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Original Article

Development and Validation of a Clinical Risk Score to Predict Immune-mediated Liver Injury Caused by Sintilimab: Assessed for Causality Using Updated RUCAM

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Abstract

Background and Aims: Immune-mediated liver injury is a fatal side effect of sintilimab. This study aimed to shed light on the associated risk factors and characteristics of this adverse event. ***Methods:*** The clinical records of 772 patients treated with sintilimab were retrospectively reviewed to investigate risk factors associated with sintilimab immune-related hepatotoxicity, as well as its incidence and outcome. The Roussel Uclaf Causality Assessment Method was used to identify cases of sintilimab-induced hepatotoxicity. Furthermore, logistic regressions were performed to compare the clinical and bloodwork characteristics of patients with and without immune-mediated liver injury caused by checkpoint inhibitors. ***Results:*** Of the 585 patients included in the study, 71 (12.1%) developed liver injury during sintilimab use. The median RUCAM score with interquartile range was 7 (6, 8). Hypoproteinemia, dyslipidemia, and the presence of thyroid peroxidase antibodies were risk factors for sintilimab-related hepatotoxicity. A nomogram model was constructed for sintilimab-induced immune-mediated liver injury based on these risk factors, which had a C-index value of 0.713 and a good calibration curve. When applied to patients with grade ≥3 and ≥4 sintilimab-induced immune-mediated liver injury, it achieved C-index values of 0.752 and 0.811, respectively. The nomogram model also showed a good prediction potential in patients ≥65 years and males. Six of the patients with sintilimab-related hepatotoxicity showed improved liver function upon treatment with steroids. ***Conclusions:*** This study demonstrated that hypoproteinemia, dyslipidemia, and the presence of thyroid peroxidase antibodies were clinically feasible prognostic biomarkers to predict liver injury in patients treated with sintilimab.

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Introduction

Sintilimab is a human anti-programmed cell death protein 1 (PD-1) IgG4-k monoclonal antibody approved in China to treat classical Hodgkin's lymphoma.[1] Monoclonal antibodies, besides improving the antitumor response, can cause various autoimmune-related adverse reactions via a different mechanism than other systemic therapies, often referred to as immune-related adverse events (irAEs)[2] that can affect multiple organs, including the skin, gastrointestinal tract, liver, and lungs.[3] The incidence of immune-related hepatotoxicity caused by immune checkpoint inhibitors ranges within 0.7–16%, depending on the dose, duration, and combination regimen.[4–6] Immune-related hepatotoxicity is asymptomatic, but some serious complications have been reported in clinical practice, including immune-mediated liver injury caused by checkpoint inhibitors (ILICI).[7] The clinical determinants of immune-related hepatotoxicity remain unclear, which complicates risk factor identification and hepatotoxicity timing prediction, and consequently delays the optimal timing of immune-mediated hepatotoxicity treatment. This study aimed to analyze the risk factors for immune-related hepatotoxicity in patients treated with sintilimab, access hepatotoxicity timing and treatment outcome, and construct a risk-scoring model for ILICI. Taken together, the findings of this study are expected to enable clinicians to better predict the risk of hepatotoxicity associated with immune therapy, begin precision treatment as soon as possible, and improve cancer patient outcomes.

Keywords: Risk factors; Hepatotoxicity; Sintilimab; Checkpoint inhibitor-related immune-mediated liver injury; Updated RUCAM.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; ILICI, immune-mediated liver injury caused by checkpoint inhibitors; irAE, immune-related adverse event; OR, odds ratio; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; ROC, receiver operating characteristic; TPO, thyroid peroxidase.

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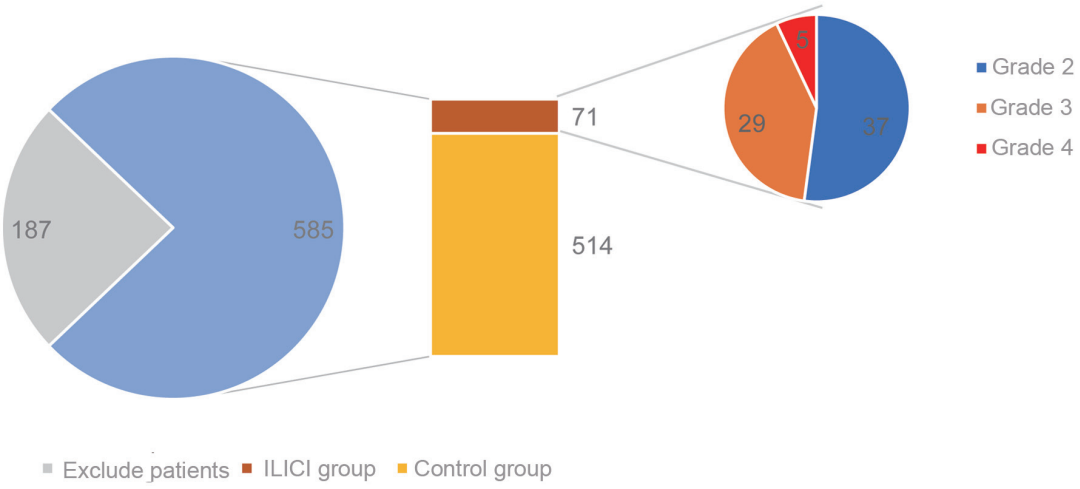

Fig. 1. Screening chart of patients enrolled in the study.

Methods

Data collection

Patients treated with sintilimab at the Fujian Medical University Union Hospital (one of the largest emergency hospitals in China) between January 2019 and May 2022 were retrospectively assessed. The Medical Records Inpatient System was used to extract patient health data, including historical epidemiology (sex, age, alcohol consumption, smoking, and family history), concomitant diseases (hypertension, diabetes, hepatitis, coronary heart disease, liver cyst, cholecystitis, and gallbladder or bile duct stones), drug combinations (nonsteroidal anti-inflammatory drugs, proton pump inhibitors, hepatoprotectors, antiemetics, and dose and frequency of sintilimab injections), and baseline laboratory indicators (liver and kidney function, thyroid function indicators, autoimmune antibodies, programmed cell death ligand 1 [PD-L1] expression).

The exclusion criteria were: (1) <18 years of age, (2) abnormal liver function including alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin 1 month before the first administration of sintilimab, (3) combined therapy with other immune checkpoint inhibitors, (4) insufficient data hindering subsequent analysis such as patients who were not routinely tested for liver enzymes and autoimmune antibodies, and (5) other reasons for liver injury including viral or drug-induced by alternative drugs. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Fujian Medical Union Hospital. Owing to the retrospective nature of the study, the requirement of written informed consent was waived.

Definition of immune-related hepatotoxicity

According to CTCAE 5.0, ILICI was defined as the occurrence of grade ≥2 liver injury after sintilimab infusion and a Roussel Uclaf Causality Assessment Method score ≥6 (range, −9 to +14 and classified as ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; and ≥9, highly probable).[8]

Statistical analysis

Stata 14 (Stata Corporation, College Station, TX, USA), SPSS (version 25.0; IBM Corp., Armonk, NY, USA), R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria), and Prism 8.0 (GraphPad Software, Boston, MA, USA) were used for data analysis. For continuous variables, normally distributed data were reported as means ± standard deviation, non-normally distributed data were reported as medians and range, and categorical variables reported as percentages. Student's *t*, chi-square, or Mann–Whitney *U* tests were performed for between groups comparisons, and Fisher's exact test was performed if necessary. Correlation analysis was performed to assess the relationship between two variables. Pearson's correlation analysis was performed for data with normal or near normal distributions, and Spearman's correlation analysis were performed for data with non-normal distributions. Stepwise iterative logistic method was adopted based on the Bayesian information criterion to further eliminate redundant variables and the Akaike information criterion model was followed. If the latter were similar, the model with fewer variables was adopted by comparing the differences between the two models.[9] Subsequently, independent risk factors related to the incidence of ILICI were determined. Statistical significance was set at $p<0.05$ (double-tailed). Harrell's concordance index (C-index) was used to evaluate the effectiveness of prediction and discrimination. Receiver operating characteristic (ROC) curve analysis showed the predictive ability of each risk factor, and combined with the nomogram, revealed the area under the curve (AUC). The R RMS package was used to generate a correction curve reflecting the relationship between the predicted and real incidences. The abscissa depicted the predicted probability, and the ordinate showed the actual probability of the patient (real incidence). Decision curve analysis further showed the net benefit to the observer and was used to evaluate the clinical value of the constructed nomogram.

Results

Patient characteristics

Between January 2019 and May 2022, 772 patients received sintilimab treatment. A total of 187 patients were excluded from the study, among whom 173 had abnormal ALT, AST, ALP, GGT, or total bilirubin levels in the previous cycle, eight had received clinical trial placebos, and six had insufficient data for analysis. The remaining 585 patients were included in the analysis, among whom 71 were included in the ILICI group, representing an ILICI incidence of 12.1% (Fig. 1). Thirty-seven patients (52.1%) had grade 2 hepatotoxicity,

29 (40.8%) had grade 3 hepatotoxicity, and five (7.0%) had grade 4 hepatotoxicity. Among 71 ILICI cases, 63 (88.7%) were probable and 8 (11.3%) were highly probable based on the updated RUCAM, and the average RUCAM score of the ILICI group was 7.06 ± 1.22. Seventeen cases (23.9%) were classified as hepatocellular type, 32 (45.1%) as cholestatic type, and 22 (31.0%) as mixed type hepatotoxicity.

The median age, sex, and incidence of tumor liver metastasis was similar between the ILICI group and the 514 patients without liver injury (Table 1). The median sintilimab use cycle in the ILICI group was two (range: 1–16), and the cumulative dose was 400 mg, which differed significantly from the non-ILICI group (p<0.0001). Among baseline laboratory indicators, red blood cell, platelet, eosinophils, and basophils counts, as well as hemoglobin, liver function indicators (ALT, AST, ALP, GGT, and total bilirubin), albumin were significantly different (p<0.05).

Independent risk factors associated with the development of hepatotoxicity in the training cohort

The samples were randomly divided into training and verification sets in a 6:4 ratio. Correlation analysis revealed no relationship between the variables of the training set (Fig. 2). Stepwise iterative logistic regression identified three independent risk factors associated with ILICI, namely dyslipidemia (odds ratio [OR]=2.546, 95% confidence interval [CI]=1.246–5.202, p<0.001), thyroid peroxidase (TPO) antibodies (OR=22.992, 95% CI=1.749–302.272, p=0.018), and hypoproteinemia (OR=4.111, 95% CI=1.733–9.755, p=0.001). Based on these risk factors, a nomogram model for predicting ILICI risk (ILICI-nomogram) was established for patients using sintilimab (Fig. 3A). Scores corresponding to the prognostic index were added to obtain the total score, and the ILICI risk probability was obtained from the total score. After 1,000 internal validations of bootstrap self-sampling, the model showed a C-index value of 0.713 (95% CI=0.632–0.794), indicating that the predictions obtained from this nomogram were consistent with the real observations and that the nomogram sensitivity met the standard. The calibration chart was in good agreement between the observed and predicted probability of ILICI risk. Decision curve analysis further showed that the nomogram had the largest net benefit over any single factor, indicating the best clinical diagnostic value for a comprehensive nomogram (Fig. 3B). The p-value of the goodness-of-fit was 0.9659, which suggested that the model was reasonable. We used the verification set and the full sample to verify the model, and the AUCs were 0.563 and 0.652, respectively (Supplementary Table 1 and Supplementary Fig. 1).

Application and evaluation of the ILICI-nomogram in grade ≥3 and ≥4 ILICI cohorts

The C-index of the grade 3 and 4 ILICI cohort was 0.752 (95% CI=0.627–0.878). The C-index of the ≥grade 4 ILICI cohort was 0.811 (95% CI=0.554–1.000). The calibration curve showed that the predicted incidence was close to the real incidence, and the nomogram agreed with the real observed outcomes (Fig. 4). ROC analysis further showed that the optimal cutoff value of the model was 10.0%; under this threshold, the decision curve of the model was above the none and all lines, indicating that the model had certain clinical practicability.

Subgroup analysis

An independent assessment of the predictive effect of the ROC model was also performed in some important subgroups of patients (Table 2). The model showed better ILICI predictive potential in males and patients ≥65 years. The C-indices for patients ≥65 years of age and men were 0.746 (95% CI=0.678–0.892) and 0.723 (95% CI=0.639–0.890), respectively (Fig. 5)

Correlation between baseline characteristics and ILICI

The relationship between baseline clinical features, various laboratory indicators, and ILICI were also evaluated (Supplementary Table 2). In the ILICI cohort, patients with positive thyroglobulin (p=0.004) and TPO (p<0.001) antibodies, dyslipidemia (p=0.035), hypoproteinemia (p=0.001), and renal insufficiency (p=0.011) were more likely to develop ILICI. Similarly, ILICI was more likely to occur in the grade ≥3 ILICI cohort with thyroglobulin antibodies (p=0.004), TPO antibodies (p=0.001), hypoproteinemia (p=0.030), and renal insufficiency (p<0.001). Female, liver metastases, thyroglobulin antibodies, antinuclear antibodies, coronary heart disease, hepatitis, dyslipidemia, choledocholithiasis, renal insufficiency, and cholecystitis were factors associated with the likelihood of developing grade ≥4 ILICI (all p<0.05). ROC analysis was performed that included the risk factors (Supplementary Fig. 2).

Clinical features in patients with ILICI

The median time from the start of immunotherapy to immune liver injury onset was 87 days, with large individual differences (1–828 days). We did not observe differences in the time to reach grade 2 or higher liver injury following stratification by the severity of liver injury (p=0.0784; Fig. 6). Of the 71 patients with liver injury, 34 were permanently discontinued, and 12 restarted sintilimab therapy; only six received corticosteroid therapy at a dose of 40 mg/qd, and their liver function indicators eventually returned to normal. Thirty-four patients received hepatoprotectors along with conventional hepatoprotective drugs, usually in combinations of two or three, and the drugs of choice are butyl disulfonic acid, compound glycyrrhizin, glutathione, polyene phosphatidylcholine, and monoammonium cysteine glycyrrhizinate.

Discussion

Risk factors and the incidence of ILICI were evaluated in cohorts of patients with cancer who received sintilimab treatment. In addition, a diagnostic, intuitive, and personalized ILICI-nomogram was developed and verified. Finally, hypoproteinemia, dyslipidemia, and TPO antibodies were identified as independent risk factors for ILICI.

The activation of regulatory T cells against cytotoxic T lymphocytes contributes to all irAEs related to immune checkpoint inhibitors; however, the potential signaling pathway underlying hepatocyte damage and ILICI remains unclear. The main possible mechanisms are based on changes in self-tolerance and T-cell-mediated immune system activation.[10] Previous studies showed that the PD-1 pathway helps the liver protect itself from immune-mediated destruction and that PD-1 or PD-L1 inhibitors restore the antitumor immunity of cytotoxic T lymphocytes by blocking the interaction between PD-1 and PD-L1. However, activated cytotoxic T lymphocytes respond to the liver.[11–13] Therefore, increased expression of PD-L1 may play a role in immune-mediated hepatotoxicity. PD-L1 expression was reported to be significantly up-regulated in patients with high body fat and that there are more T helper 1 and 17 cells in adipose tissue. Furthermore, dyslipidemia can promote the secretion of pro-inflammatory cytokines (such as interleukin-1β, monocyte

Table 1. Participant baseline epdemographic and disease characteristics

Variable	All cases, *n*=585	ILICI, *n*=71	Non-ILICI, *n*=514	*p*-value[a]
Age in years, mean (range)	60.0 (12–86)	55.4 (14–75)	58.1 (12–86)	0.708
Sex as male/female, *n*	450/135	57/14	393/121	0.474
Primary cancer type, *n*				0.031
NSCLC	198	10	185	
esophageal cancer	159	23	134	
gastric cancer	119	22	97	
lymphoma	56	11	45	
other cancers	26	2	23	
intestinal cancer	18	3	14	
liver cancer	9	0	9	
Liver metastasis as yes/no, *n*	37/548	6/65	31/478	0.547
Cycle of liver damage	2.0 (1–34)	2.5 (1–16)	/	/
Laboratory index, mean (range)				
White blood cells as $\times 10^9$/L	5.76 (0.01–92.55)	7.12 (0.01–63.52)	6.93 (0.11–65.33)	0.152
Red blood cells as $\times$ 10^9/L	3.83 (0.02–54.1)	3.95 (0.03–44.1)	4.44 (0.02–54.1)	<0.001
Hemoglobin in g/L	116 (1–205)	105.45 (1–166)	116.62 (1–205)	<0.001
Platelets as $\times$ 10^9/L	200 (0–1,373)	204.98 (0–769)	221.59 (0–1,373)	<0.001
Monocyte count, %	6.9 (0–70.8)	7.63 (0–70.8)	7.54 (0–56)	0.423
Lymphocyte count, %	22.2 (0–100)	22.73 (0–100)	24.66 (0–97.8)	<0.001
Eosinophil count, %	1.5 (0–58.8)	2.60 (0–42.7)	2.21 (0–58.8)	<0.001
Basophil count, %	0.4 (0–5.6)	0.49 (0–5.6)	0.51 (0–4.3)	0.270
ALT in IU/L	18 (1–1,375)	43.33 (4–1,375)	22.29 (1–790)	<0.001
AST in IU/L	21 (2–2,064)	45.96 (2–5,215)	25.05 (2–948)	<0.001
ALP in IU/L	76 (21–725)	104.08 (33–1,328)	84.01 (18–1,959)	<0.001
GGT in IU/L	25 (5–908)	78.92 (7–1,728)	36.95 (4–1,533)	<0.001
Total bilirubin in IU/L	9 (0.7–9.0)	11.95 (0.8–9.0)	10.52 (0.7–9.0)	<0.001
Direct bilirubin in IU/L	2.6 (0–116)	4.30 (0–112.8)	3.13 (0–125)	<0.001
Indirect bilirubin in IU/L	7.1 (0.1–9.0)	9.29 (0.1–8.0)	9.63 (0.5–9.0)	0.172
Albumin in IU/L	39.2 (17.2–56.6)	37.81 (15.3–54.6)	38.42 (17.2–56.6)	<0.001
Creatinine in μmol/L	65 (19–561)	69.89 (22–813)	70.55 (12–2,454)	0.663
Lifestyle				
Smoking, *n* (%)	334 (57.1)	35 (49.3)	297 (58.6)	0.445
Drinking, *n* (%)	271 (57.1)	31 (43.7)	240 (46.7)	0.984
Underlying disease, *n* (%)				
Hypertension	90 (15.4)	7 (9.9)	83 (16.1)	0.078
Diabetes mellitus	32 (5.5)	4 (5.6)	28 (5.4)	0.687
Coronary heart disease	9 (1.5)	2 (2.8)	7 (1.4)	0.381
Hepatitis	35 (6.0)	4 (5.6)	31 (6.0)	0.321
Stroke	10 (1.7)	4 (5.6)	6 (1.2)	0.885
Hepatic cyst	45 (7.7)	7 (9.9)	38 (7.4)	0.346
Abnormal lipids metabolism	28 (4.8)	4 (5.6)	24 (4.7)	0.063
NAFLD	14 (2.4)	1 (1.4)	13 (2.5)	0.308
Choledocholithiasis	16 (2.7)	5 (7.0)	11 (2.1)	0.221
Cholecystitis	18 (3.1)	6 (8.5)	17 (3.3)	0.200
Other characteristics				
Number of hospital visitations, mean (range)	52 (1–541)	69 (3–233)	31 (1–541)	0.052
Number of hospitalizations, mean (range)	22 (1–77)	29 (2–65)	12 (1–77)	0.085
Tumor surgical history, *n* (%)	145 (24.8)	19 (26.8)	126 (24.5)	0.640

(continued)

Table 1. *(continued)*

Variable	All cases, *n*=585	ILICI, *n*=71	Non-ILICI, *n*=514	*p*-value[a]
History of blood disease, *n* (%)	4 (0.7)	1 (1.4)	3 (0.6)	0.430
Family medical history (grade 1/2), *n*	64/2	8/0	55/2	0.923
Relapse or not, *n* (%)	18 (3.1)	3 (4.2)	15 (2.9)	0.673
PD-1 cycle, mean (range)	2 (1–34)	2 (1–16)	2 (1–34)	<0.0001
Accumulated dose (mg), mean (range)	600 (0–12,800)	400 (200–5,000)	600 (0–12,800)	<0.0001

[a]Comparison between non-ILICI and ILICI cases was performed by chi-squared, Fisher's exact, or Mann–Whitney *U* tests. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ILICI, immune-mediated liver injury caused by checkpoint inhibitors; NAFLD, nonalcoholic fatty liver disease; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death-1.

Fig. 2. Correlation of variables.

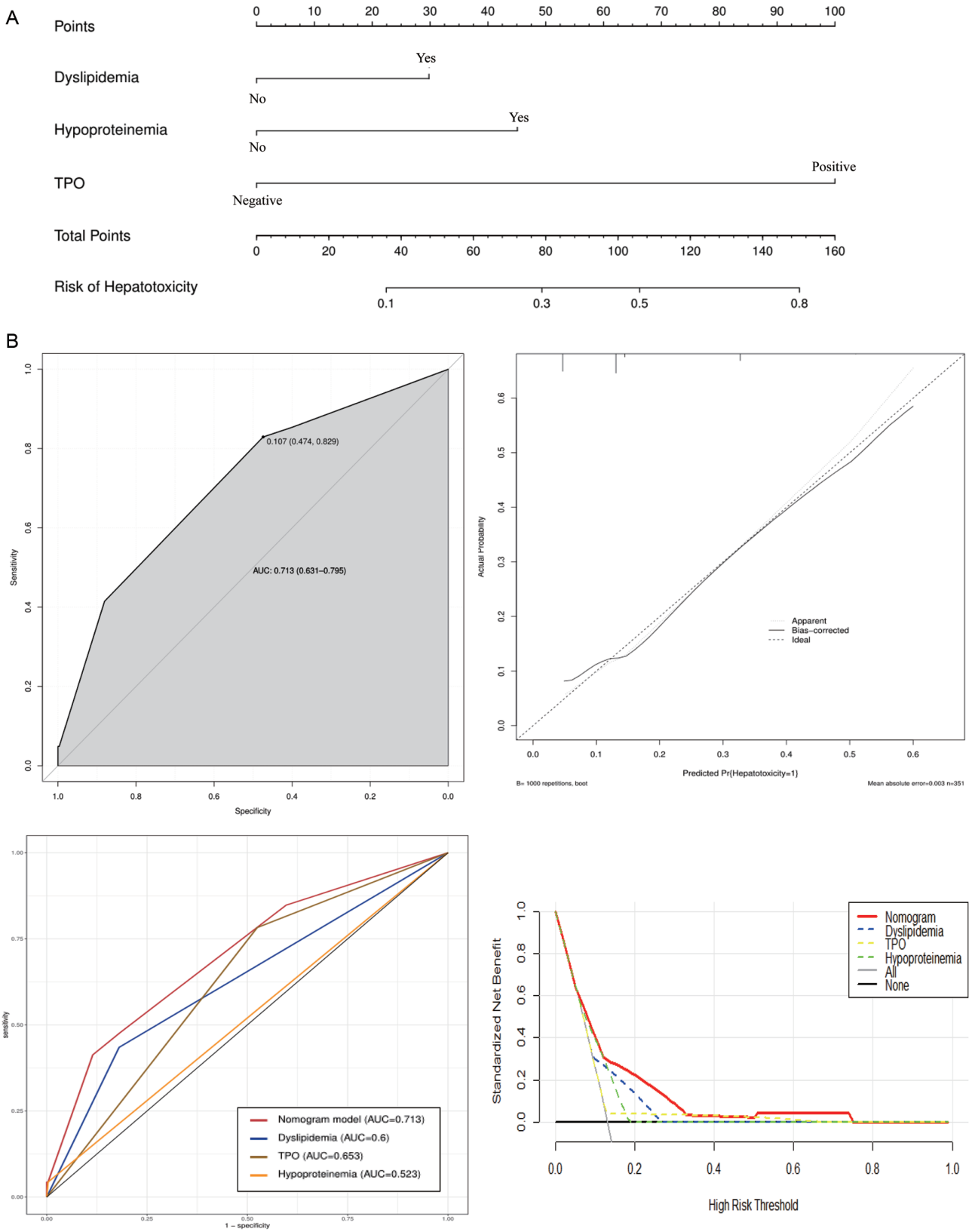

Fig. 3. Construction of the immune-mediated liver injury caused by the checkpoint inhibitor (ILICI)-related nomogram and validation in the training cohort.

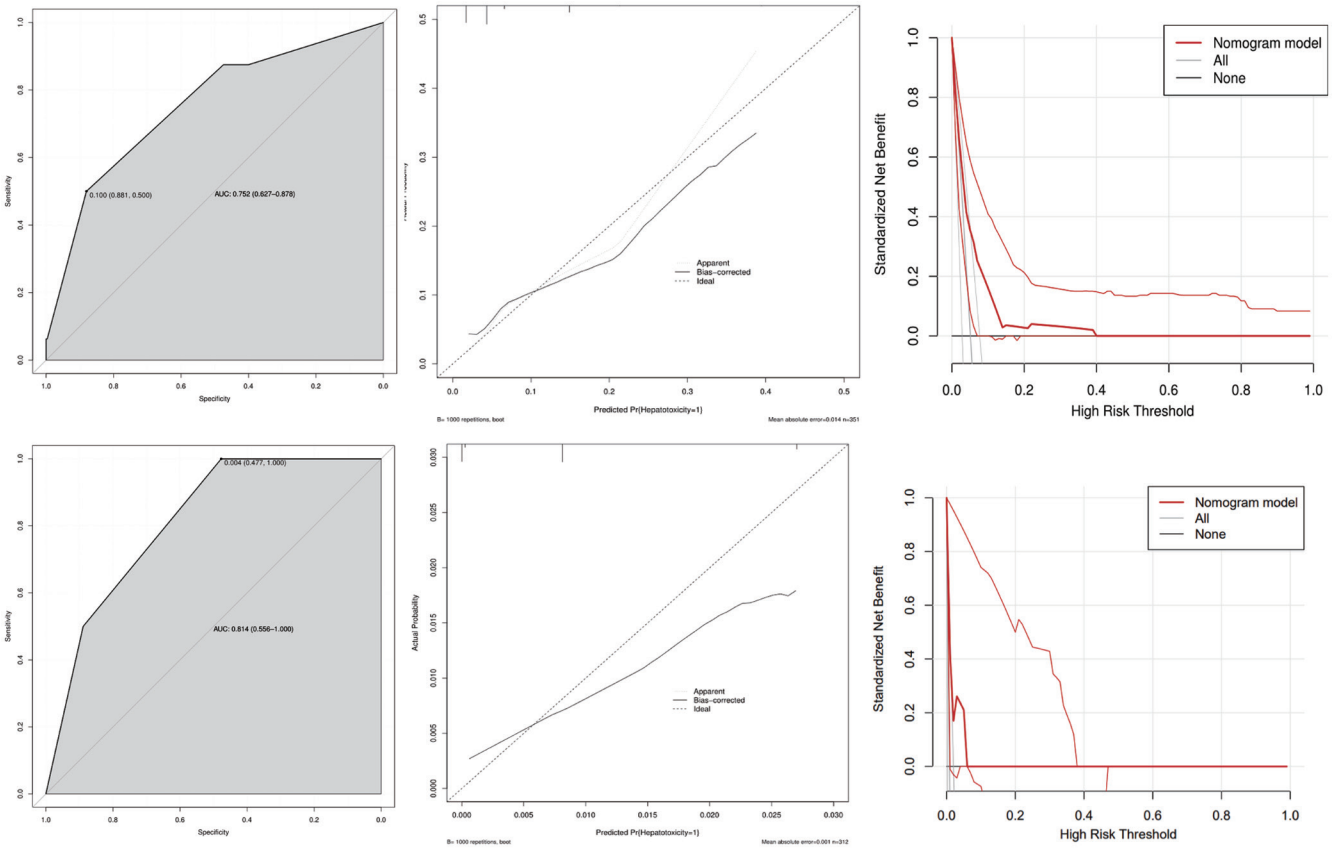

Fig. 4. Evaluation of the immune-mediated liver injury caused by the checkpoint inhibitor (ILICI)-nomogram in the grade ≥3 and 4 ILICI cohort.

chemoattractant protein-1, and tumor necrosis factor-α) by immune cells, which promote inflammation and liver tissue damage.[14] Therefore, it is reasonable to consider hyperlipidemia as a risk factor for immune-mediated hepatotoxicity.

Sharma *et al*.[15] found that the incidence of drug-induced liver injury in patients with hypoproteinemia before antituberculosis drug treatment was 2.3-fold that in nonhypoproteinemia patients. This study had similar findings, with a higher risk of ILICI, a type of drug-induced liver injury, observed in patients with hypoproteinemia. Furthermore, hypoproteinemia can reflect the degree of inflammation in the body and predict the release of various inflammatory markers. In various solid tumors, systemic inflammatory markers play an important role in the development of

Table 2. Subgroup receiver operating characteristic analysis

Subgroup	Number of patients	Area under the curve
Age in years		
≥65	101	0.7458
<65	250	0.6925
Sex		
Female	266	0.6296
Male	85	0.7230
Cancer type		
Non-small cell lung cancer	114	0.5810
Esophageal cancer	99	0.6281
Gastric cancer	72	0.6281
Lymphoma	36	0.6846
Other cancers	13	0.6250
Intestinal cancer	10	0.6500

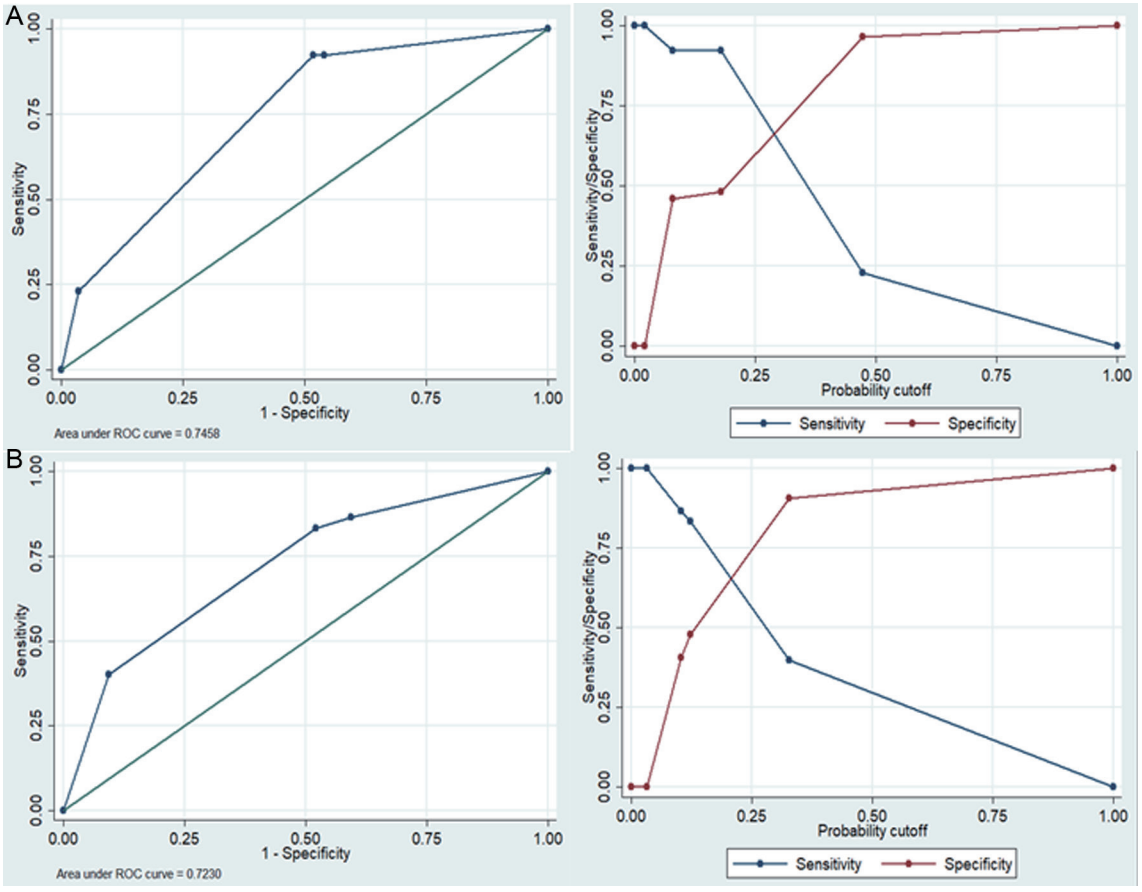

Fig. 5. Receiver operating characteristic curve analysis of (A) male patients and (B) those aged ≥60 years of age.

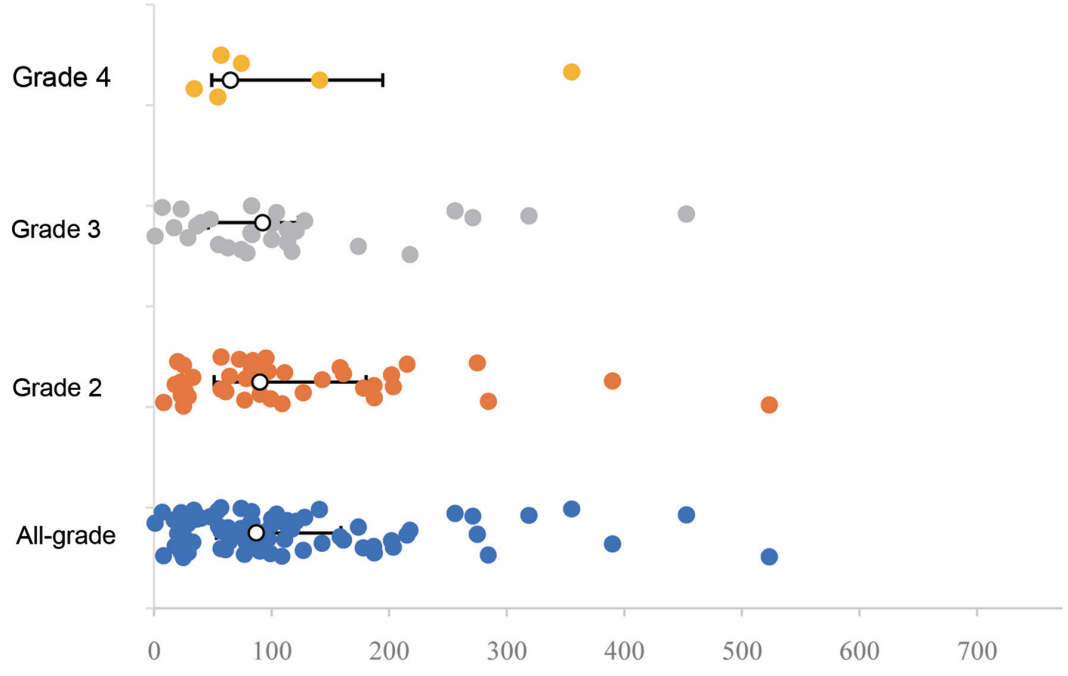

Fig. 6. Time from the initiation of immune checkpoint inhibitor therapy to the date of liver injury onset stratified by grade, with median and interquartile range.

irAEs.[16] Moreover, when plasma albumin content decreases, the properties of the immune checkpoint inhibitor binding site change, reducing the binding of the drug to plasma proteins, which results in slower drug elimination and longer biological half-life, thus increasing its toxicity to the body.[17] Therefore, patients with hypoproteinemia should be closely monitored for ILICI.

Previous studies have shown that patients with thyroglobulin antibodies in the serum are at a considerable risk of developing thyroid dysfunction during immunotherapy. Similarly, patients with autoimmune antibodies and rheumatoid factor who receive immunotherapy are at increased risk of irAEs.[18,19] Our study had similar findings. However, it is unclear why these antibodies are associated with irAEs. A possible reason is that PD-1 is regulated by T cell-independent and -dependent mechanisms, and therefore it is expressed in large quantities in activated B cells.[20] T cells enhance the therapeutic effect of anti-PD-1 antibodies and B cells are induced to produce autoantibodies, which enhance irAEs incidence.[21,22] Therefore, the presence of autoantibodies, such as antinuclear, TPO, and thyroglobulin antibodies, may be related to therapeutic efficacy and irAEs. This suggests that future research should focus on developing biomarkers to predict the onset, treatment outcome, and resolution of liver injury.

To date, risk factors for immune-mediated hepatotoxicity have been rarely studied. Cho *et al*.[23] showed an increased association between 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor use and ILICI development, with a 4.7-fold increase in risk and a 78.8% attributable risk. Tsung *et al*.[24] reported that liver injury was significantly more common in patients with liver metastasis (53% vs. 21%). However, they focused only on the analysis of influencing factors without building a prediction model. Therefore, in this study, risk factors were reassessed and an ILICI-nomogram that included patient history, clinicopathological features, peripheral blood markers, and combination therapy was created. We incorporated multiple risk factors into an easily used nomogram that conforms to the methodology criteria for prediction models, ultimately incorporating three new variables. Overall, the designed ILICI-nomogram showed a good C-index, which could be robustly applied to patients with grade ≥3 liver injury and different subgroups of patients.

The nomogram is helpful for the early identification of high-risk groups for ILICI among sintilimab-treated patients, providing exciting potential for clinical application. However, the stability of the proposed prediction model is related to the number of covariates and outcome events. Furthermore, model accuracy was determined using an internal verification approach; therefore, the insufficient sample size could lead to unsatisfactory validation set results. We aim to collect multicenter external validation data in future research. Taken together, this study shows that ILICI incidence in patients receiving sintilimab is high, with risk factors including hypoproteinemia, TPO antibodies, and dyslipidemia. The developed ILICI-nomogram herein can assist oncologists to develop better and more personalized treatment strategies for patients receiving immunotherapies.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study design, data collection, and analysis, and manuscript drafting (JY), study design, data collection, and analysis, and manuscript drafting (CZ), data analysis and manuscript drafting (SH), data analysis, and manuscript drafting (ML), data analysis (HD), data analysis, and manuscript drafting (BH), study design, data collection, and analysis, and manuscript drafting (CZ).

Ethical statement

The studies involving human participants were reviewed and approved by the Fujian Medical University Union Hospital Ethics Committee (2021WSJK027). Written informed consent for participation was not required for this study in accordance with the national legislation and institutional requirements.

Data sharing statement

The raw data supporting the conclusions of this article will be provided by the authors, without undue reservation, to any qualified researcher.

References

[1] Gao S, Li N, Gao S, Xue Q, Ying J, Wang S, *et al*. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol 2020;15(5):816–826. doi:10.1016/j.jtho.2020.01.017, PMID:32036071.
[2] Kaehler KC, Piel S, Livingstone E, Schilling B, Hauschild A, Schadendorf D. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. Semin Oncol 2010;37(5):485–498. doi:10.1053/j.seminoncol.2010.09.003, PMID:21074064.
[3] Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021;39(36):4073–4126. doi:10.1200/JCO.21.01440, PMID:34724392.
[4] Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. Cancer Immunol Immunother 2009;58(5):823–830. doi:10.1007/s00262-008-0653-8, PMID:19198837.
[5] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, *et al*. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387(10031):1909–1920. doi:10.1016/S0140-6736(16)00561-4, PMID:26952546.
[6] Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, *et al*. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 Study. J Clin Oncol 2016;34(21):2460–2467. doi:10.1200/JCO.2015.64.8931, PMID:27138582.
[7] Sakaan SA, Twilla JD, Usery JB, Winton JC, Self TH. Nitrofurantoin-induced hepatotoxicity: a rare yet serious complication. South Med J 2014;107(2):107–113. doi:10.1097/SMJ.0000000000000059, PMID:24926677.
[8] Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update[J]. Int J Mol Sci 2016;17(1):14. doi:10.3390/ijms17010014, PMID:26712744.
[9] Austin PC, Tu JV. Automated variable selection methods for logistic regression produced unstable models for predicting acute myocardial infarction mortality. J Clin Epidemiol 2004;57(11):1138–1146. doi:10.1016/j.jclinepi.2004.04.003, PMID:15567629.
[10] Shojaie L, Ali M, Iorga A, Dara L. Mechanisms of immune checkpoint inhibitor-mediated liver injury. Acta Pharm Sin B 2021;11(12):3727–3739. doi:10.1016/j.apsb.2021.10.003, PMID:35024302.
[11] Toshikuni N, Fukumura A, Hayashi N, Nomura T, Tsuchishima M, Arisawa T, *et al*. Comparison of the relationships of alcoholic and nonalcoholic fatty liver with hypertension, diabetes mellitus, and dyslipidemia. J Clin Biochem

Nutr 2013;52(1):82–88. doi:10.3164/jcbn.12-55, PMID:23341703.
[12] Sawada K, Hayashi H, Nakajima S, Hasebe T, Fujiya M, Okumura T. Non-alcoholic fatty liver disease is a potential risk factor for liver injury caused by immune checkpoint inhibitor. J Gastroenterol Hepatol 2020;35(6):1042–1048. doi:10.1111/jgh.14889, PMID:31752049.
[13] Kassel R, Cruise MW, Iezzoni JC, Taylor NA, Pruett TL, Hahn YS. Chronically inflamed livers upregulate expression of inhibitory B7 family members. Hepatology 2009;50(5):1625–1637. doi:10.1002/hep.23173, PMID:19739236.
[14] Acharya P, Talahalli RR. Aging and hyperglycemia intensify dyslipidemia-induced oxidative stress and inflammation in rats: assessment of restorative potentials of ALA and EPA + DHA. Inflammation 2019;42(3):946–952. doi:10.1007/s10753-018-0949-6, PMID:30535619.
[15] Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med 2002;166(7):916–919. doi:10.1164/rccm.2108091, PMID:12359646.
[16] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013, PMID:21376230.
[17] Cho H, Kang H, Lee HH, Kim CW. Programmed Cell Death 1 (PD-1) and cytotoxic T lymphocyte-associated Antigen 4 (CTLA-4) in viral hepatitis. Int J Mol Sci 2017;18(7):1517. doi:10.3390/ijms18071517, PMID:28703774.
[18] De Martin E, Michot JM, Rosmorduc O, Guettier C, Samuel D. Liver toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors. JHEP Rep 2020;2(6):100170. doi:10.1016/j.jhepr.2020.100170, PMID:33205034.
[19] Zhang D, Shi Y, Liu X, Liu J, Xu Y, Zhao J, *et al*. Safety and efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients with preexisting antinuclear antibodies: a retrospective cohort study. Transl Lung Cancer Res 2022;11(7):1420–1433. doi:10.21037/tlcr-22-464, PMID:35958331.
[20] Velu V, Titanji K, Zhu B, Husain S, Pladevega A, Lai L, *et al*. Enhancing SIV-specific immunity in vivo by PD-1 blockade. Nature 2009;458(7235):206–210. doi:10.1038/nature07662, PMID:19078956.
[21] Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, *et al*. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology 2017;89(11):1127–1134. doi:10.1212/WNL.0000000000004359, PMID:28821685.
[22] Williams TJ, Benavides DR, Patrice KA, Dalmau JO, de Ávila AL, Le DT, *et al*. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. JAMA Neurol 2016;73(8):928–933. doi:10.1001/jamaneurol.2016.1399, PMID:27271951.
[23] Cho YA, Han JM, Kang SY, Kim DC, Youn YJ, Choi KH, *et al*. Analysis of risk factors for hepatotoxicity induced by immune checkpoint inhibitors. J Immunother 2021;44(1):16–21. doi:10.1097/CJI.0000000000000347, PMID:33290362.
[24] Tsung I, Dolan R, Lao CD, Fecher L, Riggenbach K, Yeboah-Korang A, *et al*. Liver injury is most commonly due to hepatic metastases rather than drug hepatotoxicity during pembrolizumab immunotherapy. Aliment Pharmacol Ther 2019;50(7):800–808. doi:10.1111/apt.15413, PMID:31309615.