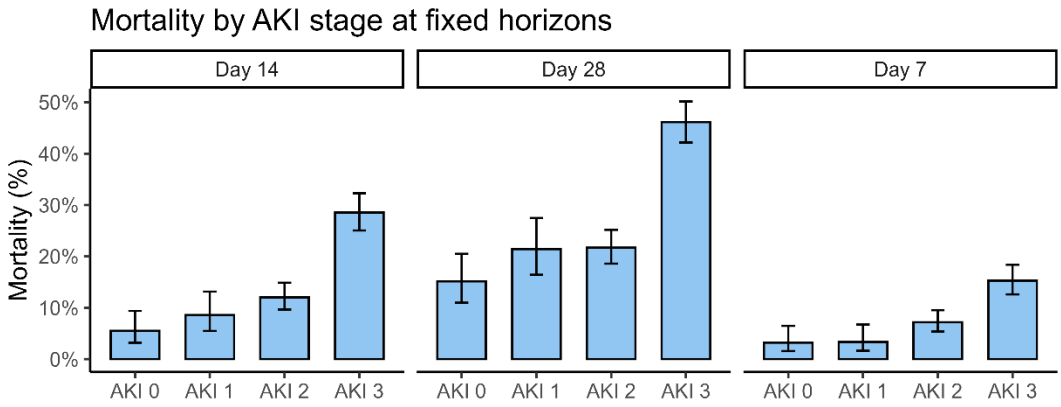
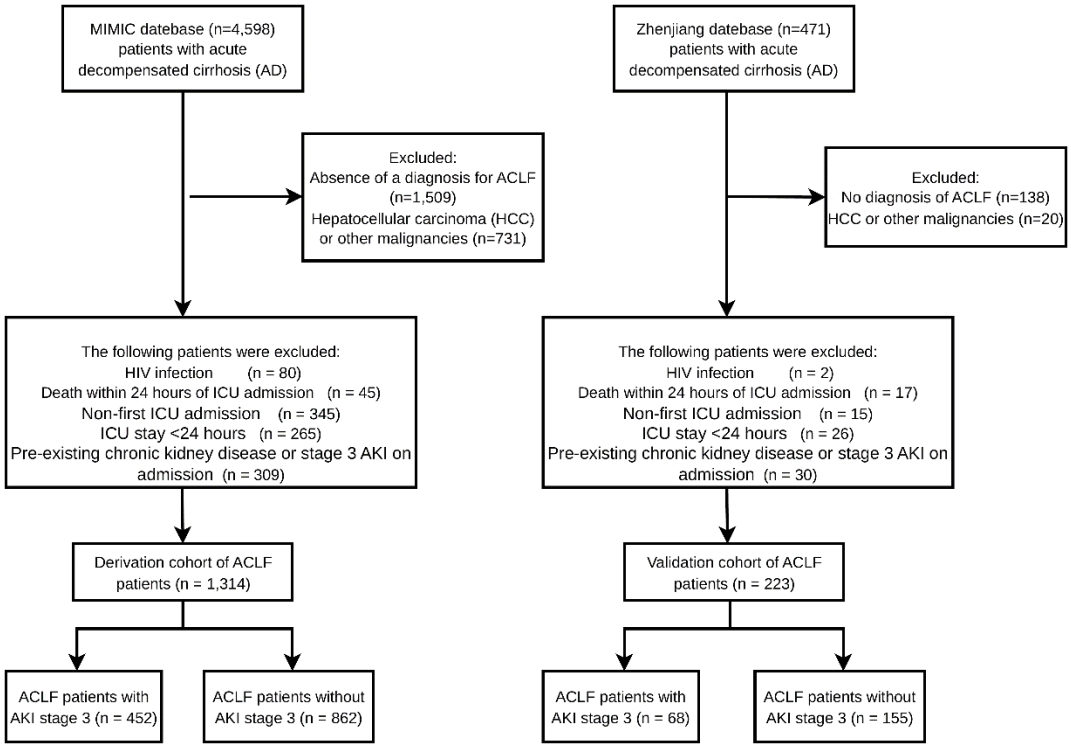
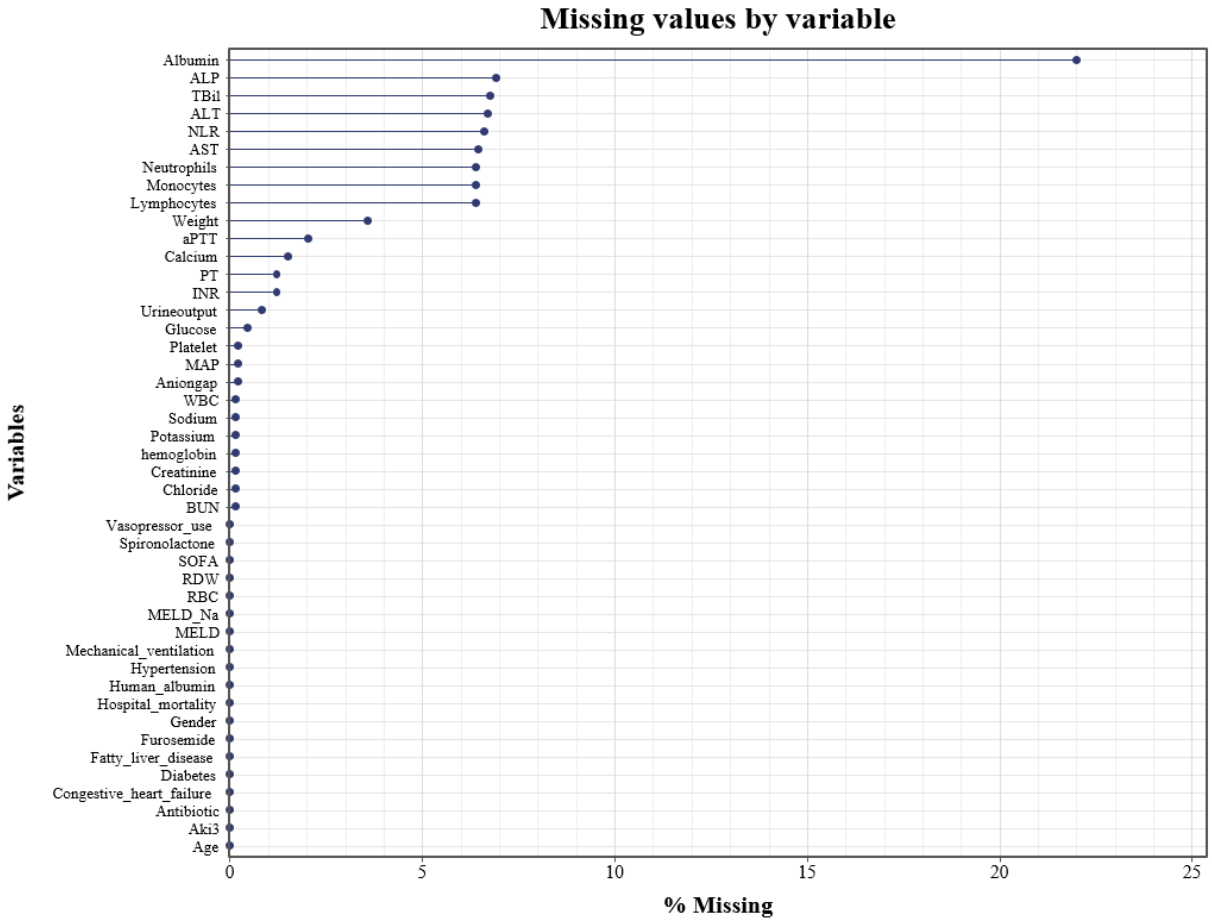
Supplementary material



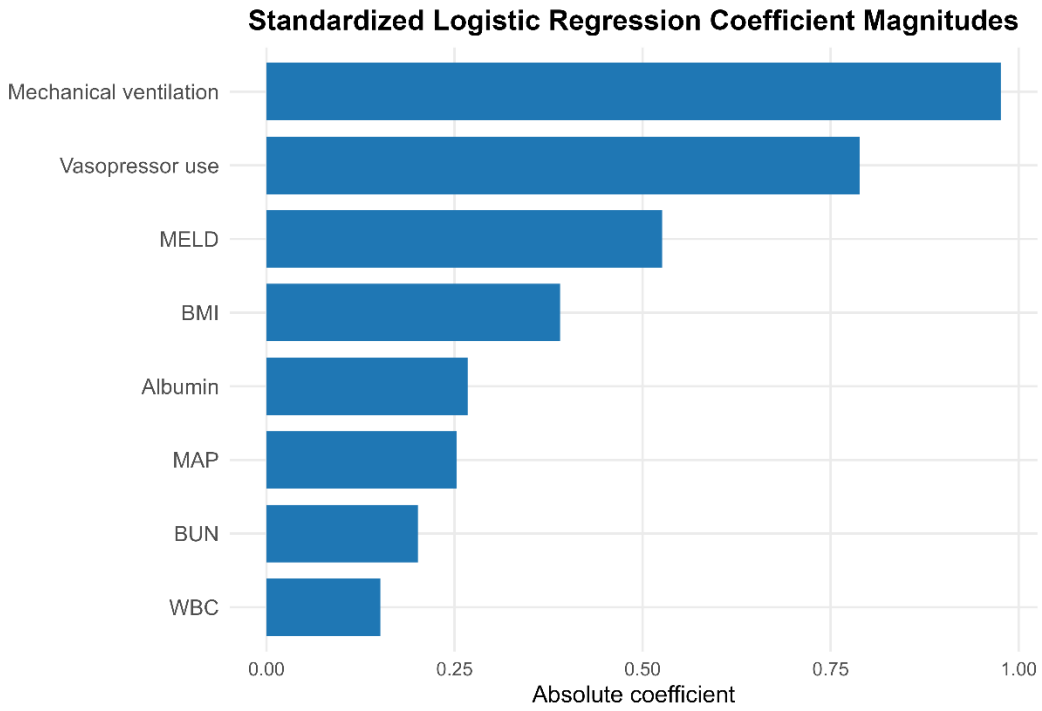
Supplementary Figure 1. Mortality of ACLF patients according to AKI stage at days 7, 14, and 28.



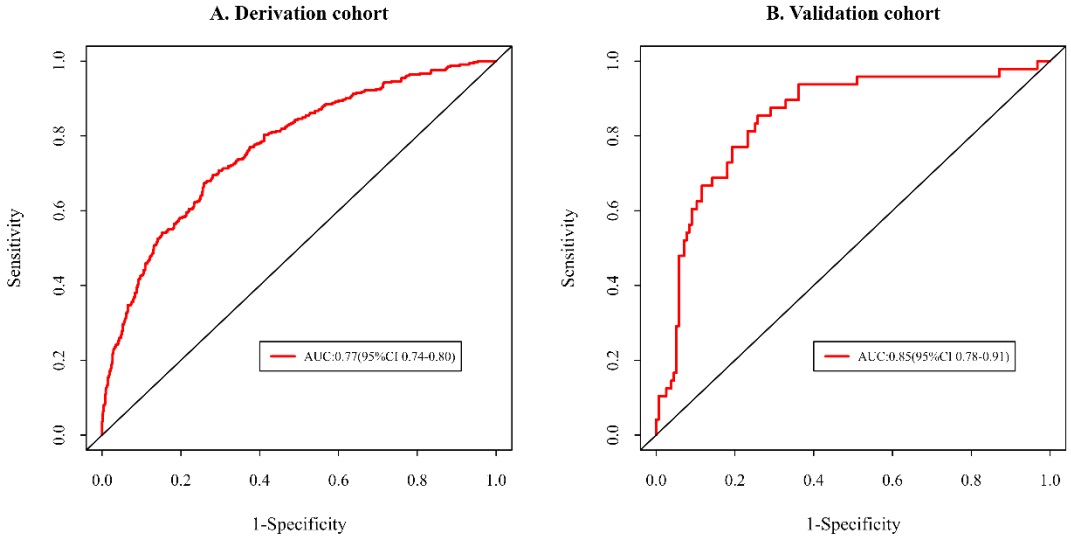
Supplementary Figure 2. Flow chart of the study (MIMIC = Medical Information Mart for Intensive Care; AKI = Acute Kidney Injury; ACLF = Acute-on-Chronic Liver Failure; HCC = Hepatocellular Carcinoma; HIV = Human Immunodeficiency Virus; ICU = Intensive Care Unit; AD = Acute decompensation)



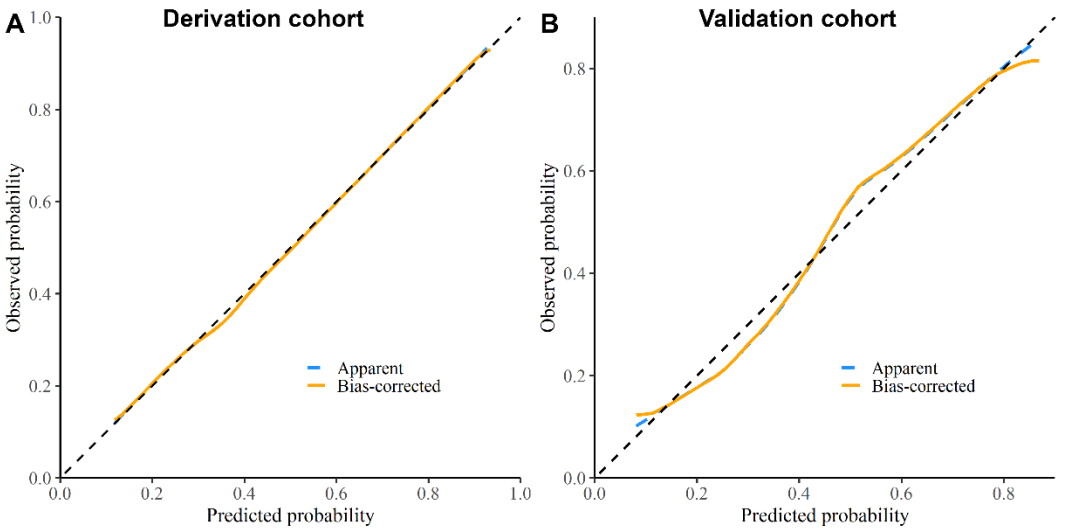
Supplementary Figure 3. Percentage of missing values for each variable in the derivation cohort.



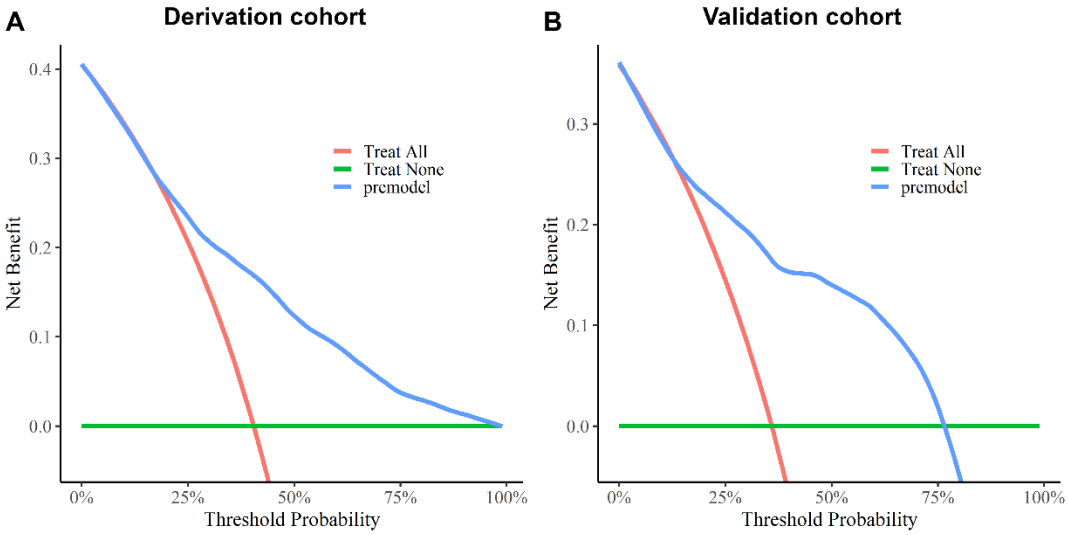
Supplementary Figure 4. Logistic regression feature importance.



Supplementary Figure 5. Receiver operating characteristic curves for the 24-hour landmark sensitivity analysis in the derivation and validation cohorts.



Supplementary Figure 6. Calibration curves for prediction of the composite endpoint in the derivation (A) and validation (B) cohorts.



Supplementary Figure 7. Decision curve analysis for prediction of the composite endpoint in the derivation (A) and validation (B) cohorts.

Supplementary Table 1 Baseline characteristics of the ACLF derivation cohort by stage 3 AKI status

Characteristics	All patients (*n* = 1314)	Without stage 3 AKI (*n* = 862)	With stage 3 AKI (*n* = 452)	*P* value
Sex, *n* (%)				0.136
Female	526 (40)	332 (38.5)	194 (42.9)	
Male	788 (60)	530 (61.5)	258 (57.1)	
Age (years)	57.4 (49.87, 65.11)	57.42 (49.87, 65.15)	57.19 (50.16, 65.04)	0.999
BMI (kg/m^2)	28.02 (24.32, 32.73)	27.15 (23.55, 31.61)	29.89 (26.20, 34.81)	< 0.001[a]
MAP (mmHg)	60 (53, 67)	62 (55, 68)	57 (50, 63)	< 0.001[a]
Urine output (mL)	1225 (750, 1900)	1458 (1020, 2115)	760 (459, 1275)	< 0.001[a]
Hospital mortality,*n* (%)				
Survivors	1009 (76.8)	749 (86.9)	260 (57.5)	< 0.001[a]
Non-survivors	305 (23.2)	113 (13.1)	192 (42.5)	
Comorbidities, *n* (%)				
Congestive heart failure	177 (13.5)	121 (14.0)	56 (12.4)	0.456
Diabetes	307 (23.4)	209 (24.2)	98 (21.7)	0.33
Hypertension	235 (17.9)	158 (18.3)	77 (17.0)	0.613

Fatty liver disease	89 (6.8)	55 (6.4)	34 (7.5)	0.505
Organ support, *n* (%)				
Mechanical ventilation	351 (26.7)	169 (19.6)	182 (40.3)	< 0.001[a]
Vasopressor use	456 (34.7)	217 (25.2)	239 (52.9)	< 0.001[a]
Medications, *n* (%)				
Antibiotic	1037 (78.9)	654 (75.9)	383 (84.7)	< 0.001[a]
Furosemide	166 (12.6)	106 (12.3)	60 (13.3)	0.675
	122 (9.3)	73 (8.5)	49 (10.8)	0.191
Spironolactone				
Human albumin	309 (23.5)	180 (20.9)	129 (28.5)	0.002[a]
Nephrotoxic drugs	92 (7.0)	51 (5.9)	41 (9.1)	0.044[a]
Organ failure, *n* (%)				
Liver	242 (18.4)	122 (14.2)	120 (26.5)	< 0.001[a]
Kidney	401 (30.5)	137 (15.9)	264 (58.4)	< 0.001[a]
Coagulation	312 (23.7)	150 (17.4)	162 (35.8)	< 0.001[a]
Brain	326 (24.8)	173 (20.1)	153 (33.8)	< 0.001[a]
Circulation	456 (34.7)	217 (25.2)	239 (52.9)	< 0.001[a]
Lung	591 (45.0)	341 (39.6)	250 (55.3)	< 0.001[a]
Sex, *n* (%)				0.055
Female	78 (35)	61 (39.4)	17 (25)	
Male	145 (65)	94 (60.6)	51 (75)	

Age (years)	56 (49, 68.5)	55 (48, 68.5)	59 (50, 68.25)	0.175
BMI (kg/m^2)	23.39 (20.84, 26.48)	23.18 (20.81, 26.13)	24.10 (21.10, 26.78)	0.252
MAP (mmHg)	87 (80.33, 93.33)	87 (80.5, 93.33)	86.83 (80, 93.58)	0.96
Urine output (mL)	1250 (950, 1515)	1400 (1000, 1600)	1000 (600, 1362.5)	< 0.001[a]
Hospital mortality,*n* (%)				
Survivors	187 (83.9)	143 (92.3)	44 (64.7)	< 0.001[a]
Non-survivors	36 (16.1)	12 (7.7)	24 (35.3)	
Comorbidities, *n* (%)				
Congestive heart failure	11 (4.9)	6 (3.9)	5 (7.4)	0.317
Diabetes	34 (15.2)	17 (11.0)	17 (25.0)	0.013[a]
Hypertension	59 (26.5)	37 (23.9)	22 (32.4)	0.247
Fatty liver disease	34 (15.2)	27 (17.4)	7 (10.3)	0.246
Organ support, *n* (%)				
Mechanical ventilation	15 (6.7)	8 (5.2)	7 (10.3)	0.243
Vasopressor use	13 (5.8)	6 (3.9)	7 (10.3)	0.069

Medications, *n* (%)				
Antibiotic	103 (46.2)	56 (36.1)	47 (69.1)	< 0.001[a]
Furosemide	107 (48.0)	70 (45.2)	37 (54.4)	0.26
Spironolactone	107 (48.0)	72 (46.5)	35 (51.5)	0.586
Human albumin	74 (33.2)	40 (25.8)	34 (50.0)	0.001[a]
Nephrotoxic drugs	35 (15.7)	25 (16.1)	10 (14.7)	0.945
Organ failure, *n* (%)				
Liver	108 (48.4)	66 (42.6)	42 (61.8)	0.013[a]
Kidney	24 (10.8)	4 (2.6)	20 (29.4)	< 0.001[a]
Coagulation	53 (23.8)	39 (25.2)	14 (20.6)	0.57
Brain	39 (17.5)	19 (12.3)	20 (29.4)	0.004[a]
Circulation	13 (5.8)	6 (3.9)	7 (10.3)	0.069
Lung	25 (11.2)	11 (7.1)	14 (20.6)	0.007[a]
Laboratory tests				
Hemoglobin (g/dL)	10.7 (8.4, 12.8)	10.7 (8.1, 12.8)	10.7 (8.75, 12.6)	0.873
Platelet (10^9/L)	71 (50.5, 104)	69 (52, 105.5)	77 (46.25, 103)	0.913
WBC (10^9/L)	5.88 (3.96, 8.45)	5.25 (3.57, 7.67)	7.74 (5.4, 10.53)	< 0.001[a]
Albumin (g/dL)	2.82 (2.42, 3.16)	2.96 (2.67, 3.27)	2.39 (2.23, 2.70)	< 0.001[a]

Anion gap (mmol/L)	11.3 (9.65, 13.8)	11 (9.3, 13.45)	12.3 (10.55, 14.83)	0.002[a]
BUN (mg/dL)	14.87 (10.04, 24.26)	12.85 (9.35, 18.33)	24.21 (13.35, 41.75)	< 0.001[a]
Calcium (mmol/L)	2.07 (1.96, 2.16)	2.07 (1.97, 2.16)	2.06 (1.93, 2.16)	0.225
Chloride (mmol/L)	101.8 (96.5, 104.9)	102.3 (97.5, 105.1)	100.65 (94.4, 104.17)	0.039[a]
Creatinine (mg/dL)	0.78 (0.64, 1.02)	0.74 (0.62, 0.86)	1.15 (0.77, 2.10)	< 0.001[a]
Glucose (mmol/L)	5.54 (4.77, 6.98)	5.45 (4.66, 6.31)	6.06 (5.04, 8.95)	0.005[a]
Sodium (mmol/L)	135.8 (132.75, 138.65)	136.7 (133.1, 138.85)	133.95 (129.2, 137.57)	0.003[a]
Potassium (mmol/L)	3.8 (3.38, 4.21)	3.78 (3.32, 4.1)	3.96 (3.46, 4.52)	0.033[a]
INR	1.97 (1.61, 2.43)	1.97 (1.6, 2.54)	1.96 (1.61, 2.37)	0.692
PT (s)	22.1 (18.85, 26.05)	22.3 (18.95, 26.75)	21.7 (18.8, 25.52)	0.327
aPTT (s)	44.3 (38.6, 51.5)	44.7 (38.35, 52.1)	43.5 (39.12, 48.92)	0.894
ALT (U/L)	63 (29, 360.5)	63 (27, 523.5)	62.5 (35.5, 124)	0.717

ALP (U/L)	143 (108, 193.5)	139 (108, 195.5)	144 (105.25, 181.25)	0.664
AST (U/L)	108 (57, 322)	108 (54, 399)	108.5 (70, 192.75)	0.777
TBil (mg/dL)	11.79 (6.86, 19.49)	10.36 (5.99, 17.1)	15.41 (9.74, 25.56)	< 0.001[a]
Lymphocytes (%)	13.9 (8.45, 22.15)	16.3 (10.87, 25.95)	9.3 (6.76, 14.94)	< 0.001[a]
Monocytes (%)	8.3 (6.4, 10.1)	8.4 (6.57, 10.15)	7.55 (6, 9.85)	0.162
Neutrophils (%)	74.8 (66.65, 83.08)	72.9 (62.6, 80.45)	80.1 (72.66, 85.59)	< 0.001[a]
NLR	5.23 (2.99, 9.71)	4.45 (2.38, 7.21)	8.23 (5.16, 12.58)	< 0.001[a]
RBC (10^{12}/L)	3.15 (2.44, 3.88)	3.16 (2.46, 3.94)	3.13 (2.33, 3.74)	0.569
RDW (%)	15.8 (14.15, 18.85)	15.4 (14.1, 18.25)	16.7 (14.57, 20.02)	0.038[a]
Severity score				
MELD	25.26 (21.63, 32.07)	24.1 (20.54, 30.47)	27.14 (24.34, 33.09)	0.002[a]
SOFA	6 (5, 8)	6 (4, 7)	8 (7, 10)	< 0.001[a]

MELD-Na	26.66 (22.62, 32.94)	25.64	(21.75, 31.86)	29.16	(25.86, 34.9)	< 0.001[a]

[a]$P < 0.05$.

Supplementary Table 2 Model comparisons between the CLIF-AKI score and other established risk scores

	AUC	SE	95% CI
CLIF-AKI score	0.8591	0.0280	0.8041-0.9141
PIRO [9]	0.7945	0.0335	0.7289-0.8601
CLIF-C ACLF score [13]	0.7297	0.0345	0.6621-0.7972
CTP score [14]	0.6744	0.0355	0.6048-0.7441
MELD score [15]	0.6334	0.0391	0.5568-0.7100
MELD-Na score [16]	0.6554	0.0382	0.5805-0.7302

$\chi^2(5) = 38.87$, $P < 0.0001$.

AUC= Area Under the Curve; SE= Standard Error; CI= Confidence Interval.

Supplementary Table 3 Subgroup analyses of the CLIF-AKI model in the derivation cohort

Subgroup	n	Events	Non-events	AUC (95% CI)
ACLF grade				
Grade 1	601	190	411	0.823 (0.785–0.860)
Grade 2	425	148	277	0.771 (0.726–0.817)
Grade 3	288	114	174	0.749 (0.691–0.808)
Mechanical ventilation				
No	963	270	693	0.755 (0.721–0.788)
Yes	351	182	169	0.814 (0.770–0.857)
Vasopressor use				
No	858	213	645	0.742 (0.704–0.780)
Yes	456	239	217	0.780 (0.738–0.822)

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; AUC, area under the receiver operating characteristic curve; CI, confidence interval. Events refer to stage 3 AKI. Subgroup analyses were performed in the derivation cohort using the predicted probabilities generated from the original CLIF-AKI model. The model was not refitted within each subgroup.