Development of a predictive model for immune-related adverse events in patients with cancer

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Abstract. It is crucial to accurately identify patients with cancer at high risk for immune-related adverse events (irAEs) caused by immune checkpoint inhibitors (ICIs). The present retrospective study analyzed the risk factors for irAEs in 992 patients with cancer treated with ICIs at Xi'an International Medical Center Hospital from December 2021 to December 2023. The patients were categorized into one group that experienced irAEs (n=276) and a control group (n=716) based on the occurrence of irAEs. The clinical characteristics of irAEs group (n=276) and control group (n=716) were analyzed to identify the risk factors of irAEs in patients with cancer. Multivariate regression analysis revealed significant differences between the two groups in terms of hypertension, primary cancer, metastasis, targeted drug combination and radiotherapy (P<0.05). A nomogram predictive model for irAEs was developed based on the relevant risk factors. The predictive model for irAEs in patients with cancer yielded an area under the receiver operating characteristic (ROC) curve of 0.672 (95% confidence interval: 0.630-0.714). In the validation set, the Hosmer-Lemeshow goodness-of-fit test demonstrated a favorable fit with a chi-square value of 0.787 and a P-value of 0.978. The developed predictive model can effectively identify high-risk patients with irAEs, facilitate early identification of irAEs, thereby optimizing the management strategies of irAEs, and ultimately improving the quality of life for patients.

Introduction

Based on the latest GLOBOCAN projections, released by the International Agency for Research on Cancer (IARC), ~20.0 million new cancer cases and 9.7 million cancer deaths were reported globally in 2022 (1). Cancer has become a formidable global challenge, significantly impacting the public health and economy. The cornerstone strategies for managing cancer encompass surgical procedures, radiotherapy, chemotherapy, targeted therapy, and breakthrough immunotherapy. Immune checkpoint inhibitors (ICIs), a prominent type of immunotherapy, have gained prominence by bolstering immune cell function and facilitating the eradication of tumor cells (2). Currently, ICIs have shown promising results in cancer treatment (3). However, ICIs may also trigger a wide array of immune-related adverse events (irAEs) in any tissue or organ, with barrier tissues such as skin, gastrointestinal tract and respiratory epithelium being the most commonly affected. Additionally, endocrine toxicity and joint inflammation are relatively common among patients undergoing therapy with ICIs (4,5). These irAEs differ from those caused by traditional chemotherapy and targeted therapy (6,7), and their underlying mechanism remains elusive. Their clinical manifestations are mostly non-specific, typically occurring weeks to months after the initiation of immunotherapy. Although most irAEs can be effectively managed, there is a risk of severe or even fatal toxicities (8,9). Therefore, prompt recognition, precise evaluation and timely intervention are crucial in the management of irAEs (10).

Some microbiome compositions (11), and circulating biomarkers (12) have been identified as potential risk factors for irAEs. However, the clinical predictive factors for irAEs risk remain unclear (13). In the present study, a predictive nomogram-based model to identify patients with cancer who may develop irAEs following treatment with ICIs, was developed and evaluated. The model is expected to help early evaluation of irAEs, thereby optimizing the management of irAEs, and ultimately improving the quality of life for patients.

Materials and methods

General information. Data from patients with cancer who received treatment with ICIs at Xi'an International Medical Center Hospital (Xi'an, China) from December 2021 to December 2023 retrospectively collected. The inclusion criteria were as follows: i) male or female, aged ≥18 years; ii) histologically confirmed solid malignant tumor; iii) receipted monotherapy with ICIs or combination therapy

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with other systemic antitumor agents during hospitalization; and iv) complete data. Exclusion criteria: i) age <18 years; ii) non-solid malignant tumor; iii) patients with severe infection, severe cardiac insufficiency, and severe acute cardiovascular and cerebrovascular accidents prior to ICIs use; iv) patients with autoimmune diseases or those who have previously or currently used immunosuppressants; and v) data is missing, which affects the judgment of results. Finally, 992 patients were included, then the patients were divided into the irAEs group (n=276) and the control group (n=716) based on the occurrence of irAEs.

Data collection. Patient sex, age, body mass index (BMI), smoking history, hypertension, diabetes, infection with hepatitis B, pulmonary disease, primary cancer, metastasis, history of radiotherapy, type of ICIs and drug combination were collected for statistical analysis.

Statistical analysis. Statistical analyses were conducted using SPSS 25.0 software (IBM Corp.) with P<0.05 considered to indicate a statistically significant difference. The number of cases (percentage) [n (%)] and the chi-square value were used to analyze differences between the two groups. Data were expressed as the mean ± standard deviation, and non-normally distributed data (for example, BMI and age) were analyzed using the Mann-Whitney test, while the type of ICIs and drug combination were analyzed using the Fisher's exact test. Multivariate analysis was performed by logistic regression analysis to determine the risk factors for irAEs. Rv.4.2.2 statistical software (https://www.r-project.org) was used to developed a nomogram prediction model for irAEs based on the results of multivariate regression. The original data set was divided into a training set (n=793) and validation set (n=199). For the prediction of irAEs in patients with cancer, the Hosmer-Lemeshow (HL) test was used to evaluate the goodness of fit of the predictive model. In HL test, P>0.05 indicated that there was a favorable fitting effect in both data sets. The receiver operating characteristic (ROC) curve was used to evaluate the performance of the classification model, and the decision curve analysis (DCA) was used to evaluate the feasibility of clinical decisions.

Results

Patient characteristics. The characteristics of the patients are summarized in Table I. The patients included 731 males and 261 females. The mean age was 60.97 (standard deviation= 11.567). As indicated in Table I, 27.8% of the patients experienced irAEs (n=276). There was no significant difference in the occurrence of irAEs between the irAEs group and the Control group in sex, age, BMI, smoking history, diabetes, infection with hepatitis B and type of ICIs (P>0.05, Table I). The difference in primary cancer, metastasis, drug combination, radiotherapy, hypertension, and pulmonary diseases were statistically significant between the irAEs group and the Control group (P<0.05, Table I).

Risk factors for irAEs in patients with cancer. Multivariate logistic regression analysis revealed that hypertension, primary cancer, metastasis, targeted drug combination and radiotherapy were risk factors for irAEs in patients with cancer (P<0.05, Table II).

Development and validation of a predictive model for irAEs in patients with cancer. A nomogram prediction model for irAEs was developed based on the results of multivariate regression (Fig. 1). The original data set was divided into a training set (n=793) and a validation set (n=199). For the prediction of irAEs in patients with cancer, the HL test calibration showed that the χ^2 was 2.909 (P=0.820) in the training set and the χ^2 was 0.787 (P=0.978) in the validation set (Fig. 2); the P>0.05 indicated a favorable fitting effect in both data sets. The area under curve (AUC) of ROC curve for the training set data was 0.672 [95% confidence interval (CI): 0.630, 0.714], while that for the validation set data was 0.776 (95% CI: 0.700, 0.853), AUC >0.5 showed favorable discrimination of the model (Fig. 3). As revealed in Fig. 4, the DCA showed that the model performs well and can be used to make beneficial clinical decisions.

Type of irAEs in patients with cancer. The incidence of irAEs was 27.8% (276/992), including endocrine toxicity in 128 cases (12.9%), pulmonary toxicity in 91 cases (9.2%), dermatologic toxicity in 49 cases (4.9%), hepatic toxicity in 48 cases (4.8%), cardiac toxicity in 22 cases (2.2%), and gastrointestinal toxicity in 13 cases (1.3%). Additionally, neurotoxicity, infusion reaction, hematological toxicity, renal toxicity and rheumatic toxicity were observed occasionally. The irAEs are categorized based on the Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf#search=%22CTCAE%20v5.0%22). Notably, among the irAEs exceeding grade 3, lung toxicity (65, 6.5%), liver toxicity (38, 3.8%), dermatologic toxicity (18, 1.8%) and cardiac toxicity (13, 1.3%) had the highest incidence. Additionally, there were 31 fatalities (3.1%) related to the irAEs, mainly including pulmonary toxicity (24, 2.4%), liver toxicity (4, 0.4%), cardiac toxicity (2, 0.2%) and neurologic toxicity (1, 0.1%, Table III). The irAEs occurred 4-28 weeks after the initiation of ICIs treatment, with a median time of 16 weeks (Fig. 5A and B).

Discussion

The development of immunotherapy has resulted in remarkable progress in the treatment of cancer (3,14). Targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death protein-1 (PD-1) and programmed death protein ligand-1 (PD-L1), representative ICIs, have been used for the treatment of malignant tumors (15,16). Currently, numerous inhibitors of CTLA-4, PD-1 and PD-L1 have been registered in China, including nivolumab, pembrolizumab, tislelizumab, toripalimab, camrelizumab, sintilimab (targeting PD-1), atezolizumab, durvalumab, sugemalimab (targeting PD-L1), and cadonilimab (targeting PD-1 and CTLA-4). With the widespread use of ICIs, the incidence of irAEs has increased, and the use of ICIs in patients with cancer creates the risk of serious or fatal toxic reactions (17). Meanwhile, the early identification, accurate evaluation and timely treatment of irAEs remain challenging (10). Therefore, further research is needed

Table I. Comparison of clinical features of the 2 groups.

Characteristics	Immune-related adverse events group (n=276)	Control group (n=716)	N=992	χ^2/Mann-Whitney	P-value
Sex				0.75	0.386
Female	78 (28.3%)	183 (25.6%)	261 (26.3%)		
Male	198 (71.7%)	533 (74.4%)	731 (73.7%)		
Age, years	60.91±21.906	60.99±11.825	60.97±11.567	97441.5	0.735
Body mass index, kg/m^2	21.91±2.985	21.67±2.011	21.74±2.324	93678.5	0.205
Smoking history				0.232	0.630
Yes	111 (40.2%)	300 (41.9%)	411 (41.4%)		
No	165 (59.8%)	416 (58.1%)	581 (58.6%)		
Diabetes				2.843	0.092
Yes	39 (14.1%)	74 (10.3%)	113 (11.4%)		
No	237 (85.9%)	642 (89.7%)	879 (88.6%)		
Infection with Hepatitis B				0.952	0.329
Yes	49 (17.8%)	109 (15.2%)	158 (15.9%)		
No	227 (82.2%)	607 (84.8%)	834 (84.1%)		
Hypertension				27.354	<0.001
Yes	100 (36.2%)	145 (20.3%)	245 (24.7%)		
No	176 (63.8%)	571 (79.7%)	747 (75.3%)		
Renal insufficiency				11.658	<0.001
Yes	21 (7.6%)	20 (2.8%)	41 (4.1%)		
No	255 (92.4%)	696 (97.2%)	951 (95.9%)		
Pulmonary disease				4.393	0.036
Yes	42 (15.3%)	75 (10.5%)	117 (11.8%)		
No	233 (84.7%)	641 (89.5%)	874 (88.2%)		
Radiotherapy				20.443	<0.001
Yes	51 (18.5%)	60 (8.4%)	111 (11.2%)		
No	225 (81.5%)	656 (91.6%)	881 (88.8%)		
Primary cancer				14.215	0.014
Lung cancer	127 (46.0%)	297 (41.5%)	424 (42.7%)		
Liver cancer	48 (17.4%)	138 (19.3%)	186 (18.8%)		
Esophagus cancer	14 (5.1%)	76 (10.6%)	90 (9.1%)		
Biliary malignant cancer	14 (5.1%)	18 (2.5%)	32 (3.2%)		
Renal cancer	7 (2.5%)	9 (1.3%)	16 (1.6%)		
Other cancers	66 (23.9%)	178 (24.9%)	244 (24.6%)		
Metastasis				39.633	<0.001
Yes	138 (50.0%)	206 (28.8%)	344 (34.7%)		
No	138 (50.0%)	510 (71.2%)	648 (65.3%)		
Type of ICIs				5.555	0.056
PD-1	244 (88.4%)	662 (92.5%)	906 (91.3%)		
PD-L1	28 (10.1%)	51 (18.5%)	79 (8.0%)		
PD-1/ CTLA-4	4 (1.4%)	3 (0.4%)	7 (0.7%)		
Drug combination				19.734	<0.001
Chemotherapeutics	166 (60.1%)	526 (73.5%)	692 (69.8%)		
Targeted drug	88 (31.9%)	158 (22.1%)	246 (24.8%)		
ICIs	2 (0.7%)	0	2 (0.2%)		
Monotherapy	20 (7.2%)	32 (4.5%)	52 (5.2%)		

ICIs, immune checkpoint inhibitors; PD-1, programmed death protein 1; PD-L1, programmed death protein ligand-1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

Table II. Risk factors for immune-related adverse events.

Variables	Coef	S.E.	Wald_Z	P-value	Odds ratio	95% confidence interval	
						Lower	Upper
Intercept	-1.620	0.139	-11.647	<0.001	0.198	0.151	0.26
Hypertension	0.553	0.182	3.038	0.002	1.738	1.217	2.483
Renal insufficiency	0.607	0.379	1.603	0.109	1.835	0.873	3.855
Pulmonary disease	0.031	0.251	0.125	0.901	1.032	0.631	1.687
Metastasis	0.710	0.17	4.189	<0.001	2.035	1.459	2.837
Radiotherapy	0.733	0.24	3.057	0.002	2.082	1.301	3.332
Liver cancer	-0.788	0.331	-2.378	0.017	0.455	0.237	0.871
Targeted drug combination	1.105	0.292	3.784	<0.001	3.021	1.704	5.355

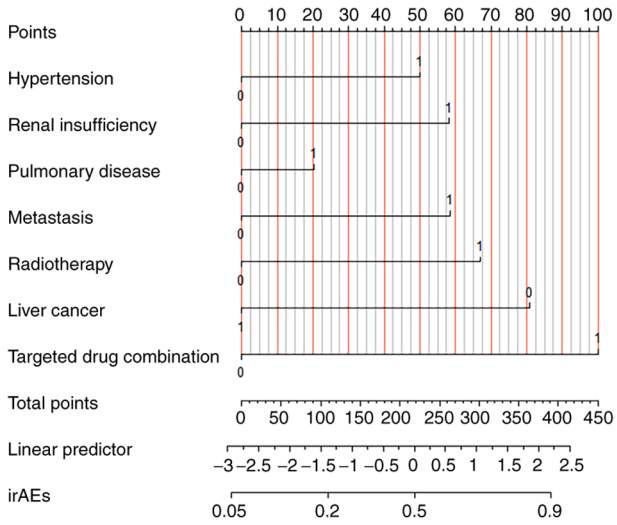

Figure 1. Nomogram of the model for predicting irAEs in patients with cancer. irAEs, immune-related adverse events.

to develop more effective ways to mitigate the risk of irAEs. To address this clinical problem, a predictive model for irAEs in patients with cancer was established in the present study.

ICIs have been used for the treatment of various cancers. In the present study, ICIs were primarily utilized for the treatment of diverse cancer types, including lung, liver, esophageal, biliary tract and renal cancer, among other types. Notably, 65.3% of the patients administered with ICIs in the present study were in the non-advanced stage, indicating that ICIs are not only used for the treatment of advanced cancers, but are also widely used in neoadjuvant, adjuvant and locally advanced cancer therapy (18,19). The study furthermore showed that there was no significant difference in the occurrence of irAEs among different types of ICIs.

Different types of irAEs were observed. In the present study, 276 patients reported irAEs during treatment with ICIs, with endocrine toxicity being the most common (n=128, 46.4%) followed by lung toxicity (n=91, 33.0%), dermatologic toxicity (n=49, 17.8%) and liver toxicity (n=48, 17.4%). Similarly, endocrine toxicity is the most common adverse event in patients undergoing treatment with ICIs (20). The immunological mechanism of endocrine adverse reactions may be that irAEs are caused by various pathways such as autoreactive T cells, autoantibodies and cytokines. The rich blood supply of endocrine glands may increase their sensitivity to these mechanisms, thus becoming one of the more commonly affected targets (21). Although the occurrence of endocrine toxicity is relatively high, its severity is usually limited to grade 1 or 2 (22). Patient's symptoms can typically be alleviated by promptly administering symptomatic treatments, and in most cases, patients are able to continue therapy with ICIs (23). The most common fatal irAEs in patients treated with ICIs is lung toxicity (24), which caused 2.4% of fatality in the present study. Most irAEs occurred at 8 to 16 weeks after beginning treatment with ICIs. Renal toxicity occurred later than other adverse reactions, with a median onset time of 28 weeks after beginning treatment with ICIs; infusion reactions mainly occurred after the first or second ICIs dose. These results are consistent with previous findings (25). The identification of risk factors for irAEs is critical for establishing a predictive model. Some biomarkers have been reported as risk factors of irAEs (10,26). In the present study, hypertension, primary cancer, metastasis, targeted drug combination and radiotherapy were identified as risk factors of irAEs in patients with cancer. However, these factors should likely have different weights in the predictive model (27).

Hypertension, one of the risk factors for irAEs, has attracted considerable attention (28). Previous studies have revealed the effects of hypertension on the immune system, which is closely related to the interactions between cytokines and T cells (29). A retrospective study indicated that the occurrence of irAEs was associated with hypertension in patients with cancer (30). Through multifactor analysis, hypertension was confirmed as an independent risk factor for irAEs (P=0.002).

The primary cancer type is the key factor affecting irAEs (31). The risk of irAEs in liver cancer was relatively low in the study. The study also found that metastasis was a risk factor for irAEs, consistent with previous findings (32). This indicates that the primary cancer type and metastatic are crucial factors in determining the occurrence of irAEs. Therefore, it is important to tailor an individualized immunotherapy regimen for a patient's cancer with different characteristics to achieve a balance between efficacy and safety.

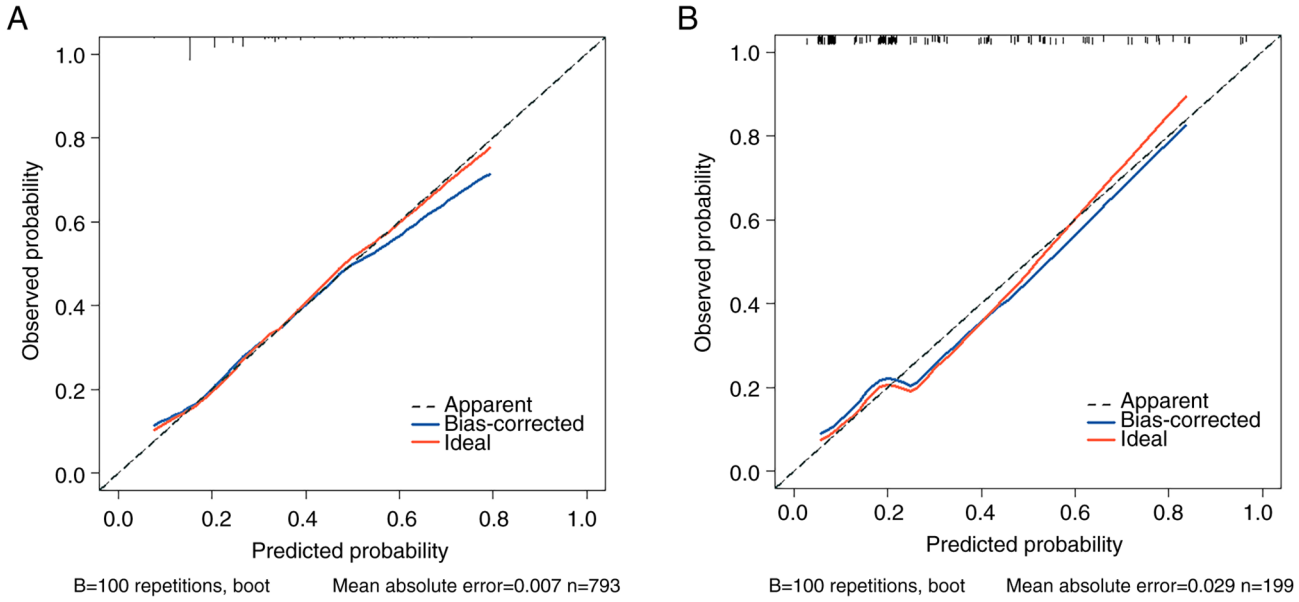

Figure 2. Performance of the model for predicting immune-related adverse events in patients with cancer. (A) Training set and (B) validation set.

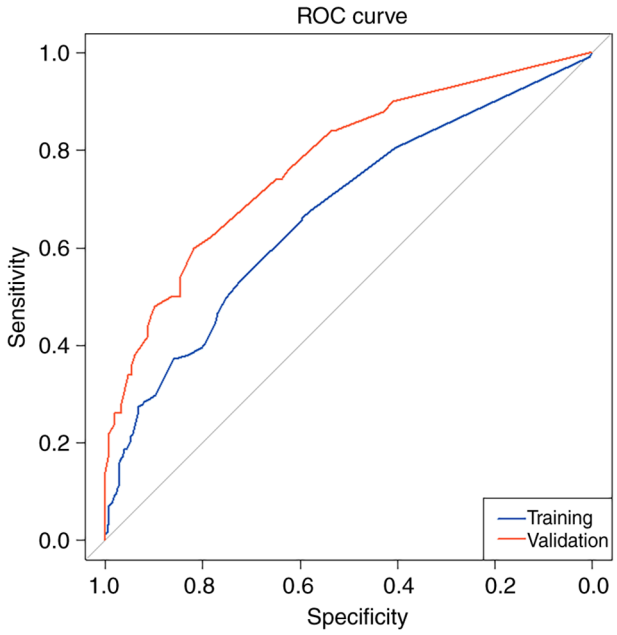

Figure 3. ROC curve of the logistic model for different data sets. ROC, receiver operating characteristic.

Radiation therapy can stimulate immune mechanisms and trigger immune responses, especially when combined with ICIs, thus affecting the safety of immunotherapy (33). Radiation therapy has also been reported as a risk factor for irAEs (34,35). Similarly, in this study, radiotherapy was identified as an independent risk factor for irAEs (P=0.002). In the present study, subgroup analysis of irAEs of 55 patients with a history of radiotherapy was conducted. Of these, 34 patients (61.8%) had undergone radiotherapy in the chest, with an average radiation dose of 51.976±12.303 Gy, and the median time of irAEs occurrence was 5 months after radiotherapy.

The use of combination therapy regimens may improve treatment efficacy but amplify irAEs (36,37). The combination of ICIs and targeted drugs has been shown to increase the risk of toxicity (38,39). Similarly, the combination of targeted drugs was identified as an independent risk factor for irAEs in the present study (P<0.001). Therefore, when formulating combination immunotherapy regimens, it is necessary to comprehensively evaluate the risk of drug combination and closely monitor the adverse reactions during the treatment.

Multivariate logistic regression analysis revealed that hypertension, primary cancer, metastasis, targeted drug combination and radiotherapy were risk factors for irAEs in the present study (P<0.05). To facilitate the identification of patients with cancer at high risk for irAEs, a nomogram-based predictive model was developed based on relevant risk factors. The HL test calibration showed that the χ^2 was 2.909 (P=0.820) in the training set and the χ^2 was 0.787 (P=0.978) in the validation set; P>0.05 indicated a favorable fitting effect in both data sets. The AUC of ROC curve for the training set data was 0.672 (95% CI: 0.630, 0.714), while that for the validation set data was 0.776 (95% CI: 0.700, 0.853); AUC >0.5 showed favorable discrimination of the model. DCA was shown in Fig. 4, which indicated that the model performed well and was feasible for making beneficial clinical decisions. The predictive nomogram-based model established in the present study has favorable predictive value for predicting irAEs risk in patients with cancer. A recent study on immune-associated pneumonia in patients with cancer demonstrated the efficacy of nomogram-based models for predicting irAE risk (40). Another study on postoperative infection complications in patients with gastric cancer also demonstrated the efficacy of the nomogram-based model (41). Therefore, the developed model can effectively identify high-risk patients with irAEs, thereby facilitating early identification of irAEs, and improving the prognosis of patients.

The present study had certain limitations. First, it was a retrospective study, and potential confounding factors could

Table III. Classification and grading of immune-related adverse events.

Classification of adverse immune events	N=992 (%)	Grade 1-2	Grade 3-4	Grade 5
Endocrine toxicity	128 (12.9)	128 (12.9)	0	0
Lung toxicity	91 (9.2)	26 (2.6)	41 (4.1%)	24 (2.4%)
Dermatologic toxicity	49 (4.9)	31 (3.1)	18 (1.8%)	0
Liver toxicity	48 (4.8)	10 (1.0)	34 (3.4%)	4 (0.4%)
Cardiac toxicity	22 (2.2)	9 (0.9)	11 (1.1%)	2 (0.2%)
Gastrointestinal toxicity	13 (1.3)	9 (0.9)	4 (0.4%)	0
Neurologic toxicity	5 (0.5)	4 (0.4)	0	1 (0.1%)
Infusion reaction	4 (0.4)	4 (0.4)	0	0
Hematological toxicity	3 (0.3)	1 (0.1)	2 (0.2%)	0
Renal toxicity	3 (0.3)	3 (0.3)	0	0
Rheumatic toxicity	1 (0.1)	1 (0.1)	0	0

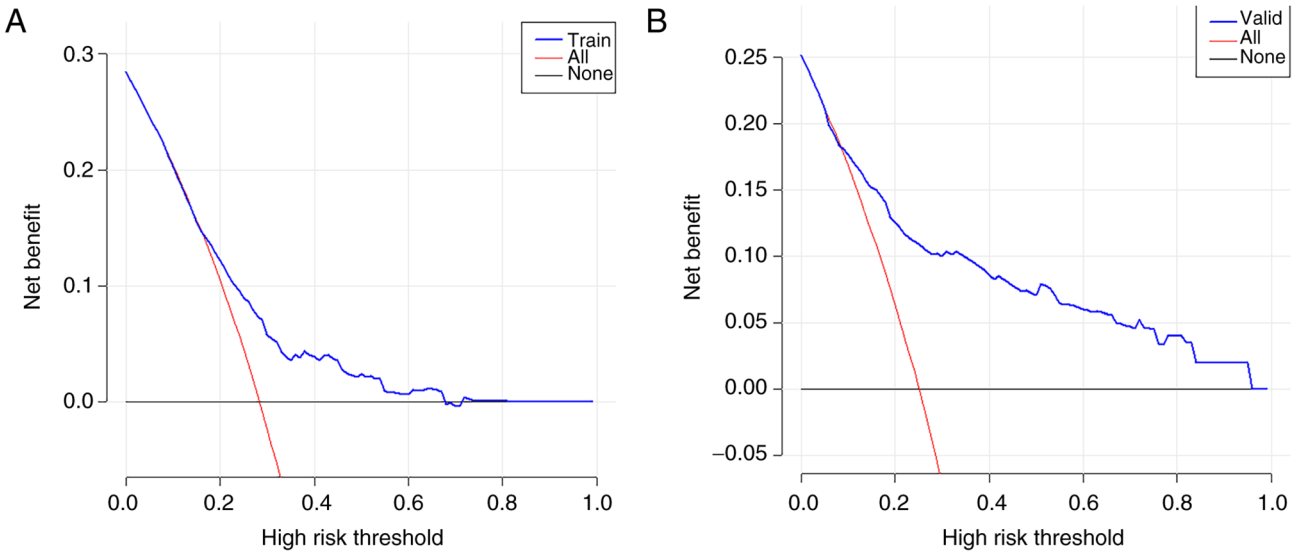

Figure 4. Clinical decision curves based on the model for predicting immune-related adverse events in patients with cancer. (A) Training set and (B) validation set).

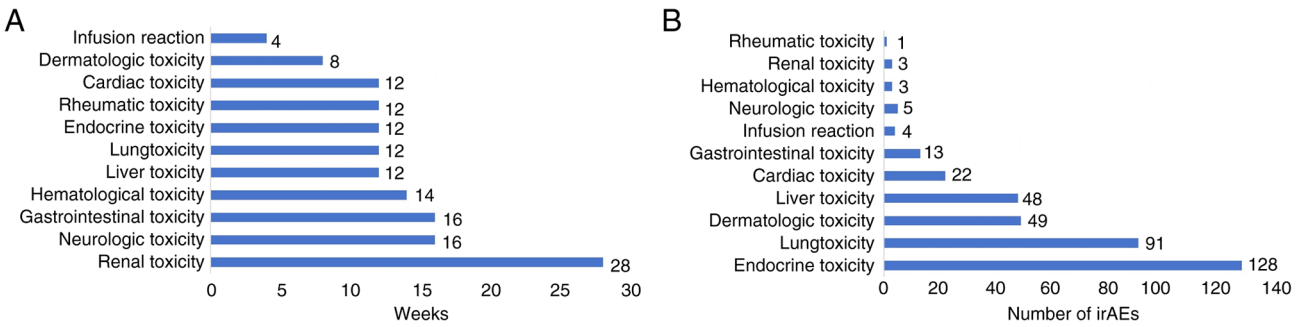

Figure 5. (A) Median time and (B) distribution types of irAEs. irAEs, immune-related adverse events.

not be ruled out. Second, newly emerged irAEs-related biomarkers (for example, cytokines and chemokines) were not considered when developing the predictive model. These biomarkers require further investigation. Finally, compared with external validation, the internal validation applied in the present study may be less robust.

In conclusion, the results of the present study indicate that hypertension, primary cancer, metastasis, targeted drug combination and radiotherapy are significant risk factors for irAEs following treatment with ICIs in patients with cancer. The predictive model is highly effective and can accurately identify high-risk groups for irAEs, laying a solid foundation

for individualized immunotherapy strategies. This model is expected to enable early evaluation of irAEs, thereby optimizing the management strategies of irAEs, and ultimately significantly improving the quality of life for patients.

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Availability of data and materials

The data generated in the present study are not publicly available due to patient privacy purposes but may be requested from the corresponding author.

Authors' contributions

YT, JS, LX and TS designed the study. YT, JS, LW and YZ collected, analyzed and interpreted the data. YT and TS wrote the original draft of the manuscript. JS and YZ reviewed the manuscript. JS and YT confirm the authenticity of all the raw data. All authors contributed to the article, and read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Ethics Committee of Xi'an International Medical Center Hospital (approval no. 202110; approval date: 2021.11.8; Xi'an, China). This was a retrospective study; therefore, the written informed consent was exempted from all participants included in the current study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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