

A model predicting short-term mortality in patients with advanced liver cirrhosis and concomitant infection

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Abstract

Infection is a common cause of death in patients with advanced cirrhosis. We aimed to develop a predictive model in Child–Turcotte–Pugh (CTP) class C cirrhotics hospitalized with infection for optimizing treatment and improving outcomes.

Clinical information was retrospectively abstracted from 244 patients at Tianjin Third Central Hospital, China (cohort 1). Factors associated with mortality were determined using logistic regression. The model for predicting 90-day mortality was then constructed by decision tree analysis. The model was further validated in 91 patients at Mayo Clinic, Rochester, MN (cohort 2) and 82 patients at Seoul St. Mary's Hospital, Korea (cohort 3). The predictive performance of the model was compared with that of the CTP, model for end-stage liver disease (MELD), MELD-Na, Chronic Liver Failure–Sequential Organ Failure Assessment, and the North American consortium for the Study of End-stage Liver Disease (NACSELD) models.

The 3-month mortality was 58%, 58%, and 54% in cohort 1, 2, and 3, respectively. In cohort 1, respiratory failure, renal failure, international normalized ratio, total bilirubin, and neutrophil percentage were determinants of 3-month mortality, with odds ratios of 16.6, 3.3, 2.0, 1.1, and 1.03, respectively ($P < .05$). These parameters were incorporated into the decision tree model, yielding area under receiver operating characteristic (AUROC) of 0.804. The model had excellent reproducibility in the U.S. (AUROC 0.808) and Korea cohort (AUROC 0.809). The proposed model has the highest AUROC and best Youden index of 0.488 and greatest overall correctness of 75%, compared with other models evaluated.

The proposed model reliably predicts survival of advanced cirrhotics with infection in both Asian and U.S. populations.

Abbreviations: ACLF = acute-on-chronic liver failure, AFP = alpha fetal protein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CHE = cholinesterase, CLIF-SOFA = Chronic Liver Failure–Sequential Organ Failure Assessment, CTP = Child–Turcotte–Pugh, INR = international normalized ratio, MELD = model for end-stage liver disease, NACSELD = the North American consortium for the Study of End-stage Liver Disease, NEU% = neutrophil percentage, PALB = prealbumin, PBC = primary biliary cirrhosis, ROC = receiver operating characteristic, SBP = spontaneous bacterial peritonitis, sCr = serum creatinine, TBIL = total bilirubin, UTI = urinary tract infection, WBC = white blood cell.

Keywords: 3-month mortality, cirrhosis, infection, MELD score

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1. Introduction

Infection is a common cause of liver decompensation and death in patients with cirrhosis. In addition, infection is a precipitating factor for development of acute-on-chronic liver failure (ACLF) and extrahepatic organ failure in cirrhosis patients. Further, infection is one of the most common reasons for rehospitalization, increased health care costs, and impaired quality of life of patients with cirrhosis.^[1,2]

Cirrhotic patients have a nearly 5-fold greater risk of developing infection than the general population due to the cirrhosis-related immunodeficiency state.^[3–7] Approximately, 25% to 35% of cirrhotic patients have infections at admission or during hospitalization.^[8,9] The mortality of cirrhosis patients with infection is around 4-fold higher than cirrhosis patients without infection.^[1,10,11] Advanced cirrhosis patients with poor liver function have higher infection risk and mortality rates; this group of patients should therefore be targeted for prevention, early diagnosis, and treatment of infection. Delays in therapy and inappropriate therapy result in increased mortality.^[6,12,13] A reliable predictor of survival would be helpful for managing this patient population. The current most widely used clinical scoring systems, including the Child–Turcotte–Pugh (CTP) score, Model of End-Stage Liver Disease (MELD), and MELD-Na do not specifically focus on advanced cirrhotic patients with infection. In this study, we propose a new predictive model from variables, which are easy to obtain and efficient for prediction of outcome for this particular group of patients in China. As a secondary aim, the proposed model was externally validated in U.S. and Korean cohorts. Lastly, the predictive performance of the proposed model was compared with that of commonly used scoring systems, that is, CTP score, MELD, MELD-Na, Chronic Liver Failure–Sequential Organ Failure Assessment (CLIF-SOFA), and the North American Consortium for the Study of End-stage Liver Disease (NACSELD) model. Our predictive model should help physicians better manage patients and make appropriate individualized treatment plans based on the condition of each patient.

2. Methods

2.1. Patient cohorts

A total of 1819 cirrhosis patients (519 from China, 1015 from the U.S., and 285 from Korea) were screened for this study. The diagnosis of cirrhosis was made by liver histopathology, or a combination of laboratory biochemistry, radiologic, and endoscopic findings, if a liver biopsy result was not available.^[14] Patients with CTP C cirrhosis who were diagnosed with infection on admission (<48 hours) were included. Patients with malignancy or concomitant human immunodeficiency virus infection, or those who received liver transplantation before the study period were excluded. The research protocol was approved by the Ethics Committees of the Tianjin Third Central Hospital, the Mayo Clinic and Seoul St. Mary's Hospital.

After screening, 244 patients admitted to Tianjin Third Central Hospital, China, between January 2010 and April 2013 were included in the test cohort. Ninety-one patients admitted to Mayo Clinic, Rochester, MN, between January 2007 and December 2013, and 82 patients admitted to Seoul St. Mary's Hospital, Korea, between January 2011 and May 2014 served as validation cohorts.

2.2. Data collection

Baseline demographic characteristics, type of infection, and the presence of organ failure were retrospectively abstracted

from the medical record. Infections were classified as follows^[14–19]:

- (1) Spontaneous bacterial peritonitis (SBP): an absolute number of polymorphonuclear cells of $\geq 250/\text{mm}^3$ or positive bacteriological culture of ascitic fluid;
- (2) Pneumonia: at least 1 of the respiratory symptoms (i.e., cough, sputum production, dyspnea, pleuritic pain) in combination with one of the following: rales and/or crepitation on auscultation; at least 1 sign of infection (i.e., shivering, body temperature $>38^\circ\text{C}$ or $<36^\circ\text{C}$, or leucocyte count $>10,000/\text{mm}^3$ or $<4000/\text{mm}^3$) in the absence of antibiotics; presence of pulmonary infiltrate on radiologic imaging by chest X-ray or computed tomography (CT) scan; or positive bacteriological culture in sputum;
- (3) Enterocolitis infection: diarrhea with the presence of leukocytes in stool or positive stool culture for pathogens, including *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, pathogenic *Escherichia coli*, or a positive *Clostridium difficile* stool assay;
- (4) Urinary tract infection (UTI): >15 urine leukocytes/high power field with either positive gram stain or positive urine bacterial culture;
- (5) Skin/soft-tissue infection: cellulitis;
- (6) Empyema: an absolute number of polymorphonuclear cells $\geq 250/\text{mm}^3$ or positive bacterial culture in pleural fluid;
- (7) Other infections: infections not included above.

Diagnostic criteria for organ failure were as follows^[14,20–29]:

- (1) Acute on chronic liver failure: defined by the Canonic Study;
- (2) Renal failure: serum creatinine (sCr) $\geq 2\text{ mg/dL}$ or urine volume $< 0.5\text{ mL/kg/h}$ for 6 hours;
- (3) Respiratory failure: $pa\text{O}_2 < 60\text{ mm Hg}$ on room air O_2 or $pa\text{CO}_2 > 50\text{ mm Hg}$ on room air O_2 and/or requirement for mechanical ventilation;
- (4) Shock: use of dopamine, dobutamine, terlipressin, or mean arterial pressure $< 60\text{ mm Hg}$ despite adequate fluid resuscitation and cardiac output.

All patients were followed for 90 days. The primary outcome was death within 3 months after hospitalization.

2.3. Statistical analysis

Continuous variables were summarized as mean \pm standard deviation (SD) and compared using Student *t* test. Categorical variables were summarized as frequency (%) and compared using Pearson Chi-square or Fisher Exact test as appropriate. Predictors of 90-day mortality were determined using logistic regression. All variables with $P < .05$ in the univariate analysis were included in the multivariate logistic regression model, and the stepwise elimination method was used to identify independent predictors. These predictors, identified by multivariate logistic regression model, were further evaluated by decision tree method to determine the most reliable predictors of death and their optimal cutoff values.^[30–33] The patients were divided into 2 groups according to these defined predictors. Each subgroup was repeatedly assessed and divided according to this 2-choice branching method. Finally, a 90-day mortality prediction model was proposed using predictors identified by the decision tree analysis. Receiver operating characteristic (ROC) curves were constructed to assess sensitivity, specificity, and respective areas under the curves (AUCs) with 95% confidence interval (95% CI). The cut-off points were determined when sensitivity and

specificity reached the peak (The best Youden index). A log-rank test for Kaplan–Meier analysis and hazard ratio were used to statistically test short-term mortality. A *P* value <.05 was considered as statistically significant. All statistical analyses were performed using SPSS software version 13.0 (SPSS Inc., Chicago, IL), JMP 10 (SAS Institute Inc., Cary, NC), R software, and MedCalc (version 11.4.2.0).

3. Results

3.1. Patient characteristics

Demographics and baseline clinical characteristics of the 244 patients in the test cohort are summarized in Table 1. The

mean (\pm SD) age was 52.1 ± 11.6 years and 169 (69%) were male. The mean MELD score was 26 ± 8 . The 90-day mortality rate was 58%.

3.2. Infection characteristics

In the test cohort, 156 (64%) patients had a single infection site, 68 (28%) had 2 infection sites, and 20 (8%) had ≥ 3 infection sites on admission. The 3-month mortality rates were 56%, 56%, and 80% for those with 1, 2, and ≥ 3 infection sites, respectively. Pneumonia was the most frequent infection ($n=157$, 64%), followed by SBP ($n=105$, 43%) and infectious enterocolitis ($n=33$, 14%), with corresponding 3-month mortalities of 63%, 62%, and 52%, respectively.

Table 1
Baseline characteristics of the test cohort.

Variable	All patients (n=244)	Alive after 90 d (n=103)	Died within 90 d (n=141)	<i>P</i>
Age, y	52.1 \pm 11.6	51.1 \pm 10.9	52.8 \pm 12.1	.278
Gender				
Male, n (%)	169 (69%)	68 (66%)	101 (72%)	.348
Female, n (%)	75 (31%)	35 (34%)	40 (28%)	
Diabetes, n (%)	53 (22%)	29 (28%)	24 (17%)	.037
Acute on chronic liver failure, n (%)	181 (74%)	61 (59%)	120 (85%)	<.001
Second infection, n (%)	28 (11%)	8 (8%)	20 (14%)	.120
Etiology of chronic liver disease				
Hepatitis B, n (%)	90 (37%)	36 (35%)	54 (38%)	.593
Alcoholic, n (%)	77 (32%)	33 (32%)	44 (31%)	.890
Cryptogenic, n (%)	18 (7%)	6 (6%)	12 (9%)	.428
Hepatitis C, n (%)	16 (7%)	10 (10%)	6 (4%)	.089
Hepatitis B and alcoholic, n (%)	16 (7%)	7 (7%)	9 (6%)	.898
Autoimmune, n (%)	12 (5%)	5 (5%)	7 (5%)	.969
PBC, n (%)	8 (3%)	2 (2%)	6 (4%)	.523
Hepatitis C and alcoholic, n (%)	3 (1%)	2 (2%)	1 (1%)	.783
Hepatitis B and hepatitis C, n (%)	2 (1%)	1 (1%)	1 (1%)	1.000
PBC and alcoholic, n (%)	1 (0%)	1 (1%)	0 (0%)	.422
PBC and autoimmune, n (%)	1 (0%)	0 (0%)	1 (1%)	1.000
Vital signs and laboratory results on admission day (mean \pm SD)				
Temperature, $^{\circ}$ C	37.3 \pm 1.0	37.4 \pm 0.9	37.3 \pm 1.0	.302
Heart rate, beats/min	92 \pm 17	89 \pm 16	94 \pm 18	.033
WBC, $\times 10^3/\text{mm}^3$	9.8 \pm 6.3	8.1 \pm 4.8	11.0 \pm 6.9	<.001
NEU (%)	79 \pm 11	77 \pm 11	81 \pm 11	.002
Platelet, $\times 10^3/\text{mm}^3$	89.6 \pm 57.0	86.4 \pm 57.5	91.9 \pm 56.7	.457
Albumin, g/L	25.6 \pm 4.7	25.5 \pm 4.4	25.7 \pm 4.9	.691
Globulin, g/L	31.2 \pm 8.6	31.9 \pm 8.7	30.7 \pm 8.6	.284
ALT, U/L	219 \pm 490	175 \pm 420	251 \pm 535	.236
AST, U/L	256 \pm 608	146 \pm 230	339 \pm 770	.006
TBIL, mg/dL	11.6 \pm 9.3	8.5 \pm 7.7	13.9 \pm 9.8	<.001
CHE, U/L	2130.48 \pm 1076.67	2119.50 \pm 882.03	2138.78 \pm 1206.53	.890
PALB, mg/dL	3.73 \pm 2.95	3.76 \pm 2.75	3.70 \pm 3.10	.890
Glucose, mmol/L	6.8 \pm 4.3	7.4 \pm 5.4	6.3 \pm 3.3	.089
BUN, mmol/L	11.0 \pm 7.7	8.8 \pm 6.9	12.6 \pm 7.9	<.001
sCr, mg/dL	1.2 \pm 1.1	0.9 \pm 0.8	1.4 \pm 1.2	<.001
Sodium, mmol/L	131 \pm 7	132 \pm 7	131 \pm 7	.062
INR	2.6 \pm 1.2	2.1 \pm 0.6	2.9 \pm 1.5	<.001
AFP, ng/mL	43 \pm 107	42 \pm 97	43 \pm 114	.964
Value of each scoring system (mean \pm SD)				
MELD	26.20 \pm 8.16	22.36 \pm 5.91	29.01 \pm 8.44	<.001
MELD-Na	28.66 \pm 7.27	25.37 \pm 5.98	31.07 \pm 7.20	<.001
CTP	12.9 \pm 1.4	12.2 \pm 1.2	13.4 \pm 1.3	<.001
CLIF-SOFA	8.1 \pm 2.6	6.8 \pm 1.9	9.0 \pm 2.6	<.001
NACSELD	-0.91 \pm 1.19	-1.49 \pm 0.83	-0.49 \pm 1.25	<.001

Second infections were defined as an infection separate from and following the first infection during the same hospitalization and would be nosocomial in origin. [23]

AFP = alpha fetal protein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CHE = cholinesterase, CLIF-SOFA = Chronic Liver Failure–Sequential Organ Failure Assessment, CTP = Child–Turcotte–Pugh, INR = international normalized ratio, MELD = model for end-stage liver disease, NACSELD = the North American Consortium for the Study of End-stage Liver Disease, NEU% = neutrophil percentage, PALB = prealbumin, PBC = primary biliary cirrhosis, sCr = serum creatinine, TBIL = total bilirubin, WBC = white blood cell.

Table 2**Univariate and multivariate logistic regression analysis.**

Parameter	Univariate analysis				Multivariate analysis			
	Beta coefficient	Standard error	Odds ratios (95% CI)	P	Beta coefficient	Standard error	Odds ratios (95% CI)	P
Renal failure	1.63	0.38	5.11 (2.44–10.69)	< .001	1.20	0.43	3.34 (1.43–7.76)	.005
Respiratory failure	2.64	1.04	13.98 (1.83–106.87)	.01	2.81	1.10	16.61 (1.93–143.07)	.01
Pneumonia	0.55	0.27	1.73 (1.02–2.92)	.04				
Hepatic encephalopathy grade	0.31	0.09	1.37 (1.14–1.64)	.001				
ACLF	1.37	0.31	3.93 (2.14–7.23)	< .001				
Diabetes	-0.65	0.31	0.52 (0.28–0.97)	.04				
WBC	0.09	0.03	1.10 (1.04–1.15)	.001				
NEU%	0.04	0.01	1.04 (1.01–1.07)	.003	0.03	0.01	1.03 (1.00–1.06)	.03
AST	0.00	0.00	1.00 (1.00–1.00)	.03				
TBIL	0.07	0.02	1.07 (1.04–1.11)	< .001	0.08	0.02	1.08 (1.04–1.12)	< .001
BUN	0.08	0.02	1.08 (1.04–1.12)	< .001				
sCr	0.56	0.17	1.74 (1.25–2.43)	.001				
Heart rate	0.02	0.01	1.02 (1.00–1.03)	.04				
INR	0.82	0.20	2.27 (1.54–3.35)	< .001	0.68	0.23	1.97 (1.27–3.06)	.003

ACLF=acute-on-chronic liver failure, AST=aspartate aminotransferase, BUN=blood urea nitrogen, INR=international normalized ratio, NEU%=neutrophil percentage, sCr=serum creatinine, TBIL=total bilirubin, WBC=white blood cell.

3.3. Organ failure characteristics

One hundred seventy-five (72%) patients had no extrahepatic organ failure, 54 (22%) patients had 1 extrahepatic organ failure, and 15 (6%) patients had ≥ 2 extrahepatic organ failures, with corresponding 3-month mortality rates of 48%, 80%, and 93%, respectively. The most frequent extrahepatic organ failure was renal failure ($n=60$, 25%), followed by respiratory failure ($n=18$, 7%), and shock ($n=9$, 4%), resulting in 3-month mortalities of 83%, 94%, and 78%, respectively.

3.4. Univariate and multivariate logistic regression analysis of factors determining 3-month survival

Table 2 summarizes univariate and multivariate analysis of variables associated with 90-day mortality. By multivariate analysis, respiratory failure, renal failure, international normalized ratio (INR), total bilirubin (TBIL), and neutrophil percentage (NEU%) were significantly associated with death, with odds ratios (ORs) (95% CI) of 16.6 (1.9–143.1), 3.3 (1.4–7.8), 2.0 (1.3–3.1), 1.1 (1.0–1.1), and 1.03 (1.0–1.1), respectively.

3.5. Prognostic model for 3-month mortality by decision tree analysis

The results of the decision tree analysis are shown in Fig. 1. After decision tree analysis by R software, INR was selected as the first predictor, with a cutoff value of 3.0. The 3-month mortality rate was 90% for patients with $\text{INR} \geq 3.0$ versus 50% for patients with $\text{INR} < 3.0$. For patients with $\text{INR} < 3.0$, the next most important (second) predictor of death was respiratory failure, with a 3-month mortality rate of 92% for those with respiratory failure versus 47% for those without respiratory failure. For patients without respiratory failure, the third predictor was NEU%. The 3-month mortality rate was 54% for patients with higher NEU% ($\geq 71\%$) versus 17% in patients with lower NEU% ($< 71\%$). The fourth predictor for NEU% $< 71\%$ patients was TBIL, with a cutoff value of 7.2 mg/dL. The 3-month mortality rates were 40% for patients with $\text{TBIL} \geq 7.2$ mg/dL versus 0% in patients with $\text{TBIL} < 7.2$. For NEU% $\geq 71\%$ patients, TBIL also served as a fourth predictor, at a cutoff value of 9.3 mg/dL. The 3-month mortality rates were 67% in patients with TBIL

≥ 9.3 mg/dL versus 42% in patients with $\text{TBIL} < 9.3$ mg/dL. The fifth predictor for patients with $\text{TBIL} < 9.3$ mg/dL was renal failure. The 3-month mortality was 73% in those with renal failure versus 35% in patients without renal failure. This analysis identified 7 subgroups with 3-month mortality rates ranging from 0% to 92%.

3.6. Assess the accuracy of the 3-month mortality prognostic model

The discriminatory values and predictive accuracies of the proposed decision tree model and MELD, MELD-Na, CTP, and CLIF-SOFA score, and NACSELD study model^[19] are listed in Table 3. According to the analysis of the AUROC curves, the decision tree model provided the best discriminatory power (AUROC 0.804) and was significantly more predictive than the MELD-Na score (AUROC 0.734). Among the 6 scoring systems evaluated, the decision tree model had the highest overall correctness of 75% and the best Youden index of 0.488.

For more convenient use in clinical practice, the patients were classified into low, intermediate, and high-risk groups (Table 4 and Fig. 2). On the basis of AUROC curves and hazard ratio analysis, the proposed 3 groups were more predictive of mortality than the 3 groups of MELD score classified by tertiles, that is, $\text{MELD} < 23$, ≥ 23 to < 28 , and ≥ 28 [AUROC: 0.771 vs 0.713 in China cohort (Fig. 3A–C)].

3.7. External validation of the proposed prognostic model

Demographics of the 91 patients in the first validation cohort and 82 patients in the second validation cohort are summarized in Table 5. For the first validation cohort, the overall 3-month mortality rate was 58%. SBP and UTI were the most frequent infections ($n=21$ each, with mortality rates of 67% and 57%, respectively). The patients were subdivided according to the prognostic model and subclassified into the low, intermediate, and high-risk subgroups (Fig. 4A–C), which had 3-month mortalities of 17%, 64%, and 84%, respectively ($P < .001$), compared with the 3 subgroups classified by MELD score, which had 3-month mortalities of 23%, 56%, and 79%. The decision tree model was more predictive of death than the MELD score

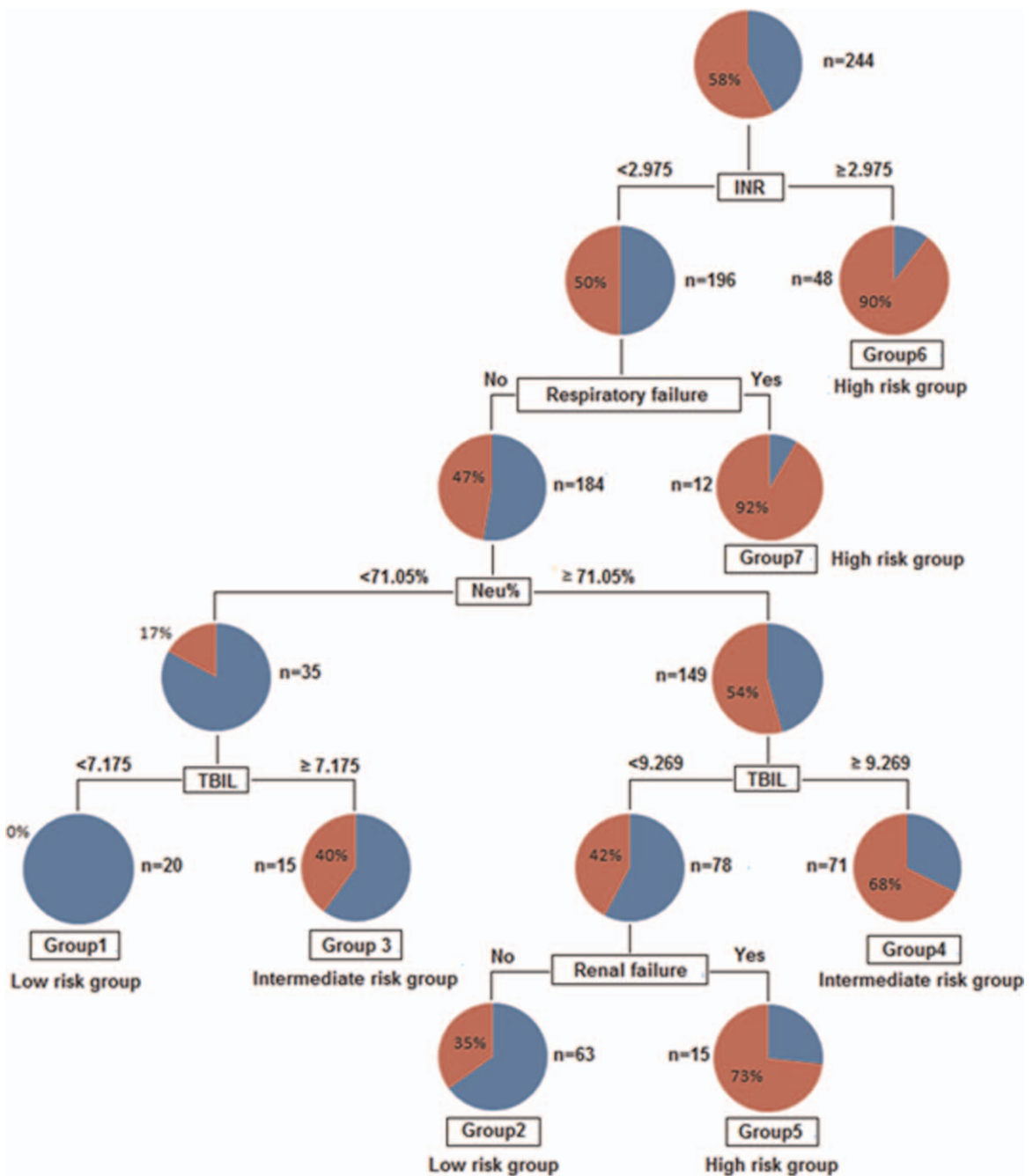


Figure 1. The decision tree model of 3-month mortality for advanced cirrhosis patients with concomitant infection. Boxes show that the factors and cutoff values differentiate groups of patients. Pie charts showed the 3-month mortality rates of each group after differentiation. The classified groups are numbered from 1 to 7.

Table 3
Prediction of 3-month mortality for infected patients with advanced cirrhosis.

Prognostic model/score	Cut-off point	AUROC (95% CI)	P	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)	Youden index
Decision tree		0.804 (0.748–0.859)	Reference	80	69	77	71	75	0.488
MELD	>24	0.744 (0.682–0.805)	.05	72	66	74	63	69	0.380
MELD-Na	>28	0.734 (0.671–0.797)	.03	67	69	74	60	68	0.360
CTP	>12	0.752 (0.690–0.814)	.2	76	66	75	66	71	0.416
CLIF-SOFA	>8	0.747 (0.686–0.807)	.07	49	83	80	54	64	0.323
NACSELD	>−1.053	0.741 (0.680–0.802)	.07	66	74	78	61	69	0.395

CLIF-SOFA = Chronic Liver Failure–Sequential Organ Failure Assessment, CTP = Child-Turcotte-Pugh, MELD = model for end-stage liver disease, NACSELD = the North American Consortium for the Study of End-stage Liver Disease, NPV = negative predictive value, PPV = positive predict value.

Table 4

Constitution of low-risk group, intermediate-risk group, and high-risk groups.

Group	3-mo mortality (%)	Including decision tree subgroup
Low-risk group	0–35	Lower INR level (<3.0), without respiratory failure, with lower NEU% (<71%) and lower TBIL level (<7.2 mg/dL); Lower INR level (<3.0), without respiratory failure, with higher NEU% (≥71%), lower TBIL level (<9.3 mg/dL) and without renal failure
Intermediate-risk group	40–68	Lower INR level (<3.0), without respiratory failure, with lower NEU% (<71%) and higher TBIL level (≥7.2 mg/dL); Lower INR level (<3.0), without respiratory failure, with higher NEU% (≥71%) and higher TBIL level (≥9.3 mg/dL)
High-risk group	73–92	Lower INR level (<3.0), without respiratory failure, with higher NEU% (≥71%), lower TBIL level (<9.3 mg/dL) and renal failure; Higher INR level (≥3.0) Lower INR level (<3.0) with respiratory failure

INR = international normalized ratio, NEU% = neutrophil percentage, TBIL = total bilirubin.

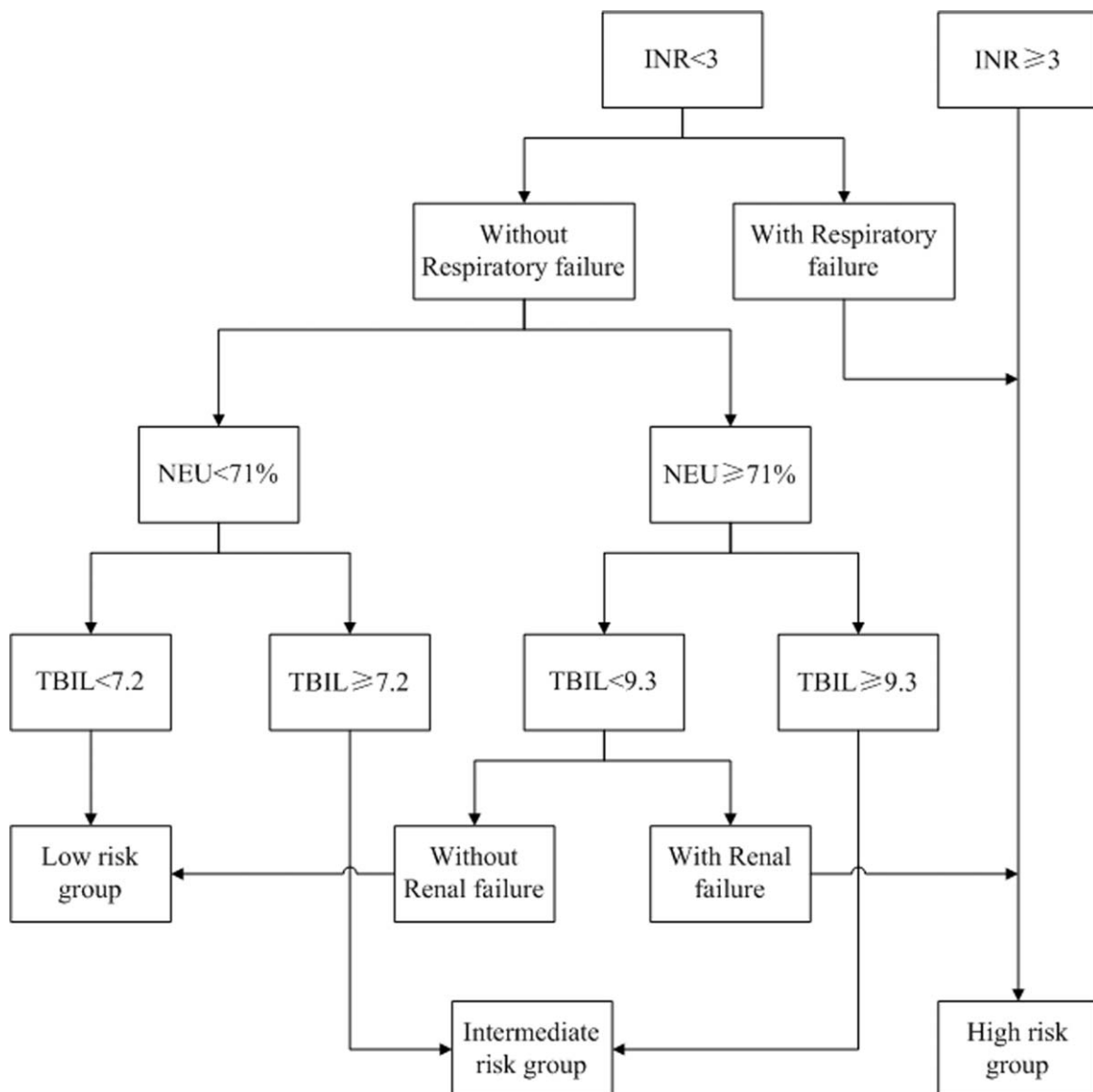


Figure 2. The patients were classified into 3 groups as low, intermediate, and high-risk groups according to the decision tree model.

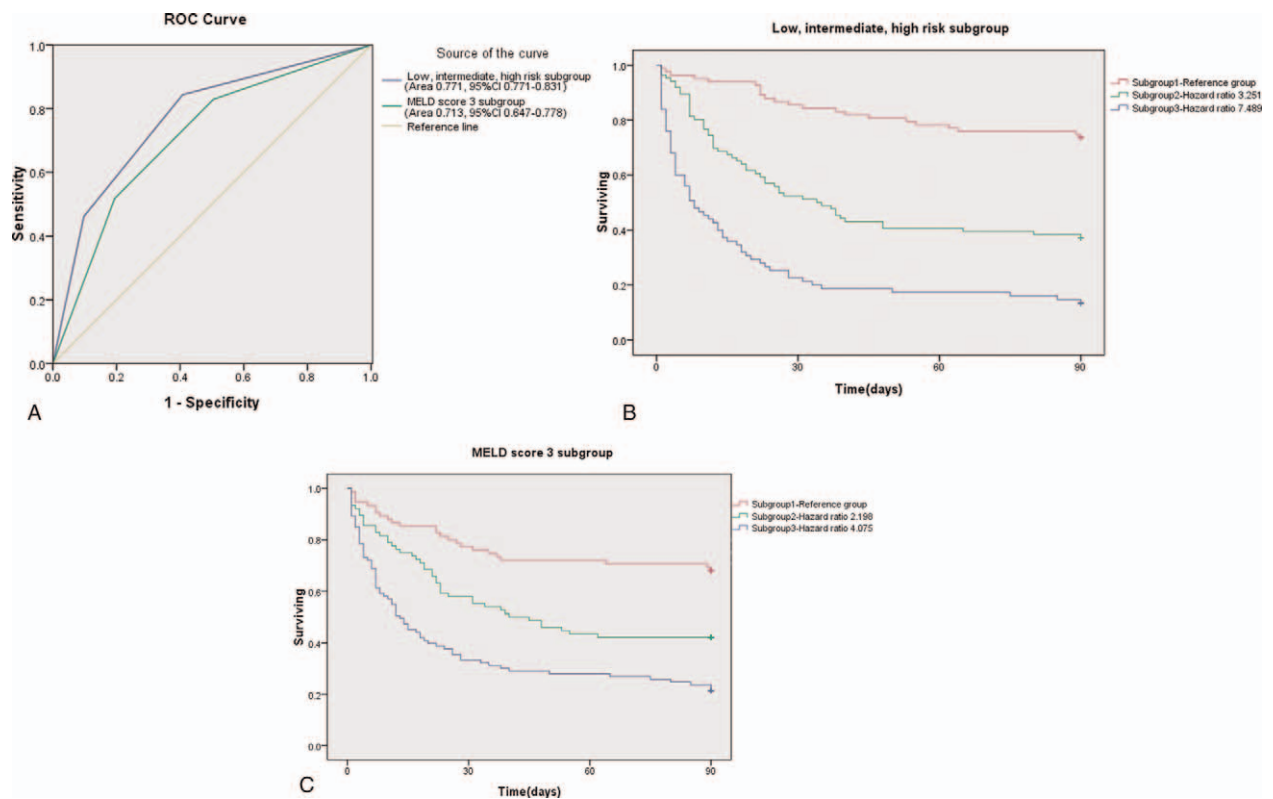


Figure 3. Three-month mortality prediction outcomes of decision tree model and MELD score for advanced cirrhosis patients with infection. (A–C) ROC curve, Kaplan–Meier curve, and hazard ratio for decision tree model and MELD score in China cohort.

model, with an AUROC (95% CI) of 0.808 (0.706–0.910) versus 0.756 (0.643–0.868).

For the second validation cohort, the overall 3-month mortality rate was 54%. SBP was the most frequent infection

(n=24, mortality rate 67%). According to the proposed prognostic model, 3-month mortalities were 21%, 52%, and 87% in the low, intermediate, and high-risk subgroups, respectively ($P < .001$). When using classified MELD score

Table 5

Baseline characteristics of validation cohort.

Variable	Mayo Clinic (n=91)	Seoul St. Mary's Hospital (n=82)
Gender		
Male, N (%)	48 (53%)	54 (66%)
Female, N (%)	43 (47%)	28 (34%)
Age, y	57.5 ± 11.4	58.3 ± 12.7
Etiology		
Alcoholic, N (%)	27 (30%)	Hepatitis B, N (%) 33 (40%)
Hepatitis C and alcohol, N (%)	13 (14%)	Alcohol, N (%) 25 (30%)
NAFLD, N (%)	11 (12%)	Cryptogenic, N (%) 7 (9%)
Hepatitis C, N (%)	9 (10%)	Hepatitis C, N (%) 6 (7%)
PSC, N (%)	5 (5%)	Hepatitis B and alcohol, N (%) 5 (6%)
PBC, N (%)	4 (4%)	Hepatitis C and alcohol, N (%) 2 (2%)
Autoimmune, N (%)	3 (3%)	PBC, N (%) 1 (1%)
Alpha-1 antitrypsin deficiency and NAFLD, N (%)	3 (3%)	Autoimmune, N (%) 1 (1%)
Cryptogenic, N (%)	3 (3%)	NAFLD, N (%) 1 (1%)
Others, N (%)	13 (14%)	Others, N (%) 1 (1%)
The test results on admission (mean ± SD)		
NEU (%)	74 ± 17	77 ± 13
Albumin, g/L	27.9 ± 6.2	25.5 ± 4.4
TBIL, mg/dL	13.3 ± 12.2	12.2 ± 10.9
sCr, mg/dL	2.3 ± 1.6	1.9 ± 1.3
Sodium, mmol/L	132 ± 6	130 ± 6
INR	2.5 ± 1.2	2.5 ± 1.1
MELD score	30.25 ± 9.42	27.90 ± 11.50

INR=international normalized ratio; MELD=model for end-stage liver disease; NEU%=neutrophil percentage; sCr=serum creatinine; TBIL=total bilirubin.

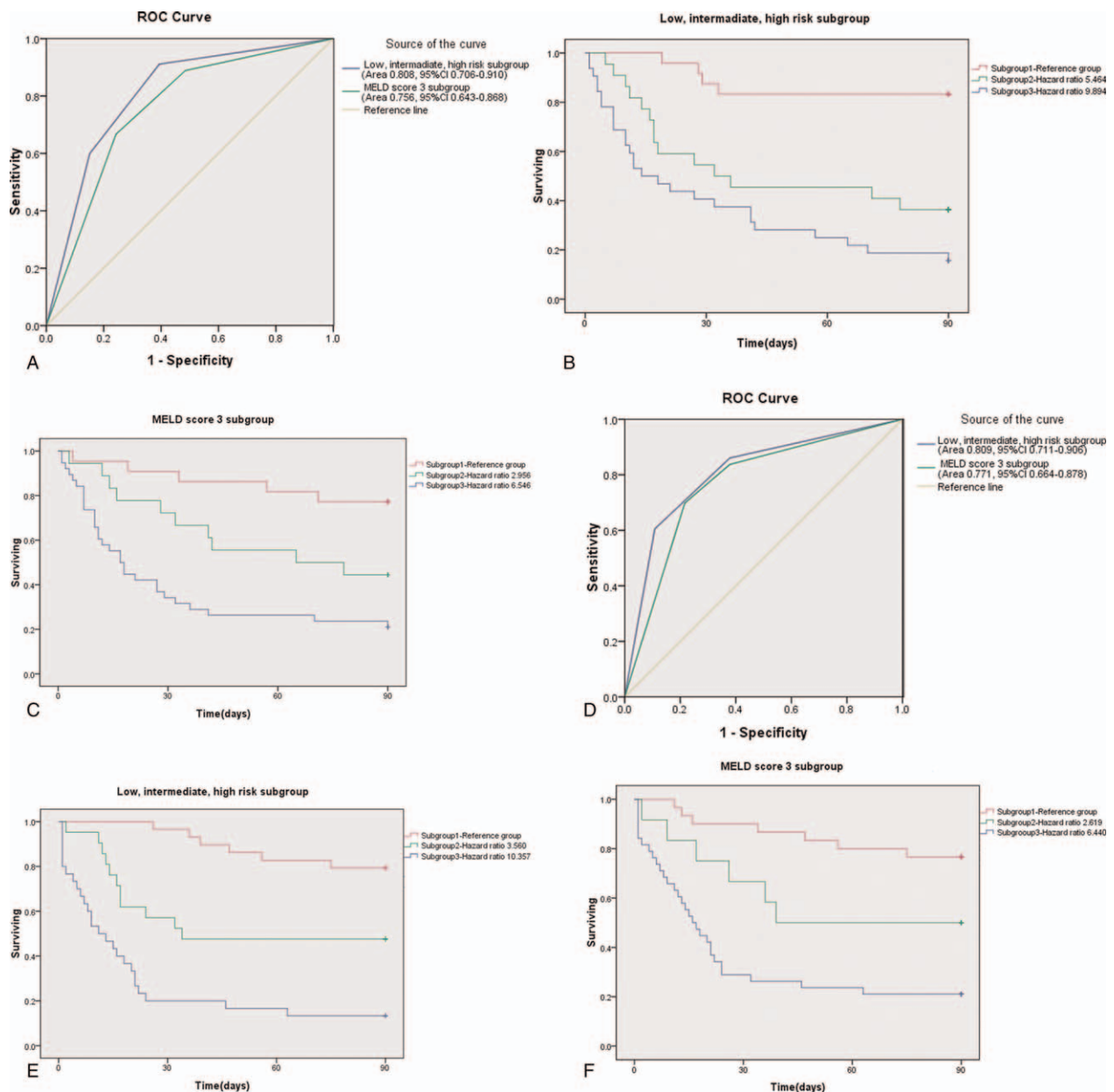


Figure 4. Three-month mortality prediction outcomes of decision tree model and MELD score for advanced cirrhosis patients with infection. (A–C) ROC curve, Kaplan–Meier curve, and hazard ratio for decision tree model and MELD score in U.S. validation cohort. (D–F) ROC curve, Kaplan–Meier curve, and hazard ratio for decision tree model and MELD score in Korea validation cohort.

model, patients had 3-month mortalities of 23%, 50%, and 79%, respectively. Consistent with the finding in the first validation cohort, the decision tree model was more predictive of death than the MELD score model, with an AUROC (95% CI) of 0.809 (0.711–0.906) versus 0.771 (0.664–0.878) (Fig. 4D–F).

4. Discussion

Patients with advanced cirrhosis are at a high risk of infection, which is commonly complicated by liver and/or extrahepatic organ failure(s), resulting in short-term death.^[1,2,34,35] In this multicenter study, the overall 3-month mortality rate of this group of advanced cirrhosis patients with infection was almost 60%, which was higher than that found in a meta-analysis reporting a 44% 3-month mortality rate of all cirrhosis patients

enrolled between 1978 and 2009 who were admitted with infection.^[11] Thus, this is a major life-threatening health problem for patients with advanced liver cirrhosis. Early diagnosis and appropriate treatment are critical for improving outcomes. This investigation identified respiratory failure, renal failure, INR, TBIL, and NEU% as independent predictors of 3-month mortality. A decision tree model built using these independent predictors was proved to have excellent performance for predicting 3-month mortality and was applicable for patients from different areas with different etiologies. This system subclassified patients into low, intermediate, and high-risk subgroups; the 3-month mortality of the low-risk subgroup was around 20%, while the 3-month mortality of the high-risk subgroup was close to 90%. The system had better discriminatory ability than the MELD score, MELD-Na score, CTP score,

CLIF-SOFA score, and NACSELD study models and may promote the more rational use of medical resources.

This study found some characteristics of infection for advanced cirrhosis patients. Approximately 36% of the patients in the test cohort had multiple infection sites. For patients who had more than 2 infection sites, the 3-month mortality rates significantly increased by over 20% compared with those with 1 or 2 infection sites. SBP and pneumonia were the most frequent infections in this multicenter study. Our findings were similar to a report from the NACSELD study, which included 18 referral centers across the US and Canada.^[14] In the present study, patients with pneumonia or SBP infections had higher 3-month mortality than those with other types of infections, and also had higher mortality rates of 62% to 75% than a previous meta-analysis, which showed mortality rates of 37% to 43% for all cirrhosis patients admitted with infections.^[11] Neither the infection type nor the number of infection site was independent risk factor for 3-month mortality. Nineteen percent of patients had virus coinfection, which was respiratory system infection. Sixteen percent of patients had fungus coinfection. The virus coinfection was not associated with 3-month mortality.

Presumably, the higher mortality rates in the more advanced cirrhosis patients in this study reflect their more severe level of liver dysfunction, which is more often complicated by other extrahepatic organ failure(s).^[1,2] In this study, renal failure and respiratory failure were independent risk factors for 3-month mortality. Many studies have shown that bacterial infections induce a profound pro-inflammatory response of the host immune system that can precipitate organ failure.^[36] The most frequent organ failure was renal failure. Bacterial infections are well-known triggers of kidney failure in cirrhosis, primarily due to the induction of the host inflammatory response and hemodynamic alterations.^[1,37-39] Many studies have shown that renal failure is a major determinant of mortality in cirrhotic patients.^[11,40,41] Consistent with the other studies, renal failure was an independent risk factor for 3-month mortality in this study. Of the patients who developed renal failure, the 3-month mortality was 81% to 84%. Respiratory failure was another independent predictor of mortality; indeed, it was the most lethal organ failure complication, being associated with 3-month mortality rates of 94% to 100%. The NACSELD study also showed that patients with cirrhosis complicated with respiratory failure had the highest 30-day mortality of any organ failure of around 61%.^[14] However, unlike the situation with renal failure, for which a number of studies have explored the underlying mechanisms of interaction with advanced cirrhosis, there are relatively few studies focusing on the mechanisms underlying respiratory failure and its progression in cirrhotic patients. This is a research area of unmet need.

TBIL and INR are both measures of liver function and components of the MELD score. As expected, multivariate logistic analysis showed that TBIL and INR were also determinants of 3-month mortality. We found that NEU% was also a determinant of 3-month mortality in this special population, with higher levels of NEU% associated with higher mortality rates. Similar to the NACSELD study,^[14] after multivariate analysis, NEU% was independent predictor for 3-month mortality. In the inflammatory process, neutrophils are rapidly recruited to sites of acute inflammation; neutrophils and the innate immune system, in particular, play a central role in the inflammatory pathology and multiple organ dysfunction.^[42-44]

We also tested the component parameters of the NACSELD study model for their utility in this model^[19]; heart rate and

second infection were statistically significant in the univariate logistic analysis, but not independent predictors for 3-month mortality in the multivariate analysis. This difference is presumably due to the difference in the study populations. In this study, the patients all had advanced cirrhosis, CTP C grade, and MELD scores around 30, compared with the broader distribution of the NACSELD study patients, with CTP grades A-C and a mean MELD of 20.

The final decision tree model included INR, respiratory failure, NEU%, TBIL, and renal failure as independent predictors. The model efficiently classified patients into low, intermediate, and high-risk subgroups. The 3-month mortality in the high-risk subgroup was almost 90%, compared with a 3-month mortality of only around 20% in the low-risk subgroup. The predictive accuracy of the model was superior to MELD, CTP, MELD-Na, CLIF-SOFA, and the NACSELD study model for advanced cirrhotic patients with infection and had the best Youden index and overall accuracy of prediction. Moreover, in the present study, we also validated the model in both an Asian and a western cohort. Overall, the results showed excellent reproducibility, suggesting that the model is generalizable to patients with similar conditions from different geographic regions. The model is readily obtained from routine physical examination and laboratory testing, and is thus available even in lower resource settings.

Although the study results were encouraging, this study still had several potential limitations. First, this was a retrospective study and the conclusions will need to be further verified by prospective studies. Second, because of the relatively small number of CTP grade C patients presenting with infection at each medical center, the predictive accuracy of the decision tree model may be limited.

In conclusion, patients with advanced cirrhosis and infection were more vulnerable to liver and/or extrahepatic organ failure with resultant high short-term mortality. SBP and pneumonia were the most frequent infections and were associated with higher short-term mortality than infections at other sites. The INR, respiratory failure, NEU%, TBIL, and renal failure all contributed independently to a model that achieved excellent discrimination of patients into low, intermediate, and high-risk subgroup. The accuracy and reproducibility of the model were validated at 2 different medical centers and this model may prove useful for physicians taking care of these patients to identify those patients at highest risk and help reduce mortality rates.

Author contributions

Ying Li, Roongruedee Chaiteerakij, Jung Hyun Kwon, and Jeong Won Jang were of the same contribution to this article (cofirst author). The work included study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content and statistical analysis.

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Stephen Cha worked on statistical analysis.

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