tumor size were independent influencing factors for thyroid irAEs in the CTCAE $\geq$ grade 2 subgroup; whereas TSH, FT3, tumor size, Ki-67, and CYFRA21-1 were all independent influencing factors for thyroid irAEs in the CTCAE grade 1 subgroup (P<0.05), suggesting that the model has greater predictive advantage for CTCAE grade 1 thyroid irAEs. Conclusion This study established a thyroid irAE prediction model based on TSH, FT3, tumor size, Ki-67, and CYFRA21-1. Active monitoring of thyroid function in patients with a predicted probability $\geq$ 47.4% may help reduce immunotoxicity risk and improve quality of life.

Full Text

Construction and Validation of a Prediction Model for Thyroid Immune-Related Adverse Events in Lung Cancer Patients

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Abstract

Background: In recent years, immune checkpoint inhibitors (ICIs) have demonstrated remarkable efficacy in lung cancer treatment, but their associated immune-related adverse events (irAEs) have garnered widespread attention. Thyroid dysfunction represents the most common endocrine irAE, making the construction of a prediction model clinically valuable.

Objective: To develop and validate a prediction model for thyroid irAEs in lung cancer patients receiving ICI therapy.

Methods: We retrospectively enrolled 243 lung cancer patients who received ICI treatment at Hebei Provincial People' s Hospital between January 2020 and March 2024. Patients were randomly divided into a training set (n=169) and a validation set (n=74) at a 7:3 ratio. Based on thyroid function, the training set was stratified into a thyroid irAE group (n=71) and a non-thyroid irAE group (n=98). General patient data and laboratory indicators were collected, with subgroup analysis performed according to the Common Terminology Criteria for Adverse Events (CTCAE). Variables were screened through univariate analysis, and independent influencing factors for thyroid irAEs were identified via multivariate logistic regression. Multicollinearity among predictors was assessed using variance inflation factor (VIF). A thyroid irAE nomogram model was constructed based on multivariate logistic regression results. The receiver operating characteristic (ROC) curve was plotted, and the area under the ROC curve (AUC) was calculated. Internal validation was performed using Bootstrap resampling, and model performance was evaluated through Hosmer-Lemeshow test, decision curve analysis (DCA), and clinical impact curve (CIC). Kaplan-Meier analysis was used to compare cumulative incidence across risk strata. Multivariate logistic regression was employed to analyze influencing factors for thyroid irAEs in patients with different CTCAE grades.

Results: In the training set of 169 lung cancer patients, 138 (81.66%) were male and 31 (18.34%) were female, with a median age of 66 years (60, 71). The thyroid irAE group comprised 71 patients (42.01%), while the non-thyroid irAE group included 98 patients (57.99%). Significant differences were observed between groups in ICI treatment cycles, Ki-67 index, tumor size, and FT3 levels ($P<0.05$). Multivariate logistic regression revealed that TSH (OR=1.636, 95%CI=1.070-2.503, P=0.023), FT3 (OR=6.868, 95%CI=2.812-16.776, P<0.001), tumor size (OR=0.965, 95%CI=0.942-0.989, P=0.004), Ki-67 (OR=1.028, 95%CI=1.008-1.048, P=0.005), and CYFRA21-1 (OR=1.050, 95%CI=1.016-1.085, P=0.003) were independent predictors

of thyroid irAEs (P<0.05). A nomogram model incorporating TSH, FT3, Ki-67, CYFRA21-1, and tumor size achieved an AUC of 0.796, specificity of 0.827, and sensitivity of 0.634 in the training set; the validation set showed an AUC of 0.730, specificity of 0.810, and sensitivity of 0.562. Bootstrap internal validation yielded a C-index of 0.796 with 75% accuracy, indicating good discrimination. Hosmer-Lemeshow test demonstrated good model fit (P>0.05). Calibration curves showed strong agreement between predicted and observed probabilities. DCA indicated good clinical net benefit across a 0–95% probability range. CIC curves confirmed that predicted thyroid irAE occurrence aligned with actual diagnoses as the threshold increased, demonstrating good clinical utility. Using the optimal probability threshold (Pr$ 0.474), 243 $lung cancer patients were stratified into high - risk (n = 94, 38.68^{2}$=28.15, P<0.001), with a hazard ratio of 2.63 (95%CI=1.770–3.905, P<0.001). Multivariate analysis across CTCAE grades showed that FT3 (OR=5.513, 95%CI=1.846–16.465, P=0.002) and tumor size (OR=0.963, 95%CI=0.928–0.999, P=0.044) were independent predictors for CTCAE $ $2 grade thyroid irAEs, whereas TSH, FT3, tumor size, Ki-67, and CYFRA21-1 were all independent predictors for CTCAE grade 1 thyroid irAEs (P<0.05), suggesting the model has greater predictive advantage for grade 1 events.

Conclusion: We established a thyroid irAE prediction model based on TSH, FT3, tumor size, Ki-67, and CYFRA21-1. Active thyroid function monitoring in patients with a predicted probability $ $47.4% may help reduce immunotoxicity risk and improve quality of life.

Keywords: Lung cancer; Immune checkpoint inhibitors; Thyroid immune-related adverse event; Prediction model

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1.1 Study Population

We retrospectively enrolled 243 lung cancer patients who received ICI therapy at Hebei Provincial People' s Hospital between January 2020 and March 2024. Inclusion criteria were: (1) age >20 years; (2) cytologically or histologically confirmed lung cancer; (3) treatment with programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors combined with chemotherapy (with or without surgery). Exclusion criteria included: (1) <2 ICI treatment cycles; (2) severely incomplete clinical data; (3) abnormal or missing baseline thyroid hormone levels; (4) history of head or neck radiotherapy; (5) use of medications potentially affecting thyroid function (e.g., thyroid hormones, antithyroid drugs, targeted agents, opioids, iodine or lithium preparations, high-dose or long-term glucocorticoids); and (6) comorbid severe diseases involving vital organs such as heart, brain, or kidneys, or other malignancies. This study was approved by the Medical Ethics Committee of Hebei Provincial People' s Hospital (Approval No. 2025-LW-0027).

Sample size was calculated based on the events per variable (EPV) criterion.

With a thyroid irAE incidence of 0.42 following ICI therapy and five planned predictor variables, we set EPV at 10, yielding a required sample size of 86. Our study ultimately included 243 patients, randomly divided into training (n=169) and validation (n=74) sets at a 7:3 ratio.

1.2 Data Collection

1.2.1 General Data Collection: We collected patient age, sex, body mass index (BMI), smoking index (daily cigarettes × years smoked), TNM (tumor-node-metastasis) stage, pathological type, ICI treatment cycles, ICI type, surgical combination status, and time to thyroid irAE onset (interval from first ICI treatment to first thyroid irAE).

1.2.2 Laboratory Indicators: (1) Ki-67 index: representing the proportion of tumor cells in the proliferative phase, determined by pathologists via microscopic examination of malignant tissue; (2) Lung cancer markers: carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCCA), neuron-specific enolase (NSE), and cytokeratin 19 fragment (CYFRA21-1); (3) Tumor size: maximum diameter on chest CT; (4) Thyroid function indicators: total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH); (5) Systemic inflammatory and metabolic indicators: neutrophil count (NEU), lymphocyte count (LYM), platelet count (PLT), albumin (ALB), direct bilirubin (CB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total cholesterol (CH), triglycerides (TG), low-density lipoprotein cholesterol (LDL), prognostic nutritional index (PNI), systemic immune-inflammation index (SII), and neutrophil-to-lymphocyte ratio (NLR). PNI was calculated as ALB + 5×LYM; SII as NEU×PLT/LYM; and NLR as NEU/LYM. All thyroid function parameters were collected before each ICI cycle (approximately 4-week intervals), while other indicators were collected before the first ICI treatment. Missing values were imputed using mean, median, or mode as appropriate.

1.2.3 Grouping: According to the Chinese Society of Endocrinology guidelines for thyroid irAE diagnosis, patients were divided into thyroid irAE group (abnormal thyroid function tests) and non-thyroid irAE group (normal thyroid function tests) based on reference ranges (TT3: 1.3–3.1 nmol/L; TT4: 66–181 nmol/L; FT3: 3.1–6.8 pmol/L; FT4: 12–22 pmol/L; TSH: 0.27–4.2 IU/mL). The thyroid irAE group was further stratified into CTCAE grade 1 subgroup (clinical diagnosis only, no intervention required) and CTCAE $ $2 subgroup (requiring intervention or resulting in death) according to CTCAE version 5.0.

1.3 Statistical Analysis

Statistical analysis was performed using SPSS 25.0. Categorical data are presented as proportions and compared using ^{2} tests. Normally distributed continuous data are expressed as mean±standard deviation and compared using

independent samples t-tests. Non-normally distributed data are presented as median (P25, P75) and compared using Mann-Whitney U tests. Variables with P<0.2 in univariate analysis were included in multivariate binary logistic regression analysis. Multicollinearity among predictors was assessed using variance inflation factor (VIF). R software version 4.4.1 was used to construct the nomogram prediction model, plot ROC curves, and calculate AUC values. Bootstrap resampling (1000 repetitions) was employed for internal validation. Calibration curves assessed agreement between predicted probabilities and observed values, while Hosmer-Lemeshow test evaluated model fit. Decision curve analysis (DCA) assessed clinical benefit, and clinical impact curve (CIC) evaluated clinical utility. Differences in onset time between CTCAE grade 1 and $ $2 thyroid irAEs were compared, and multivariate logistic regression explored associations between model predictors and different irAE grades. Risk stratification was performed based on the optimal probability threshold, and Kaplan-Meier analysis compared cumulative incidence across risk groups. P<0.05 was considered statistically significant.

2.1 Comparison of General Data and Laboratory Indicators in the Training Set

The training set included 169 lung cancer patients: 138 males (81.66%) and 31 females (18.34%), with a median age of 66 years (60, 71). The thyroid irAE group contained 71 patients (42.01%), while the non-thyroid irAE group had 98 patients (57.99%). Significant differences were observed between groups in ICI treatment cycles, Ki-67 index, tumor size, and FT3 levels (P<0.05). No significant differences were found in age, sex, BMI, smoking index, TNM stage, M stage, pathological type, ICI type, surgical combination, TT3, TT4, FT4, TSH, CEA, SCCA, NSE, CYFRA21-1, NEU, LYM, PLT, ALB, CB, ALT, AST, LDH, CH, TG, LDL, PNI, SII, or NLR (P>0.05) .

2.2 Multivariate Logistic Regression Analysis of Thyroid irAE Influencing Factors in the Training Set

Using thyroid irAE occurrence as the dependent variable (no=0, yes=1) and variables with P<0.2 in univariate analysis as independent variables (including age, BMI, ICI treatment cycles, tumor size, Ki-67, TT3, FT3, TSH, CYFRA21-1, NEU, PLT, CB, ALT, AST, CH, LDL, PNI, SII, TNM stage, and M stage), multivariate logistic regression identified TSH (OR=1.636, 95%CI=1.070-2.503, P=0.023), FT3 (OR=6.868, 95%CI=2.812-16.776, P<0.001), tumor size (OR=0.965, 95%CI=0.942-0.989, P=0.004), Ki-67 (OR=1.028, 95%CI=1.008-1.048, P=0.005), and CYFRA21-1 (OR=1.050, 95%CI=1.016-1.085, P=0.003) as independent predictors of thyroid irAEs in lung cancer patients (P<0.05) . Multicollinearity assessment showed VIF values of 1.028, 1.049, 1.115, 1.037, and 1.115 for TSH, FT3, tumor size, Ki-67, and CYFRA21-1, respectively, indicating no significant collinearity (all VIF<5).

2.3 Nomogram Prediction Model Construction

Based on multivariate logistic regression results, a nomogram model was constructed using TSH, FT3, tumor size, Ki-67, and CYFRA21-1 as predictors for thyroid irAE risk in lung cancer patients. The nomogram scoring system quantified individual prediction probability (Pr) [Figure 1: see original paper].

ROC curve analysis showed AUC values for TSH, FT3, tumor size, Ki-67, CYFRA21-1, and the nomogram model of 0.566, 0.710, 0.610, 0.599, 0.569, and 0.796, respectively. DeLong test demonstrated that the nomogram' s AUC was significantly higher than each individual predictor (P<0.001) [FIGURE:2, TABLE:3, TABLE:4].

2.5 Model Internal and External Validation

Bootstrap resampling with 1000 iterations yielded a C-index of 0.796 and 75% accuracy, indicating good discrimination. Hosmer-Lemeshow test showed good model fit (^{2}=5.96, P=0.652). The validation set ROC curve produced an AUC of 0.730 (95%CI=0.612-0.848), specificity of 0.810, sensitivity of 0.562, and accuracy of 70%, with Hosmer-Lemeshow test confirming good fit (^{2}=3.34, P=0.912).

Calibration curves demonstrated strong agreement between predicted probabilities and observed values. DCA showed good clinical net benefit across 0-95% probability thresholds. CIC curves indicated that predicted thyroid irAE occurrence aligned with actual diagnoses as the model threshold increased, confirming good clinical utility [FIGURE:3, FIGURE:4, FIGURE:5].

2.6 Comparison of Cumulative Thyroid irAE Incidence Across Risk Strata

Using the optimal probability threshold (Pr$ 0.474), $243 lung cancer patients were stratified into high-risk (n = 94, 38.68^{2}$=28.15, P<0.001). The high-risk group exhibited 2.63 times greater risk (HR=2.63, 95%CI=1.770-3.905, P<0.001) [Figure 6: see original paper].

2.7 Multivariate Logistic Analysis of Thyroid irAE Influencing Factors Across CTCAE Grades

Among 103 thyroid irAE patients, 80 were CTCAE grade 1 (median onset at cycle 2 [1.25, 3.00], latest at cycle 15) and 23 were CTCAE $ $2 grade (22.33%, median onset at cycle 1 [1.00, 3.00], latest at cycle 5). The grade 1 subgroup had later median onset than the $ $2 grade subgroup (Z=-2.696, P=0.007). Using CTCAE grade as the dependent variable (grade 1=1, $ $2=2) and TSH, FT3, tumor size, Ki-67, and CYFRA21-1 as independent variables, multivariate logistic regression showed that FT3 (OR=5.513, 95%CI=1.846-16.465, P=0.002) and tumor size (OR=0.963, 95%CI=0.928-0.999, P=0.044) were independent predictors for CTCAE $ $2 grade thyroid irAEs, whereas TSH

(OR=1.517, 95%CI=1.028-2.238, P=0.036), FT3 (OR=4.903, 95%CI=2.369-10.150, P<0.001), tumor size (OR=0.967, 95%CI=0.946-0.988, P=0.002), Ki-67 (OR=1.031, 95%CI=1.013-1.050, P=0.001), and CYFRA21-1 (OR=1.039, 95%CI=1.014-1.065, P=0.002) were all independent predictors for CTCAE grade 1 thyroid irAEs, suggesting the model has greater predictive advantage for grade 1 events .

Discussion

With the widespread application of ICIs across various cancers, irAEs have become a major clinical concern. Thyroid irAEs, the most common endocrine toxicity, are characterized by broad onset timing, delayed diagnosis, generally mild severity, but often irreversible course. Early identification of high-risk patients is crucial for optimizing treatment follow-up strategies and improving medication adherence and quality of life. Studies have shown that Eastern Cooperative Oncology Group (ECOG) performance status, tumor mutational burden (TMB), liver metastasis, and inflammatory markers can predict irAE occurrence, and some indicators correlate significantly with treatment benefit. However, most research has focused on non-small cell lung cancer (NSCLC), with limited attention to small cell lung cancer (SCLC) and organ-specific toxicities like thyroid dysfunction. This study aimed to provide evidence-based guidance for immunotherapy toxicity management in lung cancer patients by developing a thyroid irAE prediction model.

The thyroid irAE incidence of 42.4% in our study is slightly higher than or comparable to previous reports (20-44%), likely due to the high utilization rate of PD-1 inhibitors (83.54%) and enhanced clinical monitoring intensity. We found that CTCAE $ $2 grade events occurred significantly earlier, suggesting that ICI combined with chemotherapy during the first 4-6 treatment cycles may exacerbate immune toxicity. Our results identified baseline TSH, FT3, Ki-67, and CYFRA21-1 as independent risk factors for thyroid irAEs, while tumor size was a protective factor.

Baseline TSH >2.58 IU/mL was associated with increased thyroid irAE risk, consistent with previous findings and similar to the high-risk threshold (2.47 mIU/L) proposed by Muir et al. A 20-year follow-up of 2,779 community adults revealed that individuals with TSH >2 mIU/L were more prone to hypothyroidism, particularly those with positive TPO antibodies. The pathogenesis of thyroid irAEs involves immune-mediated acute destructive thyroiditis. Elevated TSH promotes reactive oxygen species (ROS) production, inducing oxidative damage to thyroid tissue, exposing autoantigens, and triggering autoimmune responses that may be amplified by ICI-mediated immune hyperactivation.

Baseline FT3 levels positively correlated with thyroid irAEs. As the biologically active form of thyroid hormone, FT3 enhances myeloperoxidase activity and ROS generation by binding to neutrophil nuclear receptors, while promoting dendritic cell maturation and pro-inflammatory cytokine secretion to augment

immune responses. Kim et al. found that high baseline T3 levels correlated with ICI treatment benefit in advanced NSCLC patients. Low-dose T3 therapy can enhance natural killer (NK) cell activity and even improve survival in squamous cell carcinoma patients. Our FT3 findings further support the hypothesis that thyroid irAEs and antitumor immunity may share common mechanisms.

Baseline tumor size $ $58 mm was associated with lower thyroid irAE risk. Studies have shown that tumor size negatively correlates with ICI efficacy in NSCLC, with a threshold of 50 mm, which aligns with the significant positive correlation between irAEs and ICI treatment response. Larger tumors exhibit higher interstitial fluid pressure, creating a hypoxic tumor microenvironment (TME) that promotes VEGF-A expression and suppresses dendritic cell maturation, antigen presentation, and immune cell function, thereby reducing thyroid irAE risk.

Ki-67, a tumor cell proliferation marker, also correlates with T-cell immune reconstitution. We found a positive association between Ki-67 and thyroid irAEs. High Ki-67 expression leads to elevated TMB and abundant abnormal protein expression, enhancing T-cell recognition and ICI efficacy. PD-1 inhibitors restore immune responses in baseline Ki-67-positive CD8+ T cells to benefit patients. A large retrospective study confirmed that high TMB significantly correlates with irAEs. During ICI therapy, tumor cell death releases more antigens that may cross-react with wild-type antigens in normal tissues, triggering thyroid irAEs. However, gastric cancer studies have reported an inverse relationship between low Ki-67 and irAEs, suggesting that the association between Ki-67 and irAEs requires further investigation across different cancer types and organ-specific toxicities.

CYFRA21-1 is important for lung cancer diagnosis and treatment response evaluation, with high baseline levels typically indicating poor prognosis. However, one study found that NSCLC patients with CYFRA21-1 >2.35 ng/mL had longer progression-free survival with ICI therapy, though it did not explore the relationship with thyroid irAEs. Our study found a positive correlation between baseline CYFRA21-1 and thyroid irAEs, possibly related to ICI sensitivity, but the underlying mechanism warrants further investigation.

We also observed heterogeneity in risk factors between CTCAE grade 1 and $ $2 events, with the model showing higher predictive value for low-grade events. A meta-analysis in NSCLC demonstrated that low-grade irAEs and organ-specific irAEs (such as endocrine events) correlate with better prognosis. Therefore, managing high-grade events requires balancing ICI efficacy against toxicity risk, and future research should focus on identifying independent risk factors for high-grade thyroid irAEs to develop more rational anticancer treatment strategies.

Current thyroid irAE diagnostic criteria remain heterogeneous, encompassing thyrotoxicosis, primary hypothyroidism, pituitary injury, and euthyroid thyroiditis. Clinical practice often overlooks pituitary and target gland hormone testing, and guidelines do not recommend routine antibody or pituitary MRI examinations. Additionally, medication interference with thyroid function tests

complicates atypical case identification. Future studies should clarify diagnostic criteria for atypical cases. We developed a prediction model for thyroid irAEs in lung cancer patients using readily available, economical, and measurable biomarkers. We recommend active thyroid function monitoring in high-risk patients (Pr$ $47.4%) to reduce missed diagnoses and enable early prevention of immunotherapy toxicity.

This study has several limitations. First, its retrospective design lacked data on thyroid-related antibodies, PD-L1 expression, and genetic mutations, preventing comprehensive risk factor assessment. Second, not all patients underwent thyroid function testing every cycle, and some receiving short-term ICI therapy lacked regular follow-up, potentially leading to missed diagnoses. Additionally, excluding patients with baseline thyroid dysfunction may have affected the true incidence. Therefore, larger, high-quality prospective studies are needed to validate the model' s accuracy and utility.

In summary, we developed a thyroid irAE prediction model based on TSH, FT3, tumor size, Ki-67, and CYFRA21-1. The model demonstrated good predictive performance in the validation set and can guide early screening to adjust follow-up frequency, reducing both over-treatment in low-risk patients and missed diagnoses in high-risk patients.

Author Contributions: NIE Jiahua conceived and designed the study, implemented the research, and drafted the manuscript. NIE Jiahua and XIA Chengwei collected and organized data, performed statistical analysis, and prepared figures and tables. YAN Ziwei collected data and revised the manuscript. WEI Limin revised the final version and took responsibility for the manuscript.

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