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Clinical Features and Factors Associated with Immune Checkpoint Inhibitor-Associated Acute Kidney Injury: A Single-Center Retrospective Study

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Abstract

Immune checkpoint inhibitor-associated acute kidney injury (ICI-AKI) is an increasingly recognized complication of cancer immunotherapy, yet its clinical heterogeneity and limited predictors pose challenges for early identification. This study aimed to characterize ICI-AKI, identify associated factors, and develop an exploratory nomogram for risk assessment. In this single-center retrospective study, 181 adults receiving ICIs at Huashan Hospital, Fudan University, between 2023 and 2025 were included, comprising 84 patients with adjudicated ICI-AKI and 97 controls without AKI during at least 6 months of follow-up. Clinical characteristics, pathological findings, treatment patterns, and kidney outcomes were evaluated. Univariable and multivariable logistic regression analyses were performed, and nomogram performance was assessed using receiver operating characteristic analysis, bootstrap internal validation, calibration analysis, and decision curve analysis. The median time from ICI initiation to AKI onset was 84 days, and most affected patients presented with stage 2 or 3 AKI. Acute tubulointerstitial nephritis (ATIN) was the most common pathological finding among the 24 biopsied patients. Multisystem complications during ICI therapy (OR, 4.552; 95% CI, 1.554–13.335), lower baseline estimated glomerular filtration rate (OR, 0.878; 95% CI, 0.827–0.933), higher baseline myoglobin (OR, 1.021; 95% CI, 1.001–1.042), and longer baseline prothrombin time (OR, 2.566; 95% CI, 1.452–4.536) were independently associated with ICI-AKI. The nomogram incorporating these variables demonstrated good discrimination, with an area under the curve (AUC) of 0.888 (95% CI, 0.837–0.939), and favorable internal calibration. These findings identify clinical and laboratory features associated with ICI-AKI and support their further investigation for risk assessment during ICI therapy.

Introduction

Immune checkpoint inhibitors (ICIs) have transformed the treatment of multiple malignancies and substantially improved patient survival [1–3]. However, their expanding use has been accompanied by an increasing incidence of immune-related adverse events (irAEs). Among these toxicities, renal involvement, particularly ICI-associated acute kidney injury (ICI-AKI), has emerged as an important and potentially life-threatening complication [4–7]. The overall incidence of ICI-AKI is estimated to be approximately 2%–5%, although the reported rates vary across different groups, and may be higher in real-world studies [7–9]. Once ICI-AKI occurs, it may result in persistent renal dysfunction, require renal replacement therapy, and lead to interruption or discontinuation of antitumor treatment. These consequences may not only compromise oncological outcomes and patients' quality of life but also impose a substantial medical and economic burden [10, 11].

Currently, the diagnosis of ICI-AKI mainly depends on clinical manifestations, laboratory findings, such as elevated serum creatinine (Scr), and the exclusion of other common causes of AKI. Kidney biopsy is considered the gold standard for diagnostic confirmation, particularly for distinguishing acute tubulointerstitial nephritis (ATIN) from glomerular diseases and other pathological subtypes [1, 12]. However, in real-world clinical practice, kidney biopsy is often limited by patients' increased bleeding risk, poor general condition, or other contraindications. In terms of treatment, corticosteroids remain the first-

line therapy for ICI-AKI, but treatment responses vary considerably among individuals, and some patients may develop steroid dependence or resistance [13–16]. Previous studies have explored the associations of age, baseline kidney function, concomitant medications, including proton pump inhibitors (PPIs) and nonsteroidal anti-inflammatory drugs (NSAIDs), and treatment-related factors, such as dual ICI blockade, with the risk of ICI-AKI. Nevertheless, the reported findings remain inconsistent, and systematic studies focusing on Chinese populations are still limited [17, 18]. More importantly, reliable predictors for the development of AKI after ICI therapy remain insufficiently defined, which poses a major challenge for early risk stratification and clinical decision-making.

Further characterisation of the clinical presentation, pathological spectrum, treatment patterns, and kidney outcomes of ICI-AKI, together with the identification of associated factors, may facilitate earlier recognition. Evaluation of longitudinal kidney function is also important for understanding recovery and prognosis after AKI [19]. Real-world clinical data may support these aims and generate hypotheses for prospective validation.

Accordingly, the present study aimed to describe the clinical and pathological characteristics of ICI-AKI, identify factors associated with its occurrence, and develop an exploratory nomogram for risk stratification, with the goal of facilitating early recognition in clinical practice.

Materials and methods

Study design

We conducted a retrospective study of adult patients who received ICIs at Huashan Hospital, Fudan University, between 2023 and 2025. Patients with adjudicated ICI-AKI were identified as the AKI group, whereas eligible contemporaneous ICI-treated patients who remained free of AKI during at least 6 months of follow-up were included in the non-AKI comparison group. Demographic characteristics, medical history, concomitant medications, and baseline laboratory parameters prior to ICI initiation were extracted from electronic medical records and compared between the two groups. Baseline laboratory parameters were defined as the most recent available laboratory test results obtained before the first administration of ICI therapy. This study was approved by the Ethics Committee of Huashan Hospital, Fudan University (No. KY2026-989).

Study Population and Definitions of ICI-associated AKI

Patients aged 18 years or older who received at least one dose of one or more ICIs between 2023 and 2025 were included in this study. In the AKI group, AKI occurred after at least one cycle of ICI therapy. According to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, AKI was defined according to KDIGO criteria as an increase in Scr by ≥ 26.5 μmol/L within 48 hours or an increase to ≥ 1.5 times baseline known or presumed to have occurred within the previous 7 days. ICI-AKI was adjudicated on the basis of the temporal relationship with ICI exposure, clinical and laboratory

findings, kidney biopsy findings when available, and the exclusion of plausible alternative causes, including hemodynamic, obstructive, infectious, and other drug-related causes. The diagnosis was independently assessed by at least three nephrologists. In the non-AKI group, renal function remained stable during follow-up, with no AKI of any grade observed. Patients with severe renal dysfunction at baseline, defined as an eGFR < 30 mL/min/1.73 m², or those receiving long-term dialysis were excluded from the study.

Definitions of AKI Severity, baseline Scr, peak Scr, and Scr response

AKI severity was staged according to the KDIGO criteria. Stage 1 was defined as an increase in Scr to 1.5–1.9 times the baseline value or an absolute increase of ≥ 26.5 μmol/L. Stage 2 was defined as an increase in Scr to 2.0–2.9 times the baseline value. Stage 3 was defined as an increase in Scr to ≥ 3.0 times the baseline value, an absolute Scr level of ≥ 354 μmol/L, or the initiation of renal replacement therapy. Baseline Scr was defined as the most recent serum creatinine value measured before the initiation of ICI therapy. Peak Scr was defined as the highest serum creatinine value recorded after the onset of AKI and before the initiation of AKI-related therapeutic interventions. A study-specific Scr response was defined as a ≥ 30% reduction in Scr from the peak value at 1, 3, or 6 months after the initiation of AKI-related treatment.

Data collection

Data were extracted from electronic medical records, including demographic characteristics, medication history, cancer type, antineoplastic treatments, and baseline laboratory parameters. Multisystem complications were defined as physician-documented clinical events occurring after ICI initiation and before AKI onset, including rash, urinary tract infection, liver dysfunction, interstitial pneumonitis, and other systemic events. For patients in the AKI group, additional data included Scr at diagnosis, peak and follow-up Scr, laboratory parameters at AKI onset, treatment strategies, and kidney biopsy findings when available. Laboratory parameters at AKI onset were defined as those measured on the date of AKI diagnosis.

Statistical analyses

Data analysis and visualization were performed using SPSS version 27.0 (IBM Corporation, Chicago, IL, USA), R version 4.5.2 (R Core Team, Vienna, Austria), and GraphPad Prism version 9.0 (GraphPad Software Inc., San Diego, CA, USA). Normally distributed continuous variables are presented as the mean ± standard deviation. Comparisons between independent groups were performed using the independent-samples t-test or one-way analysis of variance, as appropriate. For within-patient comparisons between baseline and AKI onset, the paired-samples t-test was used when the paired differences were normally distributed. Non-normally distributed continuous variables are expressed as the median with interquartile range (IQR) and were compared using the Mann–Whitney U test or

Kruskal–Wallis test for independent groups, as appropriate. The Wilcoxon signed-rank test was used for non-normally distributed paired data. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. To identify potential influencing factors, variables with $P < 0.05$ in the univariable analysis were entered into a binary logistic regression model for multivariable analysis. A stepwise selection method was used to identify independently associated factors, and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Based on the independently associated factors identified in the multivariable analysis, a logistic regression-based nomogram was constructed using the "rms" package in R. Receiver operating characteristic (ROC) curves were generated using the "pROC" package to evaluate the discriminatory performance of the model. Internal validation was performed using the bootstrap method with 500 resamples to assess model robustness. Calibration curves were generated to compare the agreement between the nomogram-predicted probabilities and the observed risk. In addition, decision curve analysis (DCA) was performed to evaluate the clinical utility of the model by quantifying the net benefit across different threshold probabilities.

Results

Baseline characteristics

A total of 209 potentially eligible patients were identified through a review of the electronic medical records for the present analysis. Of these, 28 patients were excluded: 17 because of incomplete data required for the analysis and 11 because their AKI was attributed to hemodynamic or obstructive causes rather than ICI therapy. The final analytical sample comprised 181 patients, including 84 patients with adjudicated ICI-AKI and 97 contemporaneous ICI-treated patients who remained free of AKI during at least 6 months of follow-up (Fig. 1). The baseline characteristics of the two groups are summarized in Table 1. Compared with patients who did not develop AKI, patients with AKI were older and had a higher proportion of multisystem complications following ICI therapy, including rash, urinary tract infections, and hepatic dysfunction. Regarding baseline laboratory parameters, patients in the AKI group had higher baseline Scr levels, lower baseline eGFR, and significantly higher baseline levels of myoglobin, PT, and activated partial thromboplastin time (APTT) than those in the non-AKI group. No significant differences were observed between the two groups with respect to sex, body mass index (BMI), comorbidities, including chronic kidney disease, hypertension, and diabetes, or primary tumor type. Similarly, the use of concomitant medications, including PPIs, NSAIDs, ACEIs, ARBs, and SGLT2is, as well as antitumor treatment regimens, including ICIs combined with chemotherapy and/or targeted therapy, did not differ significantly between the two groups ($P > 0.05$).

Table 1
Baseline characteristics and comparisons between patients who developed AKI and patients without AKI.

Characteristics	**Non-AKI (n = 97)**	**AKI (n = 84)**	***p*-value**
Age, years, median (IQR)	63.00 (53.50–68.00)	68.00 (61.00–72.00)	**< 0.001**
Female, n (%)	29 (29.9)	17 (20.2)	0.137
BMI, mean (SD), kg/m^2	22.53 ± 3.12	22.50 ± 3.41	0.951
Comorbidities, n (%)			
Chronic kidney disease	1 (1.0)	5 (6.0)	0.098
Diabetes mellitus	12 (12.4)	17 (20.2)	0.150
Hypertension	29 (29.9)	36 (42.9)	0.070
Multisystem complications			**< 0.001**
No	84 (86.6)	46 (54.8)	
Yes	13 (13.4)	38 (45.2)	
Primary tumor type, n (%)			0.954
Gastrointestinal	44 (45.4)	40 (47.6)	
Lung	42 (43.3)	35 (41.7)	
Breast / gynecological / Other	11 (11.3)	9 (10.7)	
Cancer stage, n (%)			0.106
Stage I	2 (2.1)	0 (0.0)	
Stage II	5 (5.3)	5 (6.9)	
Stage III	14 (14.9)	20 (27.8)	
Stage IV	73 (77.7)	47 (65.3)	
Drugs, n (%)			
PPIs	45 (46.4)	45 (53.6)	0.335
NSAIDs	5 (5.2)	1 (1.2)	0.218
ARBs or ACEIs	13 (13.4)	10 (11.9)	0.763
SGLT2is	5 (5.2)	2 (2.4)	0.453
ICI type, n (%)			0.062
Anti-PD-1	78 (80.4)	73 (86.9)	

Characteristics	Non-AKI (n = 97)	AKI (n = 84)	*p*-value
Anti-PD-L1	18 (18.6)	7 (8.3)	
Anti-PD-1 + anti-CTLA-4 combination	1 (1.0)	4 (4.8)	
Tumor treatment characteristics, n (%)			
ICIs+targeted therapy	4 (4.1)	5 (6.0)	0.735
ICIs+Chemotherapy	72 (74.2)	61 (72.6)	0.807
ICIs+targeted therapy+Chemotherapy	19 (19.6)	17 (20.2)	0.913

Table 1
Continued

Characteristics	Non-AKI (n = 97)	AKI (n = 84)	*p*-value
Baseline laboratory tests			
CRP	3.36 (0.25–13.79)	5.00 (1.37–14.36)	0.215
Leukocyturia, /μl	4.50 (1.60–12.50)	4.20 (2.15–11.20)	0.810
Hematuria, /μl	3.85 (1.60–7.90)	3.40 (1.30–7.60)	0.743
Proteinuria	21 (24.1%)	19 (29.2%)	0.481
WBC, $\times 10^9$/L	6.34 (4.93–7.31)	6.56 (4.81–8.09)	0.412
Hb, g/L	124.00 (112.50–136.00)	127.00 (114.50-140.25)	0.378
PLT, $\times 10^9$/L	219.00 (178.00-311.00)	205.00 (167.75–288.50)	0.222
Neutrophil-to-lymphocyte ratio	3.31 (2.21–4.82)	2.81 (1.89–4.49)	0.455
Scr, μmol/L	58.50 (52.25-66.00)	72.50 (59.50–86.00)	**< 0.001**
eGFR, mL/min/1.73 m²	102.60 (96.62–109.80)	92.10 (79.88–99.80)	**< 0.001**
Alb, g/L	40.00 (38.00–42.00)	39.90 (36.00–43.00)	0.885
ALT, U/L	18.00 (12.00–31.00)	18.00 (11.00–24.00)	0.274
AST, U/L	20.00 (15.00–28.00)	18.00 (15.75-24.00)	0.135
CPK, U/L	54.50 (36.75–76.75)	61.00 (47.00–94.00)	0.056
Myoglobin, ng/mL	21.00 (10.50-26.87)	29.26 (22.79–40.52)	**< 0.001**
D-dimer, mg/L FEU	0.64 (0.32–1.89)	0.62 (0.37–1.71)	0.735
INR	1.00 ± 0.07	1.02 ± 0.07	**0.041**
PT, s	11.80 (11.30–12.30)	12.60 (11.72–13.55)	**< 0.001**
APTT, s	26.80 (25.50-28.85)	28.15 (25.92–33.18)	**0.014**
FIB, g/L	3.90 (3.00-5.05)	3.75 (3.00-4.80)	0.703

ACEI, angiotensin-converting enzyme inhibitor; Alb, albumin; ALT, alanine aminotransferase; ANA, antinuclear antibody; APTT, activated partial thromboplastin time; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CPK, creatine phosphokinase; CRP, C-reactive protein; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; eGFR, estimated glomerular filtration rate; FDP, fibrin degradation products; FEU, fibrinogen-equivalent units; FIB, fibrinogen; Hb, hemoglobin; ICI, immune checkpoint inhibitor; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PLT, platelet count; PPI, proton pump inhibitor; PT, prothrombin time; Scr, serum creatinine; SGLT2i, sodium–glucose cotransporter 2 inhibitor; WBC, white blood cell count.

Characteristics	Non-AKI (n = 97)	AKI (n = 84)	*p*-value
FDP, μg/mL	2.50 (1.25–4.70)	2.50 (2.50–5.57)	0.052
ANA positive	34 (54.8)	17 (50.0)	0.650

ACEI, angiotensin-converting enzyme inhibitor; Alb, albumin; ALT, alanine aminotransferase; ANA, antinuclear antibody; APTT, activated partial thromboplastin time; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CPK, creatine phosphokinase; CRP, C-reactive protein; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; eGFR, estimated glomerular filtration rate; FDP, fibrin degradation products; FEU, fibrinogen-equivalent units; FIB, fibrinogen; Hb, hemoglobin; ICI, immune checkpoint inhibitor; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PLT, platelet count; PPI, proton pump inhibitor; PT, prothrombin time; Scr, serum creatinine; SGLT2i, sodium–glucose cotransporter 2 inhibitor; WBC, white blood cell count.

Clinical features of ICI-AKI

According to the KDIGO criteria for AKI severity staging, 17 of the 84 patients with AKI were classified as stage 1 (20.2%), 38 as stage 2 (45.2%), and 29 as stage 3 (34.5%) (Fig. 2A). The median time from ICI initiation to AKI onset was 84 days (IQR 51.5–164.0), with considerable interindividual variability. When stratified by AKI stage, no significant difference was observed in the time to AKI onset among the three groups ($P = 0.6406$; Fig. 2B). When classified by ICI regimen, the median time to AKI onset from treatment initiation was 84.5 days (IQR, 50–176) for anti-PD-1, 69 days (IQR, 62–133) for anti-PD-L1, and 81 days (IQR, 49–146.75) for anti-PD-1 plus anti-CTLA-4 therapy (Supplementary Fig. 1). Scr levels at different time points, including baseline, AKI diagnosis, and peak Scr before the initiation of AKI-related treatment, are shown in Fig. 2C. Paired comparisons among the patients with ICI-AKI showed that hemoglobin concentration, platelet count, and serum albumin levels were significantly lower at AKI onset than at baseline, whereas aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), and serum myoglobin levels were significantly higher. No significant changes were observed in the other evaluated laboratory parameters (Supplementary Fig. 2). In AKI patients, a relatively high proportion developed multisystem complications, including urinary tract infection in 17 patients (20.2%), liver dysfunction in 14 patients (16.7%), rash in 7 patients (8.3%), and interstitial pneumonitis in 5 patients (6.0%). In addition, three patients (3.6%) experienced other adverse events, including abnormally elevated creatine kinase levels, limb numbness, chest tightness, and hypokalemia (Fig. 2D). Among 24 patients (28.6%) with AKI who underwent kidney biopsy, ATIN was the most common pathological diagnosis, accounting for 12 patients (50%), followed by acute interstitial nephritis (AIN) in 3 patients (12.5%), acute tubular necrosis (ATN) in 5 patients (20.8%), and other types in 4 cases (16.7%), which included IgA nephropathy, ANCA-associated vasculitis kidney damage, and minor renal tissue lesions (Fig. 2E, Fig. 3).

Treatment of ICI-AKI

In our study, treatment for ICI-AKI was individualized and largely based on clinical experience. As shown in Fig. 4, most patients received corticosteroid monotherapy throughout the disease course, accounting

for 57 of 84 patients (67.9%). Stratified by AKI severity, corticosteroid monotherapy was administered to 12 patients with stage 1 AKI (70.6%), 23 patients with stage 2 AKI (60.5%), and 22 patients with stage 3 AKI (75.9%). In addition, 9 patients (10.7%) received corticosteroids in combination with other immunosuppressive agents (IS), including cyclophosphamide, azathioprine, mycophenolate mofetil, or infliximab. A small proportion of patients required treatment with corticosteroids and dialysis (2/84, 2.4%), whereas 16 patients (19.0%) received supportive therapy alone throughout the disease course.

To further characterize the longitudinal course of renal function, Scr trajectories from baseline and AKI onset through 1, 3, and 6 months of follow-up were descriptively examined across treatment groups within each AKI stage. Considerable interindividual variability and substantial overlap in Scr trajectories were observed across treatment groups, without a clear treatment-specific pattern (Fig. 5A-C). Subsequently, we evaluated the proportions of patients meeting the prespecified Scr-response criterion, defined as a ≥ 30% reduction in Scr from the peak value, at 1, 3, and 6 months after treatment (Fig. 5D). After excluding patients lost to follow-up, 42 patients (59.2%), 30 patients (62.5%), and 26 patients (68.4%) met the Scr-response criterion at 1, 3, and 6 months, respectively. When stratified by AKI severity, 3 patients with stage 1 AKI (21.4%), 2 patients (22.2%), and 1 patient (16.7%) achieved this Scr reduction at 1, 3, and 6 months, respectively. Among patients with stage 2 AKI, the corresponding numbers were 15 (50.0%), 11 (52.4%), and 11 (64.7%), respectively. Among patients with stage 3 AKI, 24 (88.9%), 17 (94.4%), and 14 (93.3%) met the Scr-response criterion at the corresponding time points.

Factors associated with ICI-AKI

Univariable logistic regression analysis evaluated potential factors for the development of ICI-AKI, revealing that age (OR, 1.083; 95% CI, 1.044–1.125), multisystem complications (OR, 5.338; 95% CI, 2.585–11.023), baseline Scr (OR, 1.079; 95% CI, 1.050–1.108), myoglobin (OR, 1.037; 95% CI, 1.012–1.062), PT (OR, 2.412; 95% CI, 1.633–3.562), and activated partial thromboplastin time (APTT; OR, 1.134; 95% CI, 1.047–1.229) were associated with an increased risk of AKI. Conversely, baseline eGFR (OR, 0.896; 95% CI, 0.862–0.931) was associated with a decreased risk of AKI. Other variables, including sex, BMI, comorbidities, concomitant medications, and remaining peripheral blood biomarkers, showed no significant associations (Fig. 6).

Multivariable logistic regression analysis further demonstrated that multisystem complications (OR, 4.552; 95% CI, 1.554–13.335), baseline eGFR (OR, 0.878; 95% CI, 0.827–0.933), myoglobin (OR, 1.021; 95% CI, 1.001–1.042), and PT (OR, 2.566; 95% CI, 1.452–4.536) were independently associated with ICI-AKI (Fig. 6).

Nomogram construction and validation

Based on the above analyses, four variables, including multisystem complications, baseline eGFR, myoglobin, and PT, were incorporated into the predictive model, and a nomogram was constructed to estimate the risk of ICI-AKI (Fig. 7A). The nomogram visually illustrates the relative weight and quantitative contribution of each variable to the predicted risk of AKI. ROC curve analysis showed that

the model achieved good discriminatory performance, with an AUC of 0.888 (95% CI: 0.837 to 0.939), a sensitivity of 86.9%, and a specificity of 76.6%, and an optimal probability cutoff value was 0.309 (Fig. 7B).

The calibration curve demonstrated good agreement between the model-predicted probability and the observed risk of AKI, with a mean absolute error (MAE) of 0.022. In addition, the Hosmer–Lemeshow goodness-of-fit test showed no significant deviation between the predicted and observed probabilities (P = 0.43), further supporting the favorable calibration performance of the model (Fig. 8A). DCA was further performed to assess the clinical utility of the model, showing that the nomogram provided a positive net benefit across a broad range of threshold probabilities (Fig. 8B).

Discussion

In this single-center retrospective study of patients receiving ICIs, we characterized the clinical presentation, pathological findings, treatment patterns, and kidney outcomes of patients with ICI-AKI and examined factors associated with its occurrence. The principal findings were as follows. First, ICI-AKI showed heterogeneous timing after ICI initiation, with a median onset of 84 days, and most patients presented with moderate-to-severe AKI according to KDIGO staging. Second, multisystem complications, lower baseline eGFR, higher baseline myoglobin level, and longer baseline PT were independently associated with ICI-AKI. Third, an exploratory nomogram incorporating multisystem complications, baseline eGFR, myoglobin, and PT demonstrated favorable discrimination, calibration, and clinical net benefit. These findings suggest that routinely available baseline laboratory parameters, together with clinical complications emerging during ICI therapy, may help clinicians identify patients at potentially higher risk of ICI-AKI before or during ICI therapy, thereby facilitating risk-adapted monitoring and earlier intervention.

In our study, most patients with ICI-AKI had KDIGO stage 2 or stage 3 AKI, whereas stage 1 AKI accounted for a smaller proportion. This may suggest that early or mild renal injury after ICI therapy can be underrecognized in routine oncology practice, particularly when Scr changes are subtle or attributed to other competing causes. At AKI onset, some patients also presented with urinary tract infection, liver dysfunction, rash, interstitial pneumonitis, elevated creatine kinase levels, or limb numbness. These concomitant manifestations highlight the complexity of ICI-treated patients and indicate that renal injury often occurs in a broader context of systemic illness, concomitant adverse events, or overlapping immune-related toxicities. From a clinical perspective, these findings emphasize that when multisystem complications arise after ICI administration, oncologists should maintain a high index of suspicion and closely monitor patients for impaired renal function. Among biopsied patients, ATIN was the most common pathological diagnosis, consistent with the current understanding that ATIN represents a major pathological pattern of ICI-AKI [14, 20–22]. However, given the limited number of patients who underwent biopsy, the estimated proportion of ATIN may be subject to selection bias. Regarding treatment outcomes, corticosteroid monotherapy was the predominant therapeutic strategy in our study. Follow-up results showed that a substantial proportion of patients met the prespecified Scr-response

criterion after clinical intervention. Specifically, among patients with stage 3 AKI, 88.9%, 94.4%, and 93.3% met the prespecified Scr-response criterion at 1, 3, and 6 months, respectively. Although a high proportion of patients with stage 3 AKI met the Scr-response criterion, this finding should not be interpreted as evidence of superior renal recovery or treatment efficacy, because the relative reduction from peak Scr may be influenced by the higher starting values in patients with more severe AKI. However, treatment responses varied among patients, and the optimal timing, dosage, and duration of corticosteroid therapy still require further investigation in prospective studies.

Regarding risk factors, multivariable logistic regression analysis showed that lower baseline eGFR was independently associated with the development of ICI-AKI, indicating that higher baseline eGFR was associated with lower odds of ICI-AKI. This observation is consistent with previous studies reporting baseline kidney dysfunction as an important risk factor for ICI-AKI [14, 23, 24]. Notably, despite statistically significant baseline variations in myoglobin and PT between the two groups, their absolute values in the AKI group predominantly remained within normal reference intervals. These within-reference-range differences may reflect baseline physiological or systemic vulnerability; however, further studies are needed to clarify the biological and clinical relevance of these within-reference-range differences. On one hand, ICIs can induce immune-related myositis or even rhabdomyolysis, resulting in increased myoglobin release into the circulation [24, 25]. Excessive myoglobin may aggravate renal injury by increasing tubular burden, promoting oxidative stress, and exerting direct tubular toxicity [26, 27]. Therefore, higher baseline myoglobin level may indicate pre-existing subclinical muscle injury or systemic vulnerability, which could be further amplified by ICI-related muscle toxicity during treatment. On the other hand, the longer baseline PT could point to subclinical hepatic dysfunction, suboptimal nutritional status, occult anticoagulant exposure, or tumor-related systemic vulnerability. In our study, 16.7% of patients who developed AKI had concurrent liver dysfunction at AKI onset, which partly supports the potential link between hepatic-coagulation vulnerability and ICI-AKI [28–30]. These findings suggest that ICI-AKI in clinical practice should not be viewed as an isolated renal event, but rather as a possible manifestation of broader systemic vulnerability or multi-organ immune toxicity.

To translate these findings into a clinically applicable tool, we developed an exploratory nomogram incorporating multisystem complications, baseline eGFR, myoglobin, and PT. The model achieved good discriminatory performance, with an AUC of 0.888. After internal validation using bootstrap resampling, the calibration curve showed good agreement between the predicted probability and the observed risk, with a mean absolute error (MAE) of 0.022 and a non-significant Hosmer–Lemeshow test result (P = 0.43). These findings suggest that the model showed promising performance after internal bootstrap validation. DCA further suggested that the model provided a potential net benefit across the evaluated range of threshold probabilities.

This study has several limitations. First, as a single-center retrospective study, selection bias and potential unmeasured confounding factors are inevitable. Second, the overall sample size was relatively limited, and kidney biopsy was performed in only a subset of patients owing to some clinical contraindications. Third, the prediction model has only undergone internal validation, and external

validation in large-scale, multicenter, prospective cohorts is needed to confirm its robustness, generalizability, and clinical applicability. To address these limitations, we plan to conduct future multicenter studies to expand the sample size, increase the number of biopsy-confirmed cases, and further validate the clinical predictors of ICI-AKI in larger and more diverse patient populations.

In conclusion, multisystem complications, lower baseline eGFR, higher baseline myoglobin level, and longer baseline PT were independently associated with ICI-AKI in this study. The exploratory model showed good discrimination in the development sample, yet external validation and recalibration are required before it can be used to support the early identification and clinical management of patients receiving ICI therapy.

Declarations

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of Huashan Hospital, Fudan University (No. KY2026-989). The informed consent was signed by the patients or their authorized representatives.

Data and materials availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical restrictions.

Conflict of interest statement

The authors declare that they have no competing interests.

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Authors' contributions

J.S. and P.C. collected and curated the clinical data. P.C., Q.Z. (Qian Zhang), Y.X., and M.Z. adjudicated the ICI-AKI cases. S.L. contributed the human kidney biopsy findings and histological images. J.S. performed the statistical analyses, prepared the figures, and drafted the manuscript. N.X., Y.G. and M.Z. contributed to data interpretation and critically revised the manuscript. Q.Z. (Qiong Zhan) and M.Z. conceived and designed the study.

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Figures

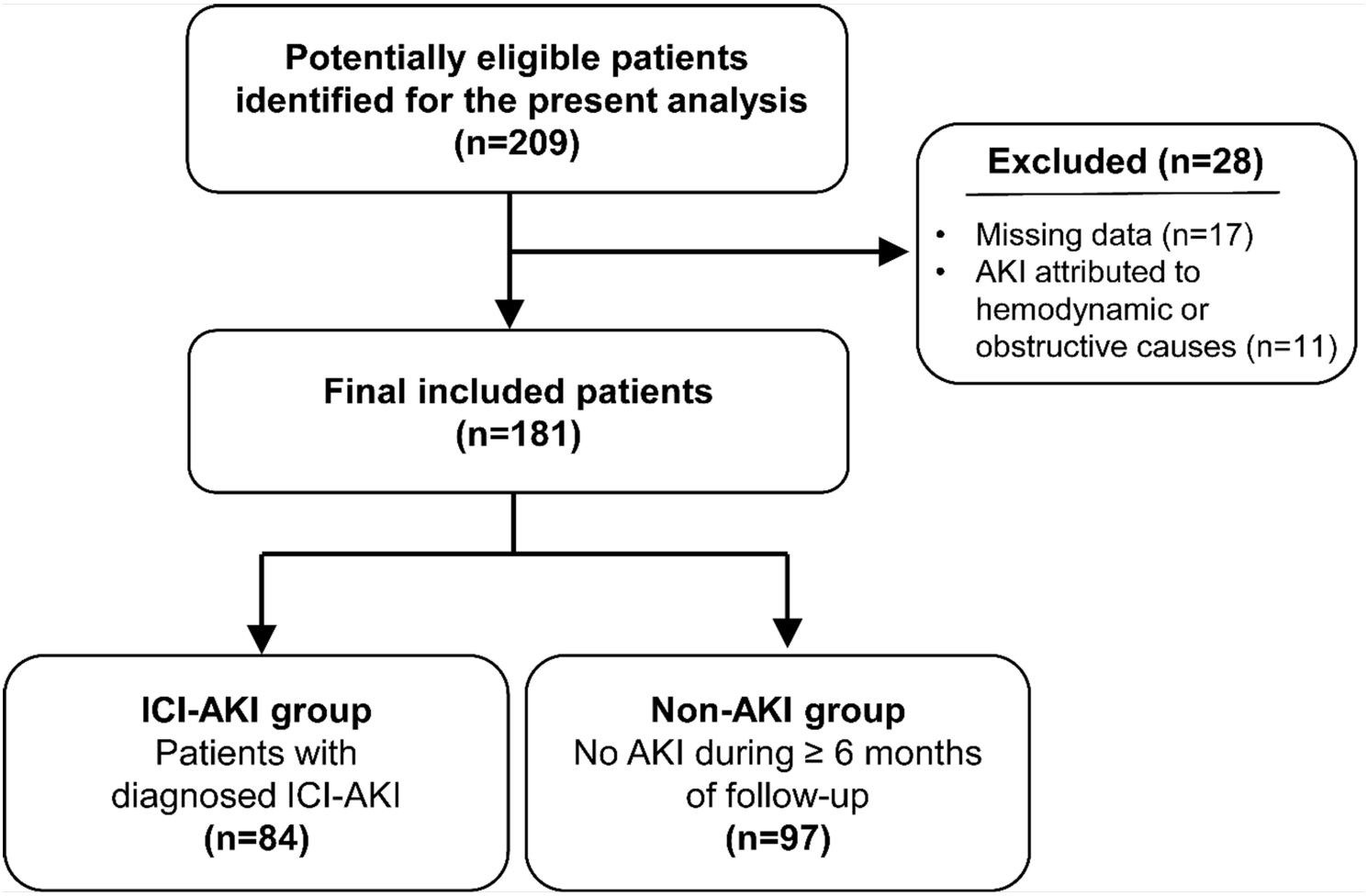


Figure 1

Flowchart of the patient selection.

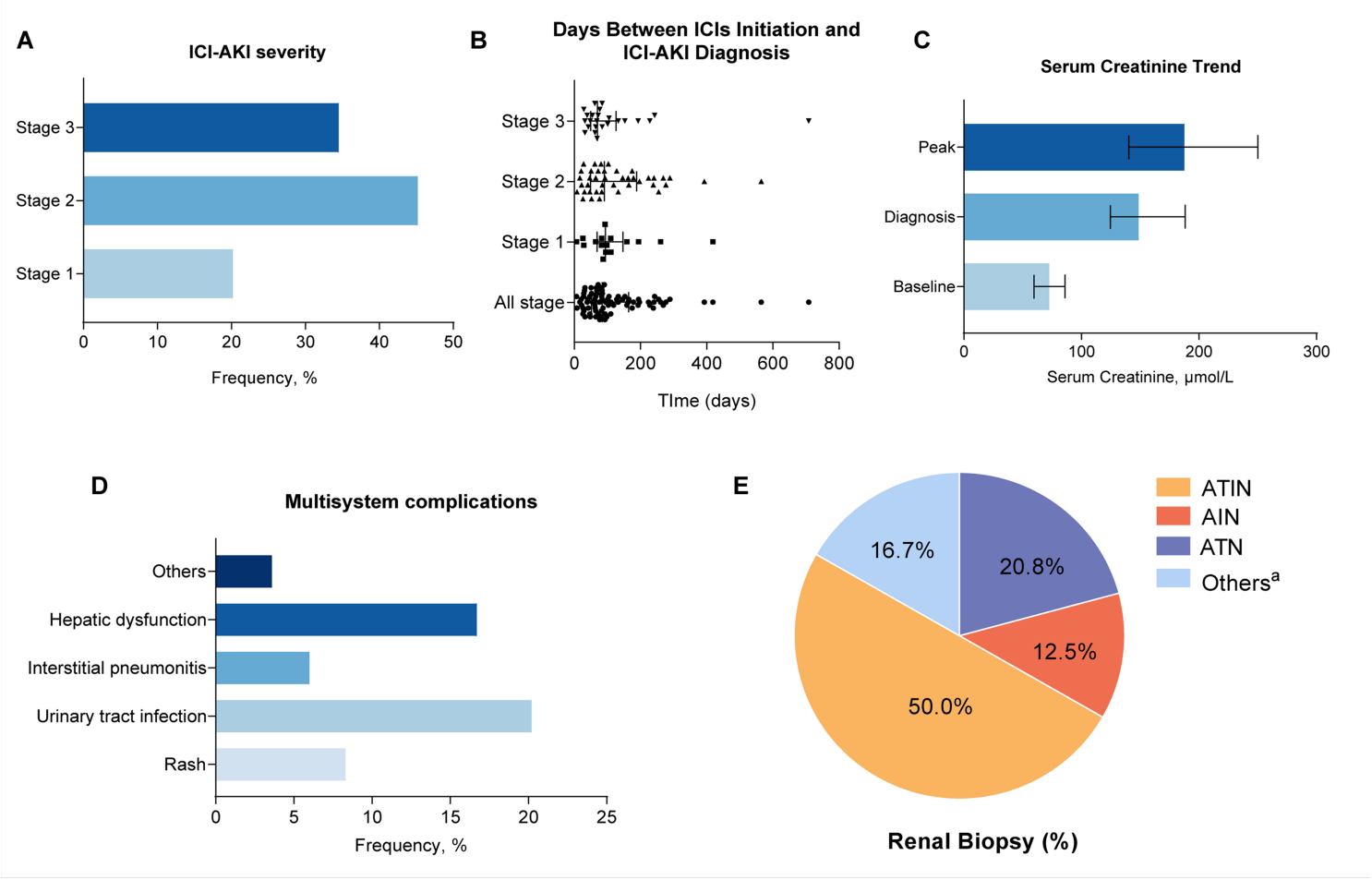


Figure 2

Clinical features of ICI-AKI. (A) Distribution of AKI severity. (B) Time from initiation of ICI therapy to AKI onset, stratified by stage, with median and interquartile range shown. (C) Trends in serum creatinine levels across different stages of AKI patients, with median and interquartile range shown. (D) Other clinical symptoms associated with ICI treatment. (E) Analysis of kidney biopsy pathological types in 24 patients. *Other pathological types included IgA nephropathy (n=2), ANCA-associated vasculitis kidney damage (n=1), and minor renal tissue lesions (n=1).

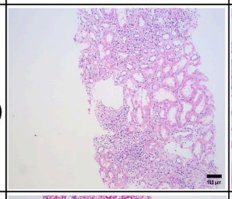
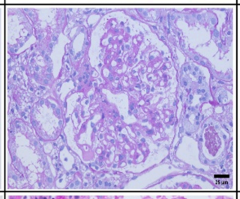
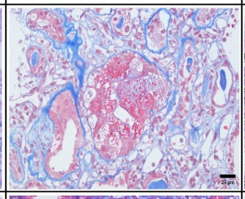
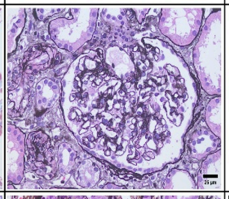
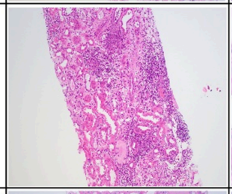
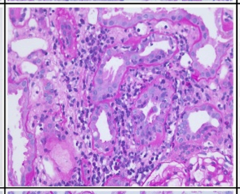
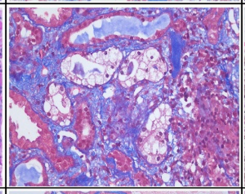
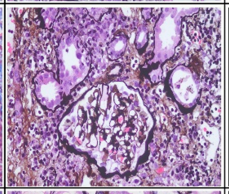
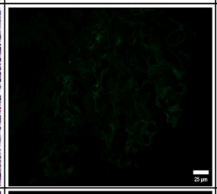
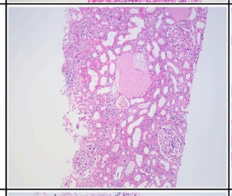
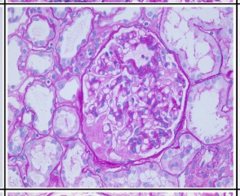
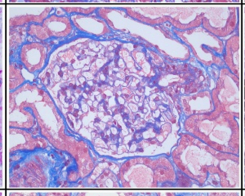
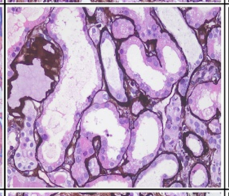
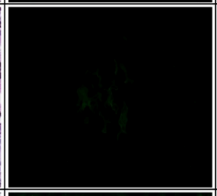
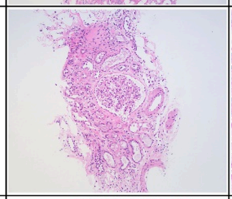
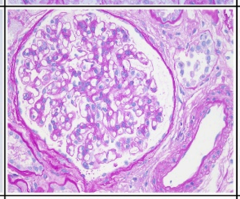
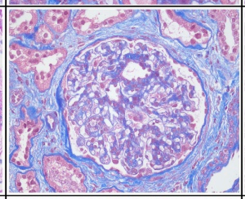
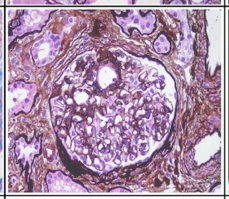
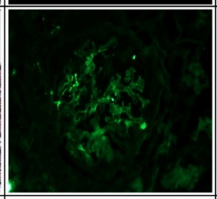
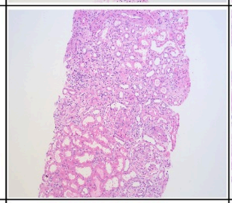
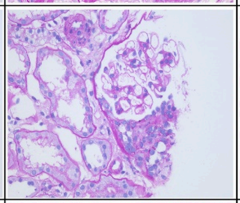
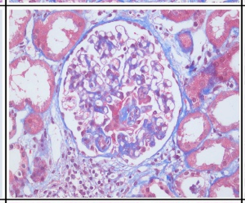
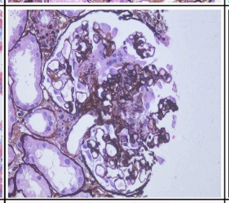
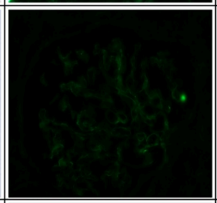
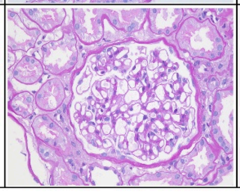
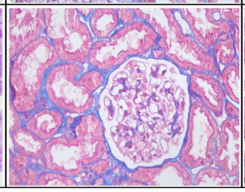
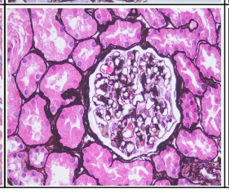
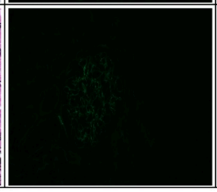
Pathological Type	Representative Image					Description
	HE (X100)	PAS (X400)	MASSON (X400)	PASM (X400)	IgA immunofluorescence staining (X400)	
ATIN (n=11, 47.8%)					/	IgA(-); focal tubulitis and tubular atrophy were observed in a few tubules, with scattered inflammatory cell infiltration in the interstitium.
AIN (n=3, 13.0%)						IgA(-); Interstitial nephritis, primarily characterized by acute lesions, with numerous glomerular sclerosis also observed.
ATN (n=5, 21.7%)						IgA(-); Focal brush border loss was observed in renal tubular epithelial cells, associated with luminal dilatation and mild tubular atrophy.
IgAN (n=2, 8.7%)						IgA nephropathy was observed, with some chronic changes including global or segmental sclerosis.
ANCA-associated vasculitis kidney damage (n=1, 4.4%)						IgA(-); focal segmental necrotizing glomerulonephritis with pauci-immune complex deposits.
Minor renal tissue lesions (n=1, 4.4%)	/					IgA(-); The renal tissue exhibited only minimal histopathological abnormalities.

Figure 3

Representative kidney biopsy images in patients with ICI-AKI. H&E-stained images are shown at ×100 original magnification; PAS, PASM, Masson trichrome-stained, and IgA immunofluorescence images are shown at ×400 original magnification. H&E, haematoxylin and eosin; PAS, periodic acid–Schiff; PASM, periodic acid–silver methenamine; ANCA, antineutrophil cytoplasmic antibody (Scale bar, 100 μm and 25 μm, respectively).

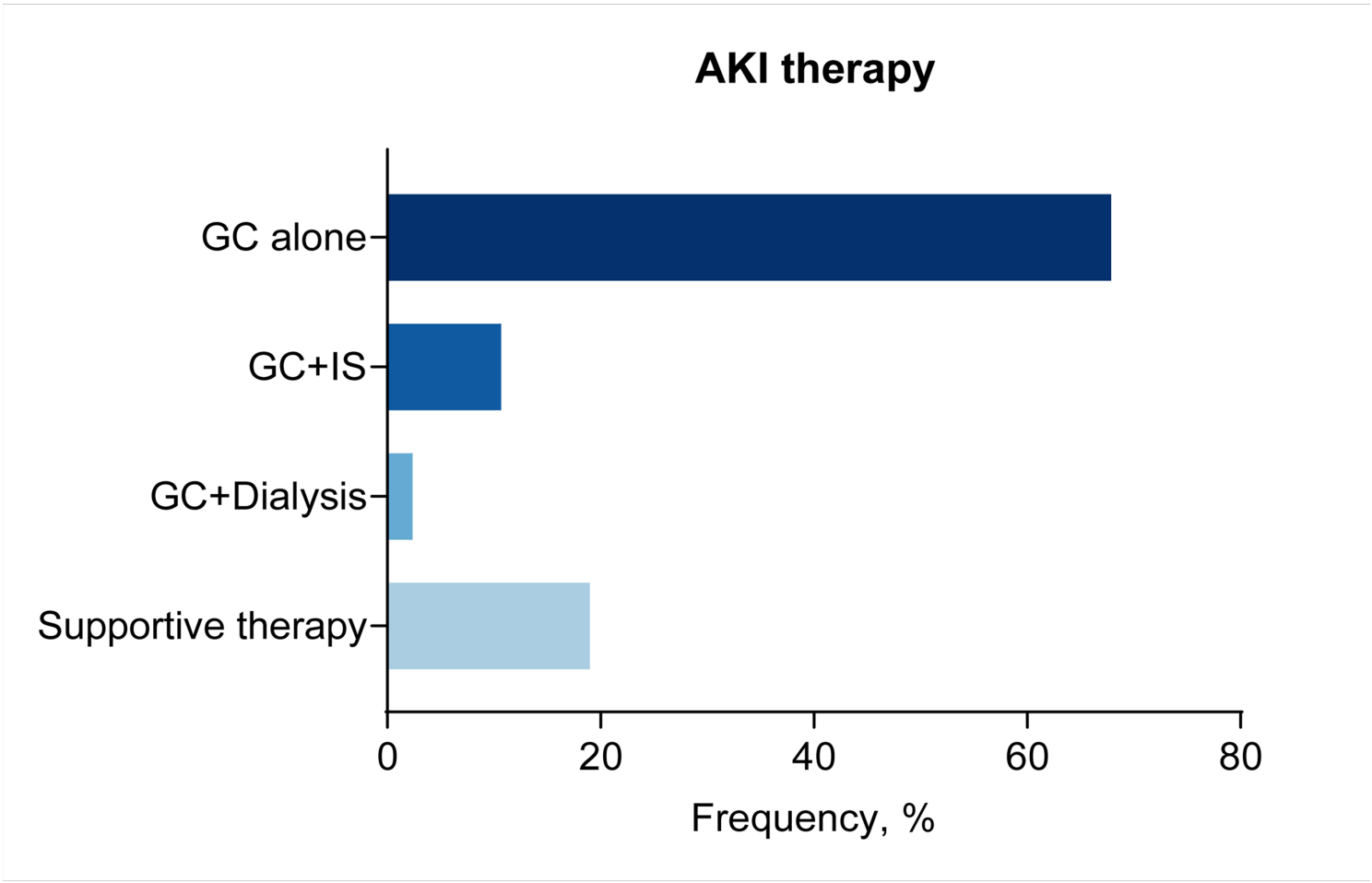


Figure 4

Different treatment strategies for ICI-AKI. GC, glucocorticoid; IS, immunosuppressive agent.

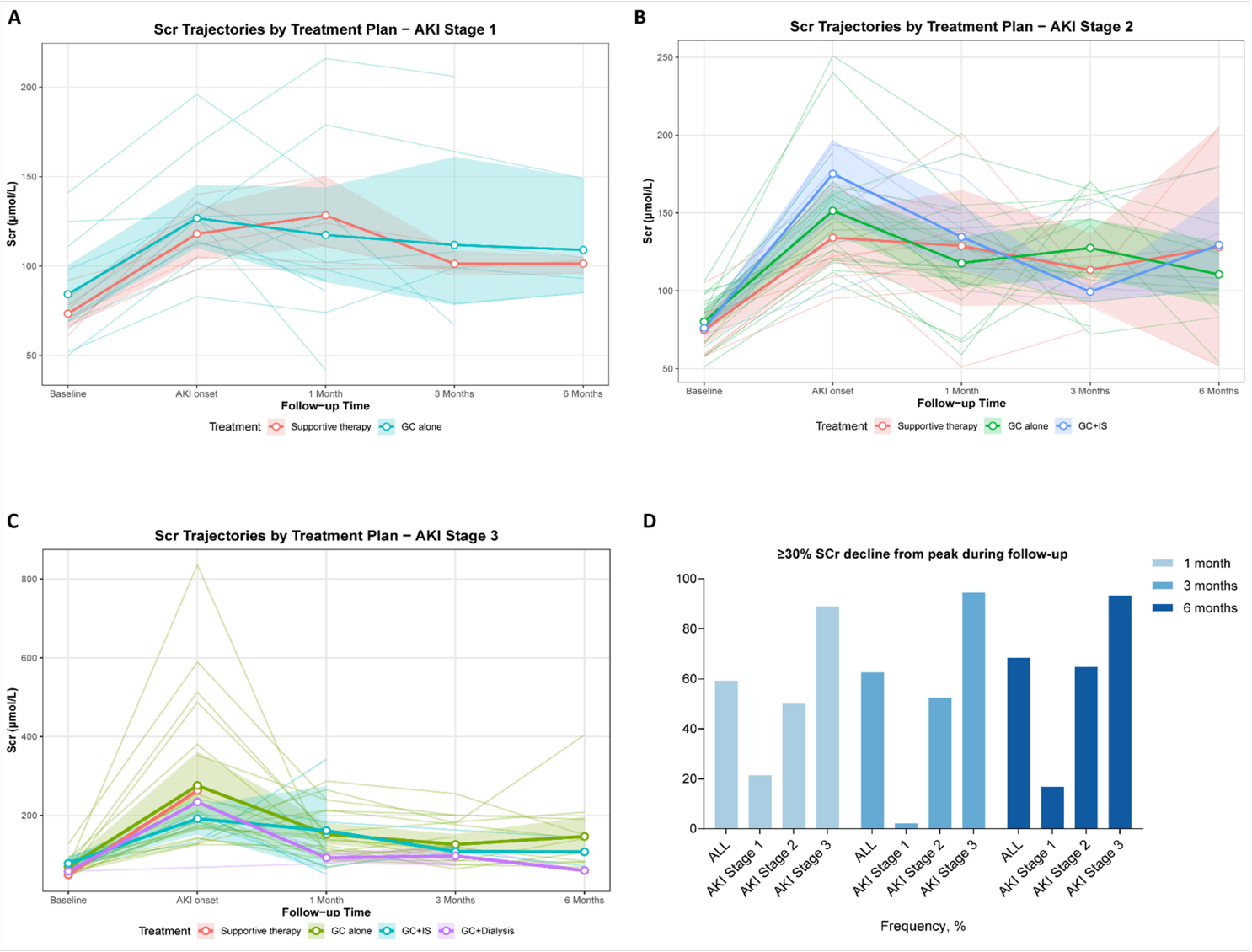


Figure 5

Longitudinal serum creatinine trajectories and achievement of the prespecified Scr-response criterion in patients with ICI-AKI. (A–C) Longitudinal Scr trajectories from baseline and AKI onset through 1, 3, and 6 months of follow-up according to treatment strategy in patients with AKI stage 1 (A), stage 2 (B), and stage 3 (C). Thin lines represent individual patient trajectories, solid-colored lines represent treatment-group means, and shaded areas indicate bootstrap 95% confidence intervals. Available observations were included at each time point, and missing values were not imputed. (D) Proportions of patients meeting the prespecified Scr-response criterion, defined as a ≥30% reduction in Scr from the peak value, at 1, 3, and 6 months of follow-up, overall and stratified by AKI stage.

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age	**1.083 (1.044 − 1.125)**	**<0.001**	0.992 (0.926 − 1.062)	0.81
Female	0.595 (0.299 − 1.183)	0.139		
BMI	0.997 (0.909 − 1.093)	0.951		
Comorbidities				
Chronic kidney disease	6.076 (0.695 − 53.084)	0.103		
Diabetes mellitus	1.797 (0.803 − 4.021)	0.154		
Hypertension	1.759 (0.953 − 3.246)	0.071		
Drugs				
PPI	1.333 (0.742 − 2.395)	0.336		
NSAIDS	0.222 (0.025 − 1.937)	0.173		
ARB or ACEi	0.873 (0.362 − 2.109)	0.763		
SGLT2i	0.449 (0.085 − 2.376)	0.346		
Multisystem complications	**5.338 (2.585 − 11.023)**	**<0.001**	**4.552 (1.554 − 13.335)**	**0.006**
CRP	0.995 (0.976 − 1.014)	0.587		
WBC	1.080 (0.959 − 1.217)	0.205		
Leukocyturia	0.999 (0.996 − 1.001)	0.28		
Hematuria	1.003 (0.994 − 1.013)	0.528		
Proteinuria	1.298 (0.628 − 2.683)	0.481		
Scr	**1.079 (1.050 − 1.108)**	**<0.001**		
eGFR	**0.896 (0.862 − 0.931)**	**<0.001**	0.878 (0.827 − 0.933)	<0.001
LDH	1.000 (0.999 − 1.001)	0.562		
CPK	1.004 (0.999 − 1.009)	0.084		
Myoglobin	**1.037 (1.012 − 1.062)**	**0.004**	**1.021 (1.001 − 1.042)**	**0.037**
D−dimer	1.015 (0.930 − 1.107)	0.742		
PT	**2.412 (1.633 − 3.562)**	**<0.001**	**2.566 (1.452 − 4.536)**	**0.001**
APTT	**1.134 (1.047 − 1.229)**	**0.002**	1.063 (0.930 − 1.216)	0.371
FIB	0.950 (0.753 − 1.198)	0.662		
FDP	1.014 (0.977 − 1.051)	0.472		
ANA positive	0.824 (0.356 − 1.904)	0.65		

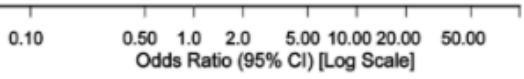


Figure 6

Logistic regression analysis and forest plot of factors associated with ICI-AKI.

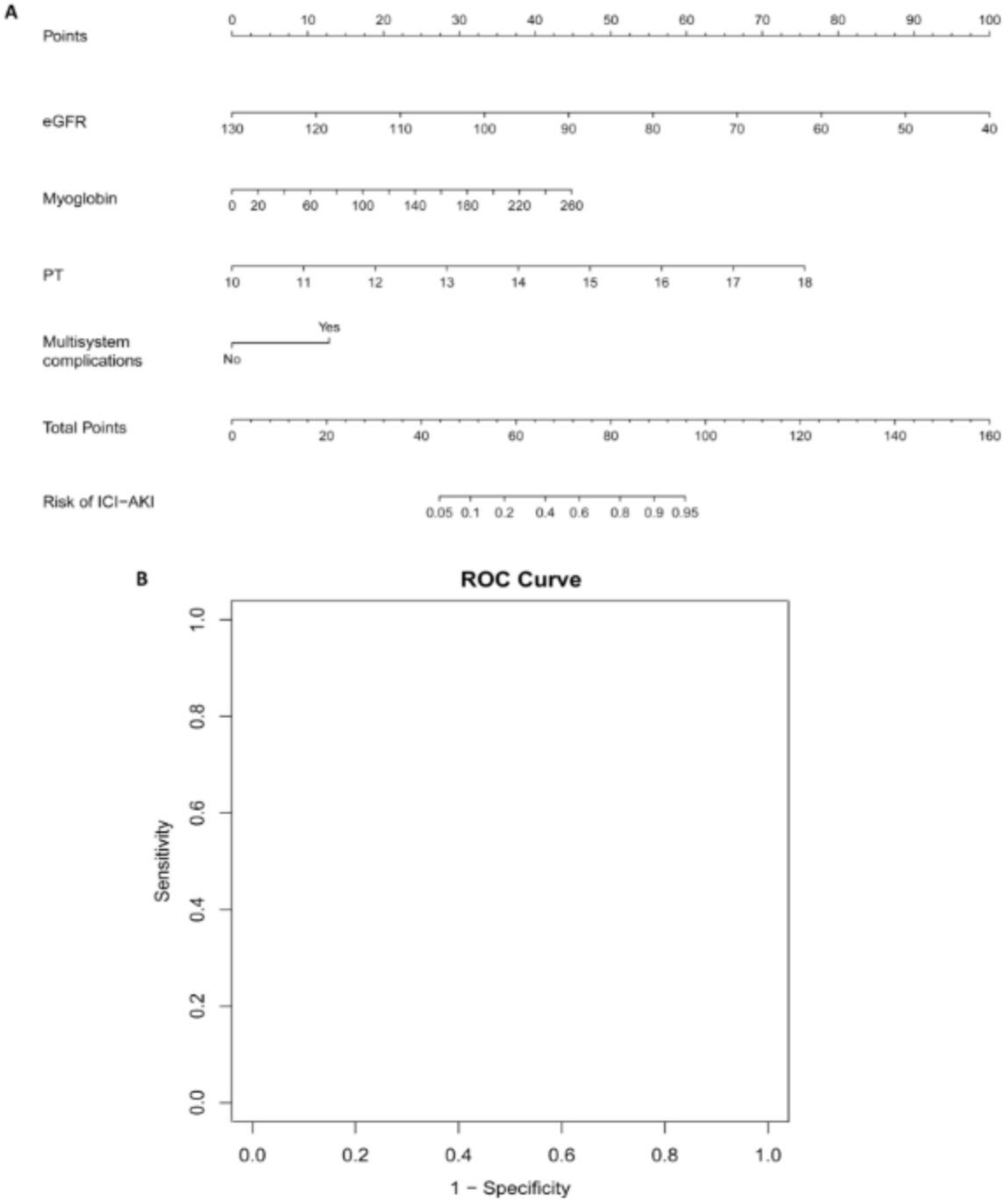


Figure 7

Nomogram construction and ROC curve analysis. (A) A nomogram was constructed using multisystem complications, baseline eGFR, myoglobin, and PT levels to predict the occurrence of ICI-AKI. (B) ROC curve analysis of the model predicting ICI-AKI occurrence.

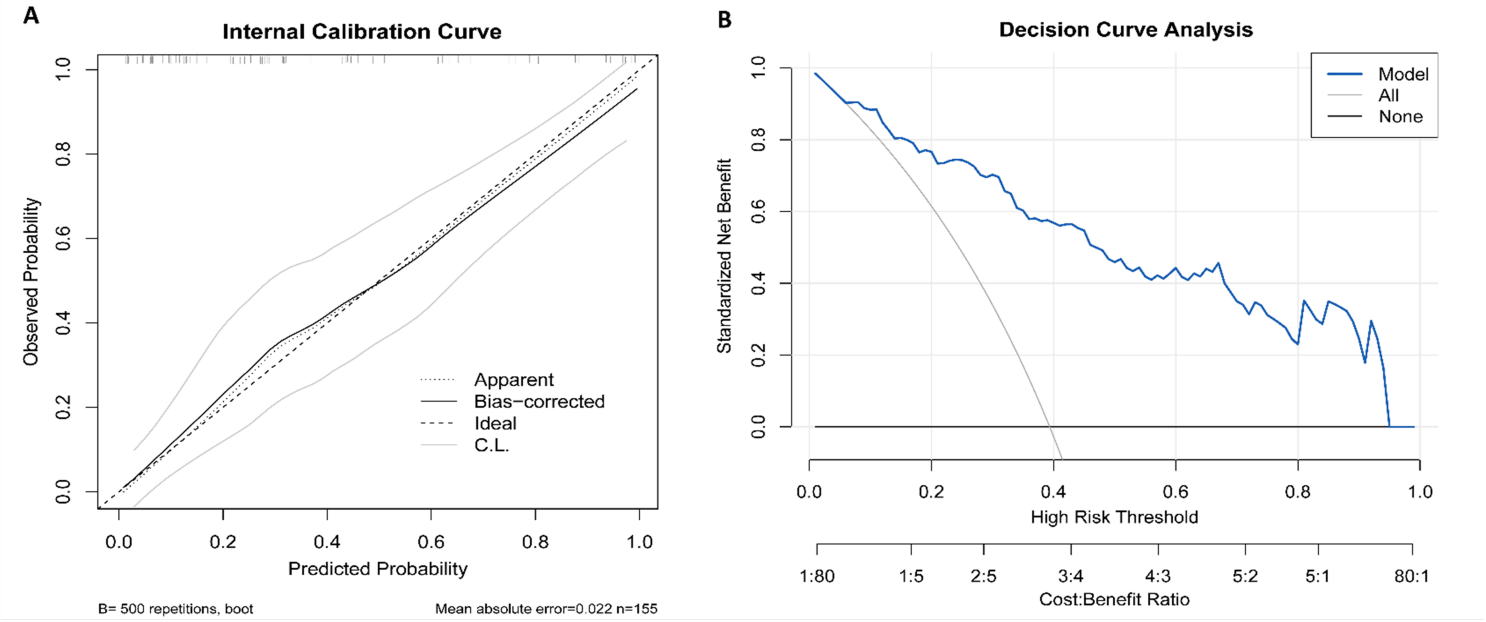


Figure 8

Calibration and clinical utility of the nomogram for predicting ICI-AKI. (A) Calibration curve for predicting ICI-AKI. The 45° reference line represents perfect agreement between predicted and observed probabilities. (B) DCA for the prediction model. The decision curve assesses the clinical utility of the nomogram incorporating multisystem complications, baseline eGFR, myoglobin, and PT for predicting the risk of ICI-AKI. The y-axis represents the net benefit, and the x-axis represents the threshold probability.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx