Original Article

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Development and validation of a nomogram model for predicting immune-mediated hepatitis in cancer patients treated with immune checkpoint inhibitors

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SUMMARY: Immune checkpoint inhibitors (ICIs) have been widely used in various types of cancer, but they have also led to a significant number of adverse events, including ICI-induced immune-mediated hepatitis (IMH). This study aimed to explore the risk factors for IMH in patients treated with ICIs and to develop and validate a new nomogram model to predict the risk of IMH. Detailed information was collected between January 1, 2020, and December 31, 2023. Univariate logistic regression analysis was used to assess the impact of each clinical variable on the occurrence of IMH, followed by stepwise multivariate logistic regression analysis to determine independent risk factors for IMH. A nomogram model was constructed based on the results of the multivariate analysis. The performance of the nomogram model was evaluated *via* the area under the receiver operating characteristic curve (AUC), calibration curves, decision curve analysis (DCA), and clinical impact curve (CIC) analysis. A total of 216 (8.82%) patients developed IMH. According to stepwise multivariate logistic analysis, hepatic metastasis, the TNM stage, the WBC count, LYM, ALT, TBIL, ALB, GLB, and ADA were identified as risk factors for IMH. The AUC for the nomogram model was 0.817 in the training set and 0.737 in the validation set. The calibration curves, DCA results, and CIC results indicated that the nomogram model had good predictive accuracy and clinical utility. The nomogram model is intuitive and straightforward, making it highly suitable for rapid assessment of the risk of IMH in patients receiving ICI therapy in clinical practice. Implementing this model enables early adoption of preventive and therapeutic strategies, ultimately reducing the likelihood of immune-related adverse events (IRAEs), and especially IMH.

Keywords: ICIs, IMH, influencing factors, risk model

1. Introduction

Cancer has become the second leading cause of death worldwide, resulting in approximately 9.6 million deaths and 182.8 million years of life lost (*1*). Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of malignancies and have been used to treat many different types of cancer. ICIs enhance the body's immune response to cancer cells by blocking negative regulatory factors expressed on immune cells or tumor cells through a unique mechanism. ICIs mainly consist of cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, programmed cell death protein (PD)-1 inhibitors (PD-1), and PD-ligand 1 inhibitors (PD-L1) (*2,3*). However, the expanded indications for ICIs and their increased use has led to the discovery of a large number of adverse events associated with ICIs, termed immune-related adverse events (IRAEs), in clinical settings.

Studies have shown that IRAEs are caused by an overactive immune response, primarily in the skin, endocrine, hepatic, and pulmonary systems (*4,5*). Owing to its unique immune characteristics, the liver is one of the organs most susceptible to the effects of tumor immunotherapy. Hepatitis caused by ICI treatment is commonly referred to as ICI-induced immune-mediated hepatitis (IMH). Research indicates that IMH is the third most common IRAE, with an incidence ranging from 5% to 10% (*6*), followed by skin toxicity (44%-68%)

and gastrointestinal adverse reactions (35%-50%) (*7*). Although most cases of IMH are asymptomatic and can be appropriately controlled with supportive therapy and corticosteroids (*8*), improper diagnosis or management can lead to immunotherapy failure, acute liver failure, and death, especially in patients with chronic liver disease (*9,10*). Previous studies have suggested that IMH accounts for a high proportion of fatal IRAEs. According to data from a global database on fatal IRAEs, 124 of the 613 reported deaths were associated with IMH (*11*). Similarly, a study by Wang *et al.* found that among 21 melanoma patients who died from IRAEs, 5 deaths (23.8%) were caused by IMH (*12*).

The mechanisms by which ICIs cause IMH have yet to be fully elucidated, and data on the clinical risk factors for IMH are very limited. Most importantly, there is no clinical model with which to accurately assess the risk of IMH in patients. This makes the prevention and management of IMH in patients receiving ICI therapy particularly challenging in clinical practice. Therefore, identifying the risk factors associated with IMH and predicting the risk of IMH in patients receiving ICI therapy is highly clinically important. This information will help clinicians quickly identify high-risk IMH patients and manage them individually, ultimately reducing the incidence of IMH at its source. In current clinical research, nomogram models are widely used to explore risk factors and predict risk (*13*). Su *et al.* recruited 2,281 consecutive patients with hepatitis B-related hepatocellular carcinoma from four tertiary hospitals in China from April 2011 to March 2022 (*14*). They utilized multivariate Cox regression to establish a nomogram risk prediction model, which accurately predicted the mortality risk of patients and effectively identified high-risk patients.

Therefore, the current study aimed to investigate the risk factors for IMH in patients receiving ICI therapy and to develop and validate a new nomogram model to predict the risk of IMH. Ultimately, this model will guide personalized strategies to prevent IMH.

2. Materials and Methods

2.1. Subjects and inclusion and exclusion criteria

This study collected relevant information from 2,663 cancer patients who received ICI therapy at Chongqing University Cancer Hospital from January 1, 2020, to December 31, 2023. The collected data include basic patient information such as sex, age, and body mass index (BMI); tumor-related data such as liver metastasis, TNM stage, and Karnofsky performance status (KPS); and biomarker data such as lymphocyte (LYM), white blood cell (WBC), and platelet (PLT) counts and alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), globulin (GLB), total bilirubin (TBIL), alkaline phosphatase (AKP), adenosine deaminase (ADA), C-reactive protein (CRP), and β2-microglobulin (β2-MG) levels. The definition of IMH in this study was based on the Guidelines for the Diagnosis and Treatment of Autoimmune Hepatitis (2021) (*15,16*). The diagnostic criteria include elevated serum aminotransferase levels, positive serum autoantibodies, elevated IgG levels, and characteristic histological changes in the liver, while excluding other potential causes. All blood tests were conducted in the laboratory of Chongqing University Cancer Hospital. Informed consent was obtained from each patient. This study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki and received ethical approval from the Ethics Committee of Chongqing University Cancer Hospital.

The inclusion criteria for this study were as follows: *i*) age ≥ 18 years; *ii*) hospitalized at least once; and *iii*) received ICI therapy with any of three inhibitors: CTLA-4, PD-1, or PD-L1. The exclusion criteria were as follows: *i*) missing critical pathological data such as ALT, AST, PLT, ALB, GLB, and ADA; *ii*) death within 48 hours of admission; *iii*) chronic hepatitis due to other causes, such as viral hepatitis, alcoholic hepatitis, nonalcoholic fatty liver disease, drug-induced liver disease, schistosomiasis, and other parasitic infections causing liver disease; *iv*) concurrent autoimmune liver diseases, such as primary biliary cirrhosis, primary sclerosing cholangitis, and overlap syndromes; *v*) primary liver cancer; and *vi*) combined use of two or more inhibitors. After applying the inclusion and exclusion criteria, 2,448 patients were included in the model, as shown in Figure 1.

2.2. Model construction and validation

Patients meeting the inclusion and exclusion criteria were randomly divided into a training cohort (n = 1,714) and a validation cohort (n = 734) at a 7:3 ratio. This process was implemented *via* the "caret" package in R software, with a fixed random seed number used throughout the study. In the training cohort, univariate logistic regression analysis was used to assess the impact of each clinical variable on the occurrence of IMH in patients. Variables with a p value < 0.2 in the results were then included in stepwise multivariate logistic regression analysis to identify independent factors influencing the development of IMH. A nomogram model was constructed on the basis of these results. The performance of the nomogram model was validated in the validation cohort. The discriminative ability of the nomogram was assessed *via* the area under the receiver operating characteristic curve (AUC). Calibration curves were generated *via* the bootstrap method with 1,000 resamples to validate the predictive accuracy of the nomogram in both the training and validation sets. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the nomogram model. Decision curve analysis (DCA) and clinical impact curve (CIC) analysis were performed *via* the "rmda" package

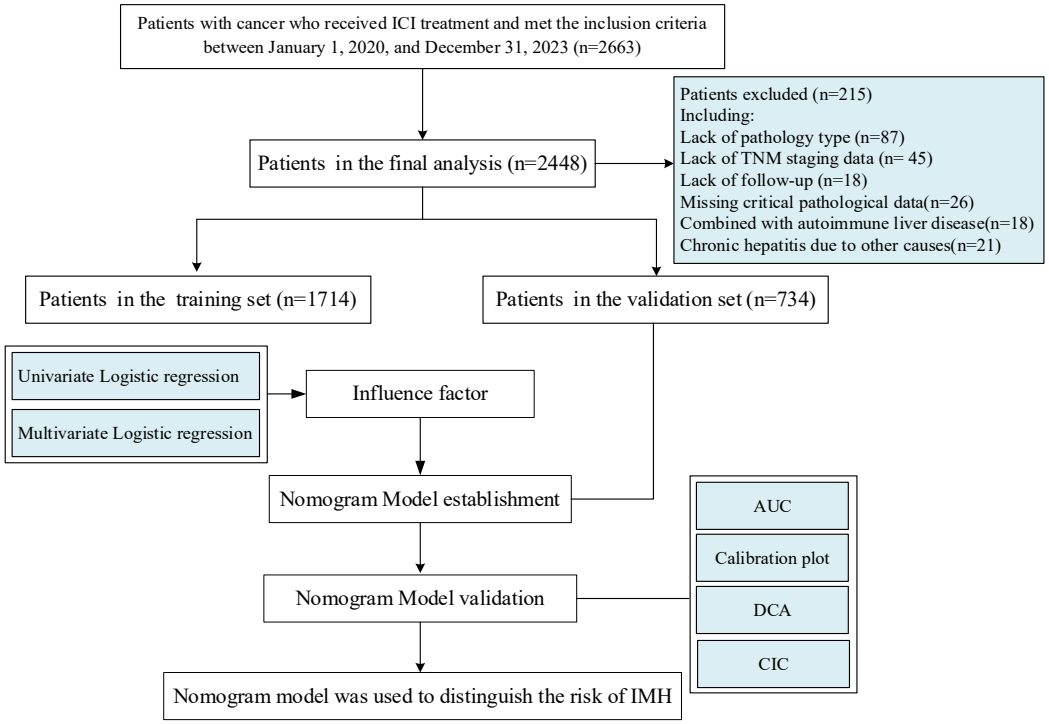

Figure 1. Flow chart for patients enrolled in the final study cohorts.

to evaluate the practical value of the nomogram model in clinical settings.

2.3. Statistical analysis

For normally distributed data, the mean ± SD was used for description, and a *t*-test was used for comparison. For nonnormally distributed data, the median (M), P25, and P75 were used for description, and nonparametric tests were used for comparison. Categorical data are expressed as frequencies and percentages, and comparisons were made *via* the chi-square test. Missing data were filled in with the "mice" package. All of the statistical analyses were performed using R version 4.1.2, and statistical significance was defined as a two-tailed p value < 0.05.

3. Results

3.1. Clinical characteristics of subjects

After applying the inclusion and exclusion criteria, 2,448 study subjects were retained, 216 (8.82%) of whom developed IMH. The median age of the included subjects was 59.00 years, and 75.82% were male. Additionally, more than half of the patients had a BMI of 18.5-23.9, were in TNM stage IV, and did not have hepatic metastases, with proportions of 57.92%, 66.79%, and 87.95%, respectively. Significant differences were observed between patients with and without IMH in terms of age, Karnofsky Performance Scale (KPS) score, and all hematological indices except for C-reactive protein (CRP) (p values for all < 0.05). Specifically, patients without IMH were older and had a higher WBC and PLT count, whereas those with IMH had higher levels of LYM, ALT, AST, ALB, GLB, TBIL, AKP, ADA, and β2-MG. Details are shown in Table 1.

3.2. Characteristics of the training and validation cohorts

This study used random sampling to allocate the 2,448 patients into the training and validation cohorts, with 1,714 patients in the training cohort and 734 patients in the validation cohort, while maintaining a 7:3 split ratio. As shown in Table 2, there were no significant differences between the training and validation cohorts (p values for all > 0.05).

3.3. Factors influencing the development of IMH

Univariate and stepwise multivariate logistic regression analyses were performed with the training cohort to investigate the factors affecting the occurrence of IMH in patients receiving ICI therapy. The detailed results are shown in Table 3. According to stepwise multivariate logistic analysis, several factors were found to increase the likelihood of developing IMH to varying degrees: hepatic metastasis, TNM stage IV, WBC, LYM, ALT, TBIL, ALB, GLB, and ADA. Hepatic metastasis and TNM stage IV disease in particular were associated with the greatest increase in IMH risk, with a 63% and 61% greater likelihood than in patients without hepatic metastasis or those with TNM stage III disease. Interestingly, age was a protective factor according to univariate and stepwise multivariate logistic analyses.

Table 1. Demographic and clinical characteristics of patients with or without IMH

Variables	Total (*n* = 2,448)	No-IMH (*n* = 2,232)	IMH (*n* = 216)	*p* value
Age (years)	59.05 ± 10.89	59.47 ± 10.79	54.69 ± 11.04	< 0.001
Sex				0.649
Female	592 (24.18)	543 (91.72)	49 (8.28)	
Male	1,856 (75.82)	1,689 (91.00)	167 (9.00)	
BMI (%)				0.284
18.5-23.9	1,418 (57.92)	1,292 (91.11)	126 (8.98)	
24-27.9	685 (27.98)	628 (91.68)	57 (8.32)	
≥ 28	129 (5.27)	112 (86.82)	17 (13.18)	
< 18.5	216 (8.82)	200 (92.59)	16 (7.41)	
TNM (%)				0.037
III	813 (33.21)	727 (89.42)	86 (10.58)	
IV	1,635 (66.79)	1,505 (92.05)	130 (7.95)	
KPS	82.40 ± 7.63	82.27 ± 7.62	83.75 ± 7.55	0.006
Hepatic metastases (%)				0.440
No	2,153 (87.95)	1,959 (90.99)	194 (9.01)	
Yes	295 (12.05)	273 (92.54)	22 (7.46)	
WBC (10^9/L)	7.53 ± 4.22	7.68 ± 4.30	5.96 ± 2.88	< 0.001
PLT (10^9/L)	216.61 ± 90.08	217.72 ± 89.50	205.21 ± 95.38	0.051
LYM (10^9/L)	1.05 ± 0.53	1.03 ± 0.52	1.21 ± 0.56	< 0.001
ALT (U/L)*	23.00 [15.00, 39.00]	22.00 [15.00, 36.00]	36.75 [20.00, 73.00]	< 0.001
AST (U/L)*	24.00 [18.00, 35.50]	23.25 [18.00, 34.00]	40.00 [23.00, 63.78]	< 0.001
ALB (g/L)	37.10 ± 5.41	37.03 ± 5.43	37.85 ± 5.19	0.032
GLB (g/L)	30.70 ± 6.60	30.43 ± 6.48	33.47 ± 7.22	< 0.001
TBIL (μmol/L)*	9.01 [6.58, 12.59]	8.84 [6.52, 12.15]	11.09 [7.81, 16.41]	< 0.001
AKP (U/L)*	88.00 [71.00, 113.62]	86.00 [70.00, 110.05]	110.00 [82.75, 165.25]	< 0.001
ADA (U/L)	10.75 ± 5.70	10.32 ± 5.28	15.15 ± 7.69	< 0.001
CRP (mg/L)*	7.54 [2.66, 37.88]	7.56 [2.66, 36.36]	7.20 [2.53, 43.79]	0.762
β2-MG (mg/L)	3.03 ± 1.28	3.00 ± 1.26	3.29 ± 1.48	0.002

Note: *Expressed as the median (M) [P25, P75].

Table 2. Clinical characteristics of the training and validation cohorts

Variables	Training cohort (*n* = 1,714)	Validation cohort (*n* = 734)	*p* value
Age (years)	58.97 ± 10.88	59.23 ± 10.91	0.583
Sex			0.471
Female	407 (23.75)	185 (25.20)	
Male	1,307 (76.25)	549 (74.80)	
BMI (%)			0.540
18.5-23.9	1,003 (58.52)	415 (56.54)	
24-27.9	465 (27.13)	220 (29.97)	
≥ 28	91 (5.31)	38 (5.18)	
< 18.5	155 (9.04)	61 (8.31)	
TNM (%)			0.591
III	563 (32.85)	250 (34.06)	
IV	1,151 (67.15)	484 (65.94)	
KPS	82.23 ± 7.70	82.79 ± 7.44	0.094
Hepatic metastases (%)			0.689
No	1,504 (87.75)	649 (88.42)	
Yes	210 (12.25)	85 (11.58)	
WBC (10^9/L)	7.57 ± 4.14	7.44 ± 4.40	0.498
PLT (10^9/L)	217.82 ± 90.54	213.80 ± 88.99	0.312
LYM (10^9/L)	1.07 ± 0.54	1.01 ± 0.51	0.130
ALT (U/L)*	23.00 [15.00, 38.85]	23.00 [15.00, 41.54]	0.697
AST (U/L)*	24.00 [18.00, 35.00]	24.60 [18.00, 38.75]	0.127
ALB (g/L)	36.99 ± 5.45	37.37 ± 5.30	0.109
GLB (g/L)	30.62 ± 6.51	30.88 ± 6.82	0.386
TBIL (μmol/L)*	8.98 [6.54, 12.38]	9.05 [6.66, 12.88]	0.231
AKP (U/L)*	88.00 [71.00, 114.00]	86.40 [71.00, 111.00]	0.219
ADA (U/L)	10.70 ± 5.63	10.87 ± 5.86	0.492
CRP (mg/L)*	7.53 [2.58, 35.75]	7.59 [2.86, 39.64]	0.635
β2-MG (mg/L)	3.02 ± 1.27	3.05 ± 1.31	0.619

Note: *Expressed as the median (M) [P25, P75].

For each 1-year increase in age, the likelihood of developing IMH decreased by 4%.

3.4. Construction and evaluation of the nomogram model

Based on the results of stepwise multivariate logistic regression analysis, a nomogram model was constructed to predict the risk of IMH in patients receiving ICI therapy, as shown in Figure 2A. The total score is obtained by adding the scores for each factor and then locating the corresponding IMH risk level on the scale. According to the nomogram, TBIL has the greatest impact on predicting IMH risk, followed by GLB, WBC, and age. LYM, ALT, ALB, and ADA have a moderate impact on predicting IMH risk in patients with breast cancer undergoing chemotherapy.

The nomogram model had an AUC of 0.817 (95% CI: 0.782-0.852) in the training set and 0.737 (95% CI: 0.664-0.811) in the validation set, indicating good performance. The model effectively identified risk levels, with ROC curve results (Figure 2B) showing strong generalizability and effective risk identification for IMH in ICI patients. Similarly, the calibration curves (Figures 3A and 3B) revealed that all the points were close to the

Table 3. Logistic regression analysis of the risk factors for IMH in the training cohort

Variable	OR (Univariable)	OR (Stepwise - multivariable)
Age (years)	0.96 (0.94-0.97, $p < 0.001$)	0.96 (0.95-0.98, $p < 0.001$)
Sex		
Female		
Male	1.23 (0.82-1.83, $p = 0.314$)	
KPS	1.02 (0.99-1.04, $p = 0.110$)	
Hepatic metastases		
No		
Yes	2.41 (1.61-3.60, $p < 0.001$)	1.63 (1.02-2.60, $p = 0.040$)
TNM		
III		
IV	1.58 (1.08-2.31, $p = 0.018$)	1.61 (1.05-2.46, $p = 0.030$)
BMI		
18.5-23.9		
24-27.9	1.04 (0.71-1.51, $p = 0.844$)	
≥ 28	1.42 (0.75-2.70, $p = 0.284$)	
< 18.5	0.87 (0.46-1.63, $p = 0.662$)	
WBC (10^9/L)	1.04 (1.01-1.08, $p = 0.007$)	1.05 (1.01-1.09, $p = 0.008$)
PLT (10^9/L)	1.00 (0.99-1.00, $p = 0.066$)	
LYM (10^9/L)	1.63 (1.24-2.15, $p < 0.001$)	1.50 (1.06-2.11, $p = 0.021$)
ALT (U/L)*	1.01 (1.01-1.01, $p < 0.001$)	1.01 (1.01-1.01, $p < 0.001$)
AST (U/L)*	1.01 (1.01-1.01, $p < 0.001$)	
ALB (g/L)	1.03 (1.02-1.05, $p < 0.001$)	1.02 (1.01-1.03, $p = 0.006$)
GLB (g/L)	1.00 (0.99-1.00, $p < 0.001$)	
TBIL (μmol/L)*	1.03 (1.00-1.06, $p = 0.029$)	1.03 (1.01-1.07, $p = 0.041$)
AKP (U/L)*	1.07 (1.04-1.09, $p < 0.001$)	1.04 (1.01-1.06, $p = 0.012$)
ADA (U/L)	1.11 (1.08-1.14, $p < 0.001$)	1.07 (1.04-1.10, $p < 0.001$)
CRP (mg/L)*	1.00 (0.99-1.01, $p = 0.110$)	
β2-MG (mg/L)	1.13 (1.02-1.26, $p = 0.023$)	

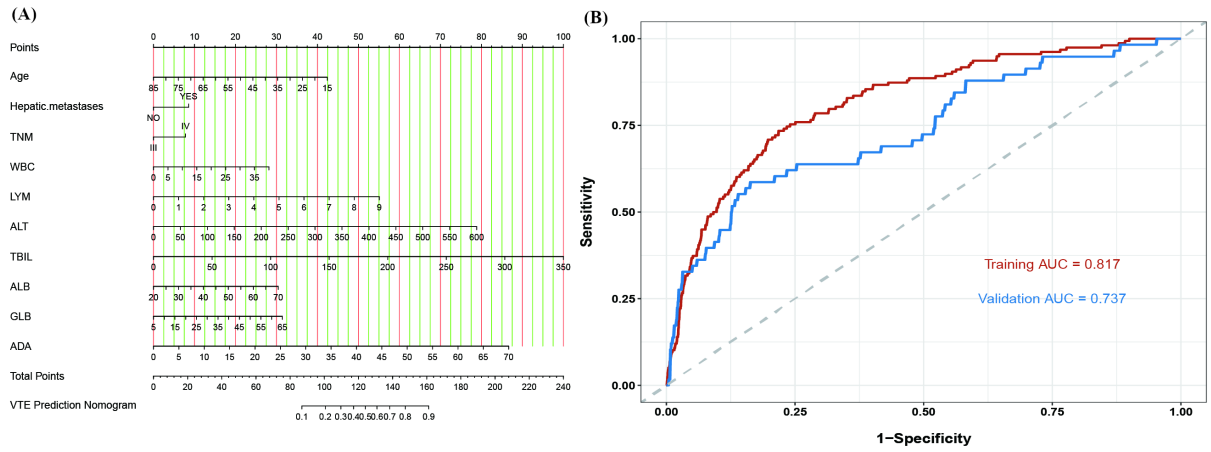

Figure 2. (A) Nomogram model for predicting IMH risk in ICI patients; (B) The ROC curve for the nomogram model.

diagonal line. The Hosmer-Lemeshow test showed that the *p* values were 0.270 and 0.857 for the training set and the validation set, respectively, indicating that the model fit well. These findings indicate that the nomogram model accurately predicts IMH risk in both the training and validation cohorts and performs excellently.

To evaluate the clinical benefit of the model, DCA was used, and the results are shown in Figures 4A and 4B. In the training cohort, the model indicated greater net benefit than the "all" and "none" lines at threshold probabilities between 1% and 39%, indicating clinical value. Similarly, the model indicated clinical applicability in the validation cohort at threshold probabilities between 1% and 35%. CIC (Figure 4C and 4D) revealed that the nomogram model can be used to indicate clinical benefits for any ICI patients.

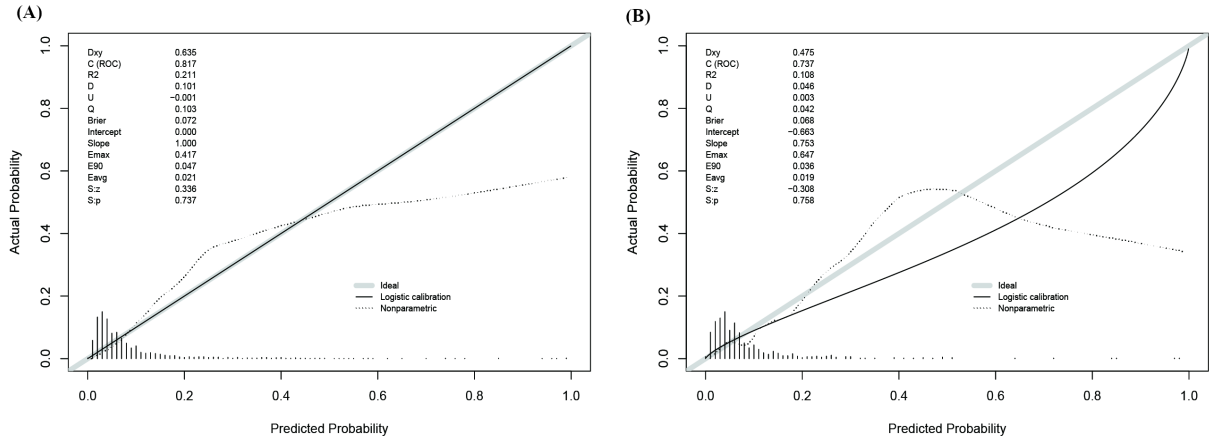

Figure 3. The calibration curves for the nomogram model. (A) training cohort; **(B)** validation cohort.

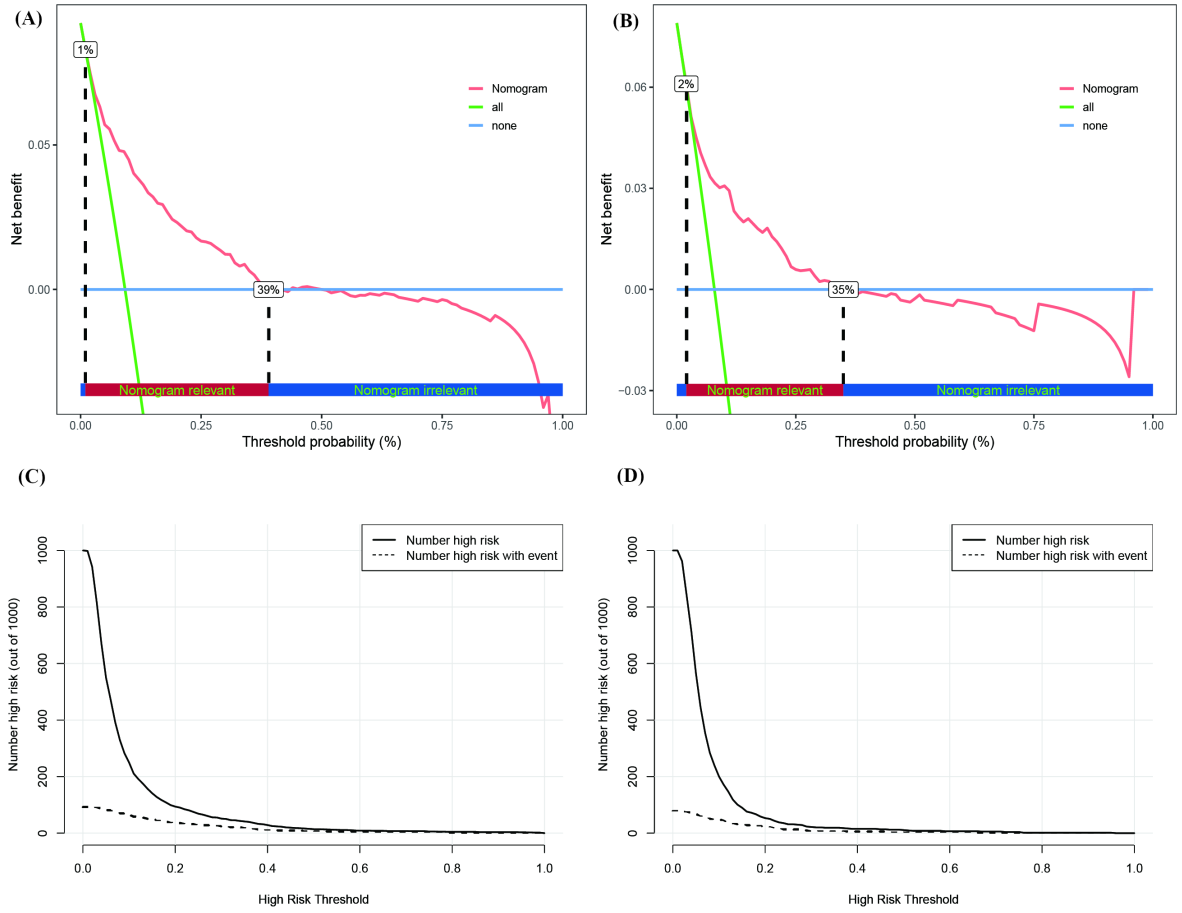

Figure 4. The DCA curves for the nomogram model. (A) training cohort; **(B)** validation cohort and CIC curves for the nomogram model; **(C)** training cohort; **(D)** validation cohort.

4. Discussion

Understanding the risk factors for developing IMH and constructing a model to predict the risk of IMH are crucial to guiding treatment interventions and improving patient outcomes. In this study, liver function data, demographic data, and relevant hematological indices of cancer patients treated with ICIs were integrated to investigate the risk factors for IMH. Based on these findings, a new risk prediction model was constructed using a nomogram to identify the risk of IMH in these patients. The nomogram model can quickly and accurately identify the risk levels of IMH without the need for invasive procedures such as liver biopsies. It is readable and practical, making it more suitable for clinical practice. This model can assist in personalized medical treatment and optimize the safety of ICIs in clinical practice.

Nomogram models play crucial roles in predicting the risk of liver-related diseases. They have been used to develop risk prediction tools for various liver diseases. For example, a nomogram model was constructed for hepatocellular carcinoma (HCC) patients treated with ICIs on the basis of clinical characteristics and the serum alpha-fetoprotein response to predict patient mortality risk (*17*). Similarly, nomogram models have been developed for patients with autoimmune hepatitis (AIH) to identify predictors of poor treatment response and advanced liver fibrosis and even to predict the risk of AIH without requiring a liver biopsy (*18*). However, no studies have proposed the use of a nomogram model to predict the risk of IMH. The current study is the first to utilize real-world data from hospitals to construct a nomogram model to predict the risk of IMH in patients receiving ICI treatment. Several studies have shown that nomogram models have greater predictive accuracy than other hepatitis risk assessment tools do. For example, Zhao *et al*. developed a nomogram model to predict acute liver failure (ALF) in patients with spontaneous rupture of hepatocellular carcinoma (SRHCC) with a high level of accuracy, achieving a C-index of 0.91 that was superior to those of the Child–Pugh and ALBI models (*19*). Similarly, Yang *et al.* constructed a nomogram model to predict 90-day mortality risk in patients with hepatitis B virus-related acute–chronic liver failure (HBV-ACLF) (*20*). This model outperformed the MELD score, Age-Bilirubin-International Normalized Ratio-Creatinine (ABIC) score, and Albumin-Bilirubin (ALBI) score in terms of prediction accuracy.

In the current study, patients with liver metastasis had a significantly increased risk of IMH, with a 1.52-fold greater risk than those without liver metastasis. However, the relationship between IMH and liver metastasis is complex. A retrospective case–control study by Storm *et al*. revealed that while liver metastasis was initially associated with an increased likelihood of IMH, this association was not significant after adjusting for covariates (*21*). Similarly, a systematic review and meta-analysis by Pan *et al*. reported that the association between liver metastasis and IMH was not statistically significant (OR: 1.47, 95% CI: 0.99-2.18; $p = 0.056$) (*11*). Therefore, the hypothesis is that liver metastasis may play a role in the occurrence of IMH. However, other factors, such as liver function and cancer staging, appear to have a greater impact on the risk of IMH in patients receiving ICI treatment. Patients with TNM stage IV disease have more severe cancer progression and often receive more intensive and frequent ICI treatment (*22*). This increases their risk of developing IMH compared to patients in other stages. Older patients tend to have reduced bodily activity and liver function compared to younger patients (*23,24*), which manifests as a lower risk of IMH in older patients in this study. Consequently, age emerged as a protective factor against IMH in the univariate and multivariate analyses.

The mechanism of IMH involves T-cell overactivation (*25*). Thus, WBCs play a crucial role in the development of IMH. Studies have shown that a small number of intrahepatic virus-specific cytotoxic T lymphocytes (CTLs) and recruited monocytes/macrophages can lead to chronic liver inflammation, increasing the risk of IMH (*26*). Additionally, T-cell-mediated immune mechanisms are related to hepatitis B virus (HBV) infection, and immunosuppressants can impair T-cell function, leading to immune-mediated hepatocyte lysis and reduced viral clearance, further increasing the risk of IMH (*27*). That said, Johnson *et al.* examined a mouse model of T-cell-mediated hepatitis induced by lymphocytic choriomeningitis virus (LCMV) infection and they reported that the severity of hepatitis was associated with the activity of cytotoxic T cells in the liver and spleen (*28*). These findings emphasize the role of T cells in liver injury and indicate that WBC dysfunction can exacerbate immune-mediated liver damage, increasing the risk of IMH.

Extensive research has shown that lymphocytes play a crucial role in IMH by mediating liver injury and disease progression (*29*). Platelets coordinate liver inflammation and damage through signaling factors such as TPL2 in iNKT cells, influencing immune-driven liver diseases and thereby increasing the risk of IMH (*30*). This finding is similar to the current study's findings. AST and TBIL are common markers of liver function and injury, and their elevation is a key feature of IMH, typically manifesting as elevated transaminases and other liver function abnormalities (*21*). Abnormal liver function often increases the risk of IMH.

Additionally, Zhang *et al*. reported that IMH is often accompanied by increased AST and TBIL levels (*31*). Owing to the unique immunological characteristics of the liver, the occurrence of IMH is often accompanied by elevated levels of ALB and GLB (*32*). In a study on the impact of ICIs on liver enzymes and attenuation, Park

et al. reported that patients treated with ICIs had higher ALB levels than those at the baseline did, indirectly indicating that IMH is accompanied by elevated ALB levels (*33*). ADA levels in body fluids reflect the activity of cellular immune responses. When IMH occurs, the liver's cellular immune response intensifies, leading to increased ADA levels (*34*). In the current study, this was evident in an increase in ADA levels of one unit, which increased the risk of IMH by 2%.

The current study had several innovative aspects. First, stringent inclusion and exclusion criteria were applied to exclude all unsuitable patients, and comprehensive characteristic data were thoroughly collected from patients in all age groups, ensuring the validity of data. Second, the direction and extent of the impact of each predictor on the occurrence of VTE in patients was investigated in the nomogram model, providing theoretical guidance for preventing VTE in clinical practice.

That said, this study had several limitations. First, this was a single-center study, with all patient data collected from one hospital. Therefore, the generalizability of the nomogram model is debatable. Future studies could involve multicenter collaboration to validate the model's performance using patient data from other centers. Second, this study was retrospective, so it has inherent limitations such as recall bias and recording bias. Finally, the impact of patients' imaging data or liver biopsy results on the risk of IMH occurrence was not considered, and these factors were not included in the model as predictors. Future research could incorporate detailed patient characteristics, such as imaging and liver biopsy data. This would increase the initial cost of the study, but it would undoubtedly enhance the model's performance and quality.

In conclusion, a model was developed to estimate the risk of IMH in cancer patients receiving ICI treatment. Based on the nomogram algorithm, this model is intuitive and straightforward, making it well-suited for assessment of the risk of patients developing IMH after ICI therapy in clinical practice. This nomogram model enables the prompt formulation of preventive and therapeutic strategies, ultimately reducing the likelihood of IRAEs, and particularly IMH. The practical use of this model in clinical settings could potentially enhance the quality of life of cancer patients.

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