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Development of a Predictive Model for Classifying Immune Checkpoint Inhibitor-Induced Liver Injury Types

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ABSTRACT

Aims: Immune checkpoint inhibitors (ICIs) have transformed cancer therapy; however, they are associated with ICI-induced liver injury (ICI-LI), which manifests as hepatocellular, mixed, or cholestatic patterns with variable treatment responses. This study aimed to develop and validate a predictive model to identify ICI-LI type using clinical data available at ICI initiation.

Methods: A retrospective analysis of 297 patients with ICI-LI was conducted. Baseline clinical data were analyzed using univariate and multivariate logistic regression to predict ICI-LI types in the training and validation cohorts. A predictive model was developed and validated using receiver operating characteristic (ROC) curve analysis.

Results: Multivariate analysis in the training cohort identified male sex (odds ratio [OR]: 3.33, 95% confidence interval [CI]: 1.57–7.06, $p=0.002$), serum albumin levels (OR: 0.42, 95% CI: 0.19–0.91, $p=0.027$), and serum alanine aminotransferase (ALT) levels (OR: 0.97, 95% CI: 0.94–0.99, $p=0.015$) as significant predictors, along with ICI regimen types selected using the Akaike information criterion. The logistic regression model, expressed as $p=1/\{1+(-(5.02+1.20\times(\text{sex [F:0, M:1]}))-0.87\times\text{albumin [g/dL]}-0.03\times\text{ALT [U/L]}-0.9\times(\text{drug [non-anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) related regimen:0, anti-CTLA-4 related regimen:1]}))\}$, achieved an area under the ROC (AUROC) of 0.73 (95% CI: 0.63–0.82) in the training cohort. At a cut-off of 0.86, the sensitivity was 60.3%, specificity 74.4%, positive predictive value 92.3%, and negative predictive value 26.9%. In the validation cohort, the AUROC was 0.752 (95% CI: 0.476–1.00).

Conclusion: This predictive model demonstrates its utility in classifying ICI-LI types.

1 | Introduction

Immune checkpoints are negative regulators that inhibit autoreactive T cells by inducing immune tolerance. Programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) are receptors expressed on T cells that deliver inhibitory signals upon binding their ligands [1]. Tumor cells escape immune responses by upregulating programmed cell death-ligand 1 (PD-L1), a process known as immune evasion. Immune checkpoint inhibitors (ICIs) block these inhibitory signals, releasing the brakes on the immune system and activating the immune response against tumors [2].

Abbreviations: ICI, immune checkpoint inhibitor; LI, liver injury; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand-1; CTLA-4, cytotoxic T lymphocyte antigen 4; CTCAE, Common Terminology Criteria for Adverse Events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal; ROC, receiver operating characteristic.

All authors have read and agreed on the content of the manuscript.

Currently, eight ICIs have been approved, including PD-1 inhibitors (nivolumab, cemiplimab, pembrolizumab), PD-L1 inhibitors (avelumab, atezolizumab, durvalumab), and CTLA-4 inhibitors (ipilimumab, tremelimumab). While anti-tumor effects have been demonstrated, immune-related adverse events (irAEs) have emerged as a significant issue in oncological treatment due to immune system imbalance [3]. Among immune-related adverse events, ICI-induced liver injury (ICI-LI) is uncommon but can result in fatal outcomes [4]. The liver is known as an immune-tolerant tissue due to its exposure to foreign antigens through the portal vein. This occurs through mechanisms in which liver resident cells such as liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells express PD-L1 or dendritic cells present anti-CTLA-4. Disturbance in these pathways activates cytotoxic T-cells (CTLs) and may lead to ICI-LI, which is therefore considered an indirect hepatotoxicity type. In contrast, conventional drug-induced liver injury (DILI) is caused by direct hepatotoxicity (e.g., acetaminophen) or idiopathic hepatotoxicity (e.g., tamoxifen) [5–7]. Grade 3 or higher ICI-LI occurs in approximately 1% of patients receiving anti-PD-1 or PD-L1 antibody drugs and in 5%–19% of those receiving combination therapy with anti-PD-1/PD-L1 and anti-CTLA-4 antibody drugs [8–10]. The common risk factors for irAEs are female sex and younger age, which also apply to ICI-LI [11, 12]. Other identified risk factors for ICI-LI include the dual use of ICIs, a history of prior ICI treatment, the use of anti-CTLA-4 antibody drugs, and the presence of fever following ICI administration [10, 13]. Additionally, conditions such as HCC and other liver diseases (such as hepatitis B or metabolic dysfunction-associated liver disease (MALFD)) are also suggested as risk factors for ICI-LI [14, 15].

The response to corticosteroids varies depending on the type of ICI-LI. Specifically, cholestatic or mixed types tend to respond less favorably to corticosteroids than the hepatocellular damage type [16]. Therefore, it is crucial to predict these types at the onset of ICI-LI using baseline clinical data available at ICI initiation. Various risk factors have been reported in the literature, but there are few definitive predictors for ICI-LI [5] and predictive models for determining the type of ICI-LI have not been sufficiently explored. Especially, early identification of cholestatic or mixed types may facilitate the timely addition of non-steroidal therapies (e.g., mycophenolate mofetil (MMF) [17] or ursodeoxycholic acid (UDCA) [18]), which, in turn, could positively impact patient outcome.

In this study, we developed and validated a model to predict the type of ICI-LI (biliary stasis or mixed type versus hepatocellular damage type) using clinical data collected during ICI initiation in patients with ICI-LI.

2 | Materials and Methods

2.1 | Patients

Between September 2014 and July 2024, a total of 1822 patients with advanced malignancies received ICIs at Kobe University. These treatments included antibodies targeting PD-1, PD-L1, and CTLA-4. Among the 1822 patients, liver injury was identified in 898 individuals following the initiation of ICI therapy. From this cohort, 297 patients with ICI-LI were enrolled in the study after excluding (i) cases of liver injury attributable to other causes and (ii) patients with immune-related sclerosing cholangitis (irSC).

This study consisted of a retrospective database analysis performed according to the Guidelines for Clinical Research from the Ministry of Health, Labour and Welfare of Japan. The study protocol complied with the Helsinki Declaration and was approved by the institutional review boards of the Kobe University Graduate School of Medicine (approval no. B200118, approved on July 20, 2020).

2.2 | Treatment Protocol

In ICI monotherapy, in patients with lung cancer, nivolumab 240 mg per body every 2 weeks ($n = 13$), pembrolizumab 200 mg per body every 3 weeks ($n = 43$), atezolizumab 1200 mg per body every 3 weeks ($n = 19$) or durvalumab 1500 mg per body every 3 weeks ($n = 16$) was administered. In patients with urologic cancer, nivolumab 240 mg per body every 2 weeks ($n = 40$), pembrolizumab 200 mg per body every 3 weeks ($n = 25$) or avelumab 10 mg/kg every 2 weeks ($n = 10$) was administered. In patients with head and neck cancer, nivolumab 240 mg per body every 2 weeks ($n = 29$), pembrolizumab 200 mg per body every 3 weeks ($n = 17$), atezolizumab 1200 mg per body every 3 weeks ($n = 1$) or avelumab 10 mg/kg every 2 weeks ($n = 1$) was administered. In patients with malignant melanoma, nivolumab 240 mg per body every 2 weeks ($n = 18$), pembrolizumab 200 mg per body every 3 weeks ($n = 3$) or ipilimumab 3 mg/kg every 3 weeks ($n = 3$) was administered. In patients with mesothelioma, nivolumab 240 mg per body every 2 weeks ($n = 3$) was administered. In patients with esophageal cancer, nivolumab 240 mg per body every 2 weeks ($n = 12$) or pembrolizumab 200 mg per body every 3 weeks ($n = 1$) was administered. In patients with gastrointestinal cancer, nivolumab 240 mg per body every 2 weeks ($n = 5$) or pembrolizumab 200 mg per body every 3 weeks ($n = 3$) was administered. In patients with hepatocellular carcinoma, atezolizumab 1200 mg per body was administered. In ICI combination therapy, patients with lung cancer ($n = 3$), urologic cancer ($n = 6$), head and neck cancer ($n = 1$), malignant melanoma ($n = 8$), mesothelioma ($n = 2$) or gastrointestinal cancer ($n = 1$) received ipilimumab 3 mg/kg and nivolumab 80 mg per body every 3 weeks for 4 doses, followed by nivolumab monotherapy 240 mg per body every 2 weeks.

2.3 | Laboratory Data

Patient demographics, including age, sex, height, weight, Eastern Cooperative Oncology Group performance status, primary cancer type, and the specific ICI administered, were documented at the initiation of ICI therapy. Hematologic and biochemical analyses were conducted using standard methods on venous blood samples obtained in the fasting state. Additionally, ICI-induced adverse events other than LI that emerged following ICI treatment were also recorded.

2.4 | Diagnostic Criteria for ICI-Induced Liver Injury

We meticulously monitored the patient's general condition through routine blood tests conducted at intervals of at least 4 weeks following the initiation of ICI therapy to diagnose ICI-LI. This monitoring is aimed at evaluating the occurrence of adverse effects, including ICI-LI. ICI-LI was defined as liver injury with a grade of 1 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE ver. 5.0) and was diagnosed when liver enzyme elevations were observed in patients with a history of ICI administration. The severity of adverse events was graded using CTCAE ver. 5.0, with the higher grade between aspartate aminotransferase (AST) or ALT being applied. We excluded those with liver injury whose AST or ALT levels exceeded three times the upper limit of the institution's standard at the beginning of treatment. We ensured that hepatitis B and C infections were ruled out, and other potential causes of liver disease were excluded, such as excessive alcohol consumption (> 80 g/day), other concomitant therapies (e.g., use of hepatotoxic medications), autoimmune hepatitis, primary biliary cholangitis, and hemochromatosis. Patients who showed typical image changes or pathological changes in the bile ducts and were diagnosed with irSC were also excluded. Additionally, we employed ultrasonography, contrast-enhanced computed tomography, or magnetic resonance imaging to exclude LI caused by liver metastases or bile duct obstruction (Figure 1).

The type of ICI-LI was classified based on the ratio of serum alanine aminotransferase (ALT) to alkaline phosphatase (ALP), expressed as the *R*-value, calculated as follows: $R = (\text{ALT/ULN})/(\text{ALP/ULN})$, where ULN represents the upper limit of normal. Liver injury was categorized into three types: (i) Hepatocellular ($R \geq 5$), (ii) mixed ($2 < R < 5$), and (iii) cholestatic ($R \leq 2$) [19].

2.5 | Statistical Analysis

Within the scope of this investigation, patients were randomly divided into training and validation sets in an 8:2 ratio.

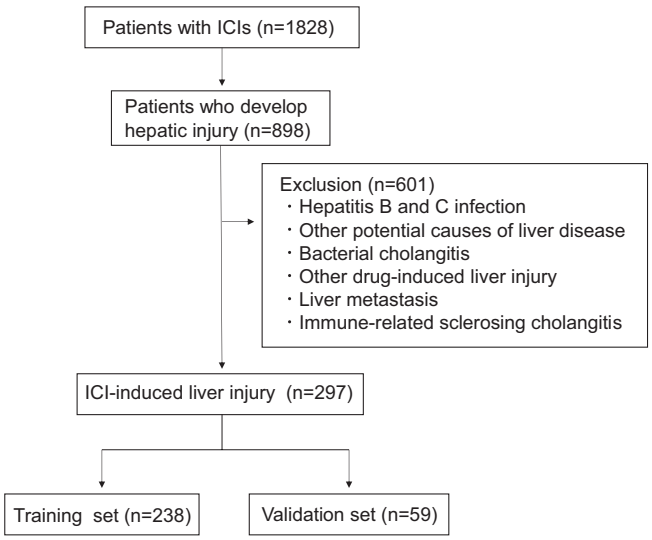

FIGURE 1 | Consort diagram showing inclusion and exclusion criteria.

Subsequent analyses were conducted on these distinct sets. Continuous variables are presented as medians (interquartile range). Evaluation of differences in categorical variables was based on the chi-square test or Fisher's exact test. Continuous variables were compared between two groups using the Mann–Whitney U test and among three groups using the Kruskal–Wallis test. A stepwise selection of variables based on the Akaike information criterion was used for univariate and multivariate binomial logistic regression analysis. The following covariates, considered likely to be associated with the type of ICI-LI, were included: age, sex, serum albumin, ALT, ALP, c-reactive protein, lymphocyte count, and drug type of ICI. Clinical factors for the covariates were assessed at the time of ICI initiation. A regression equation was formulated using the selected variables and transformed into a logistic function to calculate the probability.

The predictive value of the regression equation was evaluated using receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated using the maximum Youden index (sensitivity+specificity−1) as the cut-off level when comparing the type of ICI-LI and the regression equation. Predictive values were classified as low (area under the ROC curve [AUROC] = 0.50–0.70), moderate (AUROC = 0.70–0.90), or high (AUROC = 0.90–1.0).

Statistical significance was established at the threshold of $p < 0.05$. Statistical analysis was conducted using EZR, version 1.68, developed at Saitama Medical Center, Jichi Medical University, Saitama, Japan. This software encompasses a user-friendly graphical interface designed for R, an open-source programming language developed by The R Foundation for Statistical Computing (Vienna, Austria) [20].

3 | Results

3.1 | Patient Characteristics

Table 1 provides an overview of the demographic characteristics of the 297 patients included in this study. Among these patients, 86 (29.0%) were women, and 211 (71.0%) were men. The median age was 69.0 years (62.0–73.0). The primary indications for ICI therapy were lung cancer ($n = 94$, 31.6%), urologic cancer ($n = 81$, 27.3%), and head and neck cancer ($n = 49$, 16.5%). Regarding the types of ICIs administered, most patients received anti-PD-1 antibody drugs ($n = 217$, 73.1%), followed by anti-PD-L1 antibody drugs ($n = 56$, 18.9%), a combination of anti-CTLA-4 and anti-PD-1 antibody drugs ($n = 21$, 7.1%), a combination of anti-CTLA-4 and anti-PD-L1 antibody drugs ($n = 0$, 0%), and anti-CTLA-4 antibody alone ($n = 3$, 1.0%). Liver injury was classified as grade 1, 2, 3, and 4 in 197 (66.3%), 36 (12.1%), 46 (15.5%), and 18 (6.1%) patients, respectively. Liver injury was classified according to *R* values as hepatocellular, mixed, or cholestatic in 45 (15.2%), 61 (20.5%), and 191 (64.3%) patients, respectively. The data for each type of ICI-LI is provided in Table S1.

Patient characteristics, stratified into a training set ($n = 238$) and a validation set ($n = 59$), are presented in Table 2. No statistically significant differences were observed in patient characteristics between the training and validation sets.

TABLE 1 | Characteristics of the study patients ($n = 297$).

Age (years)[a]	69.0 (62.0–73.0)
Sex (female/male)	211/86
ECOG PS (0/1/2/3)	114/146/24/2
ICI treatment details	
Anti PD-1	217 (73.1%)
Anti PD-L1	56 (18.9%)
Anti CTLA-4	3 (1.0%)
Combination of anti PD-1 and anti CTLA-4	21 (7.1%)
Combination of anti PD-L1 and anti CTLA-4	0 (0%)
Primary cancer type	
Lung cancer	94 (31.6%)
Urologic cancer	81 (27.3%)
Head and neck cancer	49 (16.5%)
Malignant melanoma	32 (10.8%)
Mesothelioma	5 (1.7%)
Esophageal cancer	13 (4.4%)
Gastrointestinal cancer	9 (3.0%)
Hepatocellular carcinoma	6 (2.0%)
Albumin (g/dL)[a]	3.8 (3.5–4.1)
AST (U/L)[a]	21 (18–26)
ALT (U/L)[a]	16 (13–24)
ALP (U/L)[a]	88.2 (71.75–105)
CRP (mg/dL)[a]	0.39 (0.09–1.87)
γ-GTP (U/L)[a]	31 (22–55)
Total bilirubin (mg/dL)[a]	0.5 (0.4–0.7)
Platelet count ($\times 10^4/mm^3$)[a]	23.55 (19.6–29)
Lymphocyte counts (/μL)[a]	1239 (897–1710)
Liver injury	
Grade 1	197 (66.3%)
Grade 2	36 (12.1%)
Grade 3	46 (15.5%)
Grade 4	18 (6.1%)
Liver injury classified into *R*-values	
Hepatocellular type	45 (15.2%)
Mixed type	61 (20.5%)
Cholestatic type	191 (64.3%)
Duration of ICI therapy (days)	127 (43–309)
Number of ICI cycles	6 (3–15)
Until onset (weeks)	6.0 (2.1–18.0)
Therapy	
Corticosteroid	57 (19.2%)
MMF	2 (0.7%)
UDCA	36 (12.1%)

Abbreviations: ECOG-PS, Eastern cooperative oncology group performance status; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CRP, c-reactive protein; γ-GTP, γ-glutamyl transpeptidase; MMF, mycophenolate mofetil; UDCA, ursodeoxycholic acid.
[a]Values are expressed as medians (interquartile range).

Additionally, no significant differences were observed between the sets regarding the primary indications for ICI therapy, types of ICIs administered, severity of liver injury, or liver injury types.

3.2 | Analysis in the Cohort of Training Set

Significant differences were observed in the training set in sex distribution across the types of ICI-LI (hepatocellular/mixed/cholestatic), as follows: male percentage: 48.7/71.2/76.9, $p = 0.003$; albumin levels 4.1/3.9/3.7 g/dL, $p = 0.002$; and ALT levels 21/20/15 U/L, $p = 0.001$. The grades of liver injury by type of ICI-LI (hepatocellular/mixed/cholestatic) were distributed as follows: among patients with the hepatocellular type, grades 1, 2, 3, or 4 were observed in 6 (15.4%), 5 (12.8%), 14 (35.9%), and 14 (35.9%) patients, respectively; among patients with the mixed type, grades 1, 2, 3, and 4 were observed in 27 (51.9%), 8 (15.4%), 14 (26.9%), and 3 (5.8%) patients, respectively; and among those with the cholestatic type, grades 1, 2, 3, or 4 were observed in 123 (83.7%), 14 (9.5%), 10 (6.8%), and 0 (0.0%) patients, respectively ($p < 0.001$).

3.3 | Univariate and Multivariate Analyses in the Training Set

The results of the univariate analysis, which examined clinical factors at the initiation of ICI therapy predicting mixed or cholestatic types of ICI-LI, are presented in Table 3. Among these, sex, serum albumin, and ALT levels were identified as significant predictors.

A multivariate binomial logistic regression analysis was performed, including age, sex, serum albumin, ALT, ALP, c-reactive protein, lymphocyte count, and ICI drug type as covariates. This analysis revealed that male sex (odds ratio [OR], 3.33; 95% confidence interval [CI], 1.57–7.06; $p = 0.002$), serum albumin levels (per 1 g/dL increment) (OR, 0.42; 95% CI, 0.19–0.91; $p = 0.027$), and ALT levels (per 1 U/L increment) (OR, 0.97; 95% CI, 0.94–0.99; $p = 0.015$) were statistically significant predictors for mixed or cholestatic types of ICI-LI. Furthermore, the

TABLE 2 | Characteristics of the study patients in the training and validation sets.

	Training set ($n = 238$)	Validation set ($n = 59$)	p
Age (years)[a]	69.0 (62.25–73.0)	69.0 (62.0–73.0)	0.483
Sex (female/male)	69/169	17/42	1.000
ECOG PS (0/1/2/3)	(84/123/21/1)	(30/23/3/1)	0.074
ICI treatment details			
Anti PD-1	175 (73.5%)	42 (71.2%)	0.744
Anti PD-L1	45 (18.9%)	11 (18.6%)	1.000
Anti CTLA-4	3 (1.3%)	0 (0%)	1.000
Combination of anti PD-1 and anti CTLA-4	15 (6.3%)	6 (10.2%)	0.392
Combination of anti PD-L1 and anti CTLA-4	0 (0%)	0 (0%)	
Primary cancer type			
Lung cancer	70 (29.4%)	24 (40.7%)	0.118
Urologic cancer	64 (26.9%)	17 (28.8%)	0.747
Head and neck cancer	40 (16.8%)	9 (15.3%)	0.847
Malignant melanoma	30 (12.6%)	2 (3.4%)	0.057
Mesothelioma	3 (1.3%)	2 (3.4%)	0.259
Esophageal cancer	10 (4.2%)	3 (5.1%)	0.727
Gastrointestinal cancer	9 (3.8%)	0 (0.0%)	0.213
Hepatocellular carcinoma	6 (2.5%)	0 (0.0%)	0.603
Albumin (g/dL)[a]	3.8 (3.5–4.1)	3.8 (3.5–4.1)	0.885
AST (U/L)[a]	21 (18–26)	21 (17.5–26)	0.990
ALT (U/L)[a]	16 (12–24)	16 (13–21)	0.780
ALP (U/L)[a]	87.66 (71.14–103.95)	92.05 (74.9–111.3)	0.286
CRP (mg/dL)[a]	0.38 (0.09–1.90)	0.8 (0.1–1.77)	0.785
γ-GTP (U/L)[a]	30 (21–53.75)	32 (25.5–59)	0.221
Total bilirubin (mg/dL)[a]	0.6 (0.4–0.7)	0.5 (0.4–0.65)	0.613
Platelet count ($\times 10^4/mm^3$)[a]	23.55 (19.62–29.23)	23.4 (19.05–27.90)	0.684
Lymphocyte counts (/μL)[a]	1262 (906–1709)	1094 (868.5–1717)	0.244
Liver injury			0.480
Grade 1	156 (65.5%)	41 (69.5%)	
Grade 2	27 (11.3%)	9 (15.3%)	
Grade 3	38 (16%)	8 (13.6%)	
Grade 4	17 (7.1%)	1 (1.7%)	
Liver injury classified into *R*-values			0.204
Hepatocellular type	39 (16.4%)	6 (10.2%)	
Mixed type	52 (21.8%)	9 (15.3%)	
Cholestatic type	147 (61.8%)	44 (74.6%)	
Duration of ICI therapy (days)	127 (43–295.5)	139 (43–322)	0.915
Number of ICI cycles	6 (3–14.75)	6 (3–15)	0.932

(Continues)

TABLE 2 | (Continued)

	Training set ($n=238$)	Validation set ($n=59$)	p
Until onset (weeks)	6.05 (2.7–17)	5.9 (2–24)	0.989
Therapy			
Corticosteroid	45 (18.9%)	12 (20.3%)	0.854
MMF	2 (0.8%)	0 (0.0%)	1.000
UDCA	32 (13.4%)	4 (6.8%)	0.187

Abbreviations: PS, performance status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CRP, c-reactive protein; γ-GTP, γ-glutamyl transpeptidase; MMF, mycophenolate mofetil; UDCA, ursodeoxycholic acid.
[a]Values are expressed as medians (interquartile range).

type of ICI regimen (anti-CTLA-4 regimen) (OR, 0.40; 95% CI, 0.13–1.22; $p=0.108$) was also identified as an independent factor using a stepwise selection method based on the Akaike information criterion, though it did not reach statistical significance (Table 3).

3.4 | Establishment of Predictive Regression Equations in the Training Set

Based on the regression coefficients, the following equation was derived to represent the probability transformation in the logistic regression model for predicting the likelihood of mixed or cholestatic ICI-LI (P):

$$P = 1/\{1+e(-(5.02+1.20\times(\text{sex [F: 0, M: 1]}) - 0.87\times\text{albumin [g/dL]} - 0.03\times\text{ALT [U/L]} - 0.9\times(\text{drug [non}-\text{anti}-\text{CTLA}-4\text{ related regimen: 0 anti}-\text{CTLA}-4\text{ related regimen: 1]}))\}$$

The ROC curve analysis yielded an AUROC of 0.73 (95% CI, 0.63–0.82) (Figure 2). With a cut-off value of 0.86, the sensitivity was 60.3%, the specificity was 74.4%, the positive predictive value was 92.3%, and the negative predictive value was 26.9% for predicting the likelihood of mixed or cholestatic types of ICI-LI.

3.5 | ROC Analysis in the Validation Set

The regression equations derived from the training set were applied to the validation cohort. ROC analysis yielded an AUROC of 0.752 (95% CI, 0.476–1.00) for predicting mixed or cholestatic types of ICI-LI (Figure 3).

4 | Discussion

In this study, we developed a predictive model to identify the type of ICI-LI using clinical data from patients treated with ICIs. Univariate analysis in the training set identified male sex, serum albumin levels, and ALT levels as significant predictive factors. Multivariate analysis, incorporating eight covariates, identified male sex, serum albumin levels, ALT levels, and the type of ICI regimen (e.g., anti-CTLA-4 regimen) as independent predictive factors. Logistic regression analysis demonstrated high accuracy (AUC 0.73), with fair sensitivity (60.3%) and specificity (74.4%). Using a cut-off value at 0.86, we can differentiate between hepatocellular or mixed and cholestatic types of ICI-LI by substituting values into the obtained regression equation. The regression model indicated that male sex was a positive predictor, whereas high serum albumin levels, elevated ALT levels, and the ICI regimens (e.g., anti-CTLA-4) were negative factors for mixed or cholestatic types.

Although the hepatocellular type is generally the most common type of ICI-LI [21], the cholestatic type was most frequently observed in our cohort. The hepatocellular pattern of liver injury is associated with anti-CTLA-4 agents [22]; however, our study included relatively few patients receiving these regimens. This difference in treatment profiles likely accounts for the observed discrepancy. The regression equation indicated that male sex was associated with mixed or cholestatic types of ICI-LI, whereas high serum albumin levels, elevated ALT levels, and ICI regimens (e.g., anti-CTLA-4) were linked to the hepatocellular type of ICI-LI. These findings align with Hountondji et al. [22], who reported a significant association between hepatocellular type ICI-LI and anti-CTLA-4 antibodies. Although female has been reported as a risk factor for the incidence of overall ICI-LI [23], this study focuses on predicting the type of ICI-LI among those who have already developed ICI-LI, so it is considered compatible. In our study, logistic regression analysis in the validation set demonstrated high accuracy (AUC 0.752), further validating the utility of our prediction model.

The hepatocellular type of ICI-LI was the most commonly observed (39%–54%), followed by the cholestatic type (17%–37%) and the mixed type (19%–29%) [16, 22, 24]. Various risk factors for ICI-LI have been identified in the literature. For hepatocellular type ICI-LI, risk factors include younger age, use of ICIs containing anti-CTLA-4 antibodies, a history of malignant melanoma, low ALP levels, and high lymphocyte counts [25, 26]. Conversely, cholestatic type ICI-LI is more commonly associated with ICIs containing anti-PD-1/PD-L1 antibodies [5, 27]. It is known that biliary epithelial cells highly express PD-1 ligands (PD-L1 and PD-L2), but not CTLA-4 ligands [28, 29]. Thus, inhibition of the PD-1/PD-L1 pathway may lead to the non-hepatocellular type of ICI-LI. Furthermore, corticosteroid therapy is more commonly used in hepatocellular type ICI-LI, whereas mixed or cholestatic types often require a combination of corticosteroids and additional agents, such as mycophenolate mofetil or ursodeoxycholic acid [16, 22, 27].

TABLE 3 | Univariate and multivariate analysis of predictors for mixed or cholestatic types of ICI-induced liver injury.

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***p***
Age	1.010	0.977–1.050	0.494			
Sex (male)	3.220	1.590–6.530	0.001	3.330	1.570–7.060	0.002
Albumin	0.364	0.171–0.777	0.009	0.418	0.190–0.910	0.027
ALT	0.972	0.951–0.994	0.013	0.969	0.940–0.990	0.015
ALP	1.000	0.994–1.010	0.723			
CRP	1.150	0.937–1.410	0.182			
Lymphocyte counts	1.000	0.999–1.000	0.332			
ICI drug type (anti-CTLA-4 regimen)	0.448	0.162–1.240	0.122	0.399	0.130–1.220	0.108

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; CRP, c-reactive protein; ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte antigen 4.

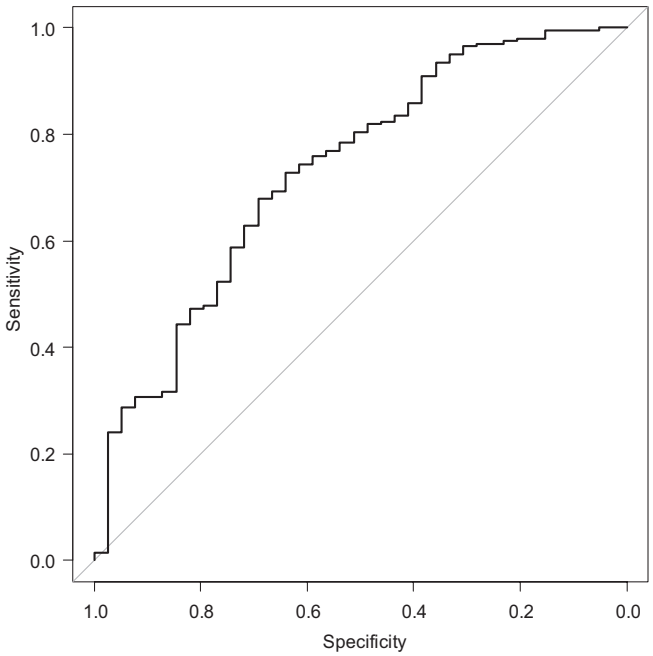

FIGURE 2 | ROC curve of prediction for mixed or cholestatic types of ICI-LI with cut-off value. The area under ROC curve (AUROC) was 0.73 (95% CI, 0.63–0.82).

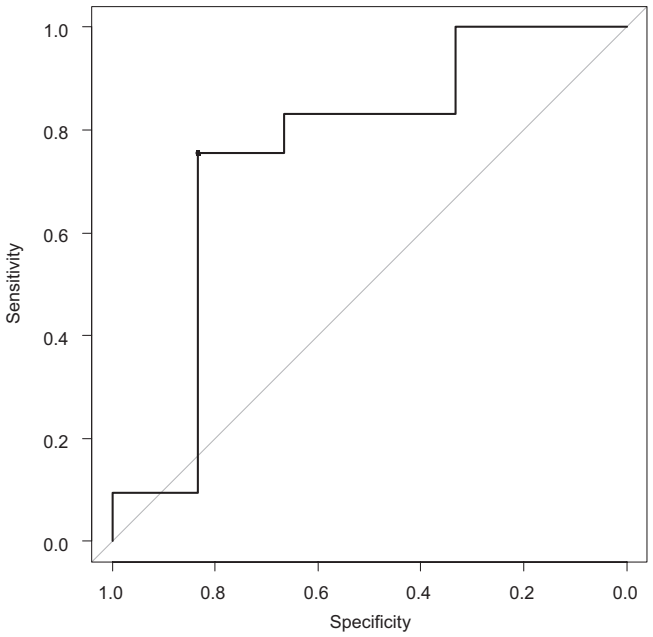

FIGURE 3 | ROC curve was applied using the regression equations derived from the training set to the validation set with cut-off value. The area under ROC curve (AUROC) was 0.75 (95% CI, 0.48–1.00).

Corticosteroids remain the first-line treatment for ICI-LI. For grade 1 liver injury, discontinuation of ICIs alone is often sufficient. However, persistent liver damage in grade 2 or grade 3 injury requires corticosteroid treatment. In cases resistant to corticosteroids, second-line treatment of 500-1000 mg of MMF twice daily can be considered [30]. In some limited literature, other immunosuppressive treatments such as azathioprine [31], tacrolimus [32] and infliximab [33] were effective. Corticosteroids generally exhibit a high response rate in hepatocellular type ICI-LI; however, the response is lower in mixed or cholestatic types, which are more difficult to treat. Given the potential for progression to severe liver injury, early initiation of optimal treatment is crucial for improving patient outcomes and preventing further complications.

A key strength of this study is developing a predictive model based on patient data obtained at the initiation of ICI therapy. The type of ICI-LI was classified using the maximum values of ALT and ALP, which may take time to diagnose after onset. However, this predictive model allows for a faster approach to patient management. Although it is generally desirable to perform a liver biopsy and conduct pathological evaluation before steroid therapy, especially in a severe case of ICI-LI, steroid treatment needs to be initiated first. In such cases, this predictive model can help to evaluate the type of ICI-LI. While several studies have examined risk factors for ICI-LI during and after treatment, our study facilitates early risk assessment and therapeutic intervention. The creation of this predictive model optimizes treatment selection and represents a significant step toward personalized management strategies.

The advent of immune checkpoint inhibitors has led to a paradigm shift in oncology, offering new treatment options for various cancers. As the use of ICIs as first-line therapies increases, the incidence of ICI-LI is expected to rise, meaning clinicians will likely encounter more cases of ICI-LI in clinical practice. The prediction model we developed can assist in the early identification and management of ICI-LI, potentially improving patient outcomes.

However, this study has several limitations. First, it is a retrospective, single-center study, which may limit the generalizability of the results. Second, the relatively short observation period may not fully capture long-term outcomes. Third, a small number of patients with chronic liver disease and hepatocellular carcinoma ($n = 6$) were included in this analysis. Because liver disease has been reported as a risk for ICI-LI and they have received a combination of ICI and molecular targeted therapy (atezolizumab and bevacizumab), which may have affected the results. Fourth, about 70% of patients with grade 1 liver injury who did not undergo liver biopsy were included in this study. They were diagnosed with ICI-LI based on clinical and overall assessment. However, diagnosing grade 1 liver injury without liver biopsy is not possible; thus, accumulating cases with grade2 or higher is needed for further study. Fifth, ALT and ALP, which are included in the diagnostic criteria, were incorporated into both the univariate and multivariate analyses. This may introduce an endogeneity bias. Further multicenter prospective studies with larger sample sizes and longer follow-up periods are also needed to validate and refine the model.

In conclusion, we have developed a predictive model to identify the type of ICI-LI, incorporating clinical factors such as male sex, serum albumin levels, ALT levels, and ICI regimen type. This model shows promise in predicting the likelihood of different ICI-LI types and can inform treatment decisions. Given the increasing use of ICIs, this model may serve as a valuable tool for clinicians to manage ICI-LI more effectively.

Ethics Statement

Informed consent was obtained in the form of an opt-out on the website in the present study. The study protocol complied with the Helsinki Declaration and was approved by the institutional review board of the Kobe University Graduate School of Medicine (approval no. B200118, approved on July 20, 2020).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.