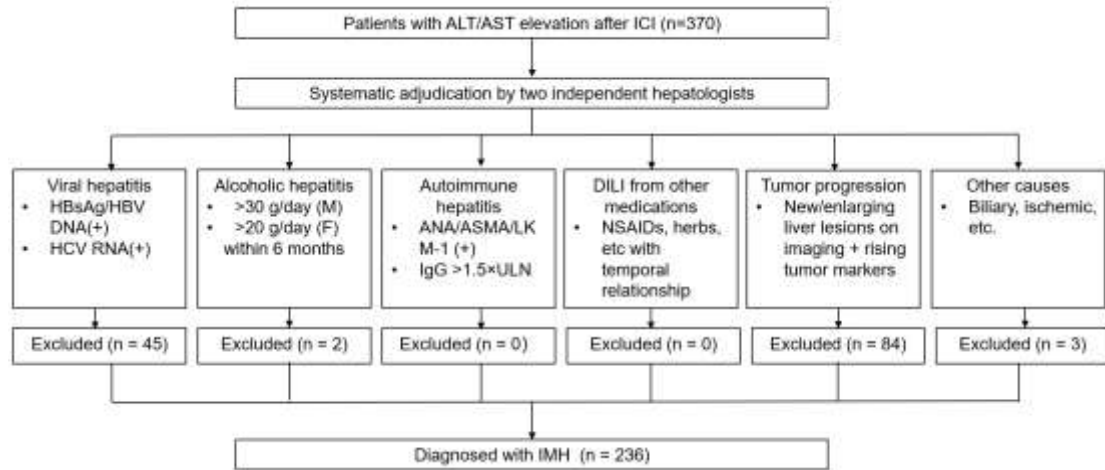
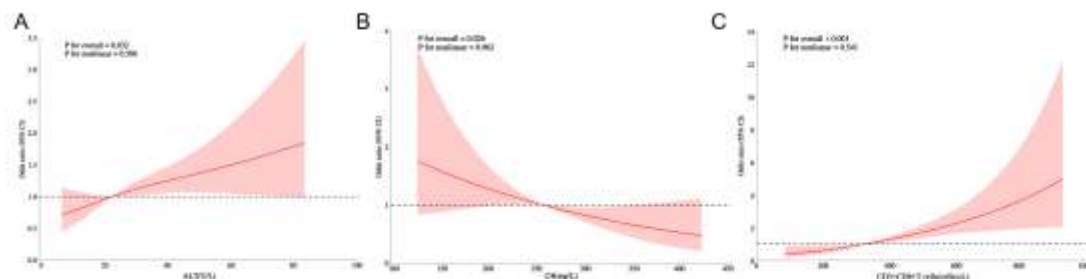




Supplementary Figure 1 Flowchart of the adjudication process for immune-mediated hepatitis. ANA, Antinuclear antibody; ASMA, Anti-smooth muscle antibody; DILI, Drug-induced liver injury; HBV, Hepatitis B virus; HCV, Hepatitis C virus; ICI, Immune checkpoint inhibitor; IgG, Immunoglobulin G; IMH, Immune-mediated hepatitis; LKM-1, Liver-kidney microsomal antibody type 1; NSAIDs, Nonsteroidal anti-inflammatory drugs; ULN, Upper limit of normal.



Supplementary Figure 2 Restricted cubic spline plots for the association between continuous predictors and the risk of immune-mediated hepatitis. A: ALT (U/L); B: Complement C4 (mg/L); C: CD3+CD8+ T cell counts (cells/ μ L). ALT, Alanine transaminase; C4, Complement component 4; CD3+CD8+ T cells, Cluster of differentiation 3-positive cluster of differentiation 8-positive T lymphocytes.

Supplementary Table 1 Comparison of baseline characteristics between included and excluded patients

Variables	Excluded patients (<i>n</i> = 2200)	Included patients (<i>n</i> = 544)	<i>P</i>
Gender, n(%)			0.259
Female	636(28.91%)	144(26.47%)	
Male	1564(71.09%)	400(73.53%)	
Age (years)	58.00(51.00,65.00)	59.00 (52.00, 66.00)	0.628
Primary cancer type			0.426
Malignant melanoma	66(3.00%)	9(1.65%)	
Hepatocellular carcinoma	105(4.77%)	25(4.60%)	
Lung cancer	1120(50.91%)	297(54.60%)	
Cholangiocarcinoma	71(3.23%)	19(3.49%)	
Lymphoma	82(3.73%)	27(4.96%)	
Head and neck cancer	127(5.77%)	29(5.33%)	
Gastrointestinal cancer	410(18.64%)	90(16.54%)	
Urologic cancer	24(1.09%)	7(1.29%)	
Other types of tumors	195(8.86%)	41(7.54%)	

ICI agent type			0.059
Anti PD-1	1942(88.27%)	482(88.60%)	
Anti PD-L1	217(9.86%)	60(11.03%)	
Anti CTLA-4	22(1.00%)	0(0%)	
Combination of anti PD-1 and anti CTLA-4	19(0.86%)	2(0.37%)	
Combination of anti PD-L1 and anti CTLA-4	0(0%)	0(0%)	

*Excluded patients due to missing data ($n = 2200$); ICI, Immune checkpoint inhibitor; PD-1, Programmed cell death-1; PD-L1, Programmed cell death ligand-1; CTLA-4, Cytotoxic T-lymphocyte associated protein-4.

Supplementary Table 2 Optimal cut-off values derived from the training cohort and their diagnostic performance in the training and validation cohorts

Variables	Cut-off (training)	Cohort	AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
ALT (U/L)	> 20.15	Training	0.71 (0.65-0.76)	0.67 (0.62-0.72)	0.58 (0.51 - 0.65)	0.79 (0.72 - 0.86)	0.79 (0.72 - 0.86)	0.58 (0.51 - 0.65)

C4(mg/L)	< 211.5	Validation	0.72 (0.63-0.81)	0.72 (0.64-0.79)	0.66 (0.76)	(0.56 - 0.80)	(0.70 - 0.81)	(0.72 - 0.64)	(0.54 - 0.75)
		Training	0.62 (0.54-0.71)	0.36 (0.29-0.44)	0.16 (0.23)	(0.08 - 0.59)	(0.49 - 0.30)	(0.17 - 0.39)	(0.30 - 0.47)
		Validation	0.66 (0.51-0.80)	0.34 (0.22-0.47)	0.36 (0.53)	(0.18 - 0.32)	(0.16 - 0.32)	(0.16 - 0.36)	(0.18 - 0.53)
		Training	0.71 (0.63-0.79)	0.73 (0.66-0.79)	0.85 (0.92)	(0.79 - 0.47)	(0.34 - 0.77)	(0.70 - 0.61)	(0.47 - 0.75)
		Validation	0.74 (0.62-0.86)	0.78 (0.68-0.87)	0.92 (1.00)	(0.85 - 0.53)	(0.35 - 0.78)	(0.68 - 0.80)	(0.62 - 0.98)
		Training	0.71 (0.63-0.79)	0.73 (0.66-0.79)	0.85 (0.92)	(0.79 - 0.47)	(0.34 - 0.77)	(0.70 - 0.61)	(0.47 - 0.75)

Data are optimal cut-off values derived from the training cohort using the Youden index, with diagnostic performance metrics reported as value (95% confidence interval). PPV, Positive predictive value; NPV, Negative predictive value; AUC, Area under the curve; CI, Confidence interval. Cut-off Values were applied to the validation cohort without re-optimization. PPV and NPV are prevalence-dependent (IMH prevalence: Training 43.4%, validation 42.1%). ALT, Alanine transaminase; C4, Complement component 4.

Supplementary Table 3 Sensitivity analysis: Comparison of the primary model and the model excluding patients with baseline ALT > ULN

Model		n	Predictor	OR (95%CI)	P value	AUC (training)	AUC (validation)
		(IMH/No-IMH)					
Primary model		544 (236/308)	ALT (U/L)	1.04 (1.01-1.06)	0.028	0.81 (0.74-0.88)	0.80 (0.70-0.90)
			CD3+CD8+ cells(cell/ μ L)	T 1.01 (1.01-1.02)	0.002		
			C4 (mg/L)	0.99 (0.97-1.00)	0.038		
Sensitivity model (exclude baseline ALT > ULN)		468 (210/258)	ALT (U/L)	1.03 (1.01-1.05)	0.035	0.79 (0.72-0.86)	0.78 (0.67-0.89)
			CD3+CD8+ (cell/ μ L)	T cells 1.01 (1.01-1.02)	0.003		
			C4 (mg/L)	0.99 (0.98-1.00)	0.042		

Data are odds ratios (OR) with 95% confidence intervals (CI) and area under the receiver operating characteristic curves (AUC). P values are from multivariable logistic regression. The sensitivity model excluded patients with baseline ALT > upper limit of normal (ULN). IMH, Immune-mediated hepatitis; ALT, Alanine transaminase; C4, Complement component 4.

Supplementary Table 4 Sensitivity analysis: Comparison of the primary model and the model excluding patients with hepatocellular carcinoma

Model	n	Predictor	OR (95%CI)	P value	AUC (training)	AUC (validation)
	(IMH/No-IMH)					
Primary model	544	ALT (U/L)	1.04 (1.01-1.06)	0.028	0.81 (0.74-0.88)	0.80 (0.70-0.90)
		CD3+CD8+ cells(cell/ μ L)	T 1.01 (1.01-1.02)	0.002		
		C4 (mg/L)	0.99 (0.97-1.00)	0.038		
Sensitivity model (exclude patients with hepatocellular carcinoma)	519	ALT (U/L)	1.03 (1.01-1.08)	0.031	0.80(0.73-0.87)	0.79(0.68-0.90)
		CD3+CD8+ (cell/ μ L)	T cells 1.02 (1.00-1.05)	0.002		

C4 (mg/L)	0.98 (0.96-1.00)	0.041
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Data are odds ratios (OR) with 95% confidence intervals (CI) and area under the receiver operating characteristic curves (AUC). P values are from multivariable logistic regression. The sensitivity model excluded patients with hepatocellular carcinoma (HCC). IMH, Immune-mediated hepatitis; ALT, Alanine transaminase; C4, Complement component 4; HCC, Hepatocellular carcinoma.