JOURNAL OF HEPATOLOGY
The Home of Liver Research
EASL

RESEARCH ARTICLE | ARTICLES IN PRESS

Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure

Jiaqi Li † • Xi Liang † • Shaoli You † • ... Shaojie Xin • Jun Li •

on behalf of the Chinese Group on the Study of Severe Hepatitis B (COSSH) • Show all authors • Show footnotes

Open Access • Published: June 03, 2021 • DOI: https://doi.org/10.1016/j.jhep.2021.05.026

SEPTIEMBRE 2021

INTRODUCTION

- *Early determination of prognosis* is very important in patients with HBV-ACLF, as it can be used to guide clinical management and to decrease the high short-term mortality rate.
- The *MELD and the MELD-Na scores* have been widely used to predict the outcome of end-stage liver disease.
- Recently, 2 large prospective multicentre cohorts of ACLF, the CANONIC study and the COSSH study, indicated that ACLF has *regional phenotypic specificities* due to the disease aetiology and precipitants.
- The aim of this study was to develop a *new simplified prognostic score* to accurately predict outcomes in patients with *HBV-ACLF* (and replace CLIF-C, ACLF (CLIFC ACLF) and the COSSH-ACLF scores.

PATIENTS-METHODS

ACFL DEFINITIC … d chronic liver disease, r… cute deterioration o… CLF comprises 3 gr… B.

PATIENTS:

- The conditio…
  - Patients … *owing precipito…* alopathy (HE), bac…
- *All patients …* …A-positive pati…

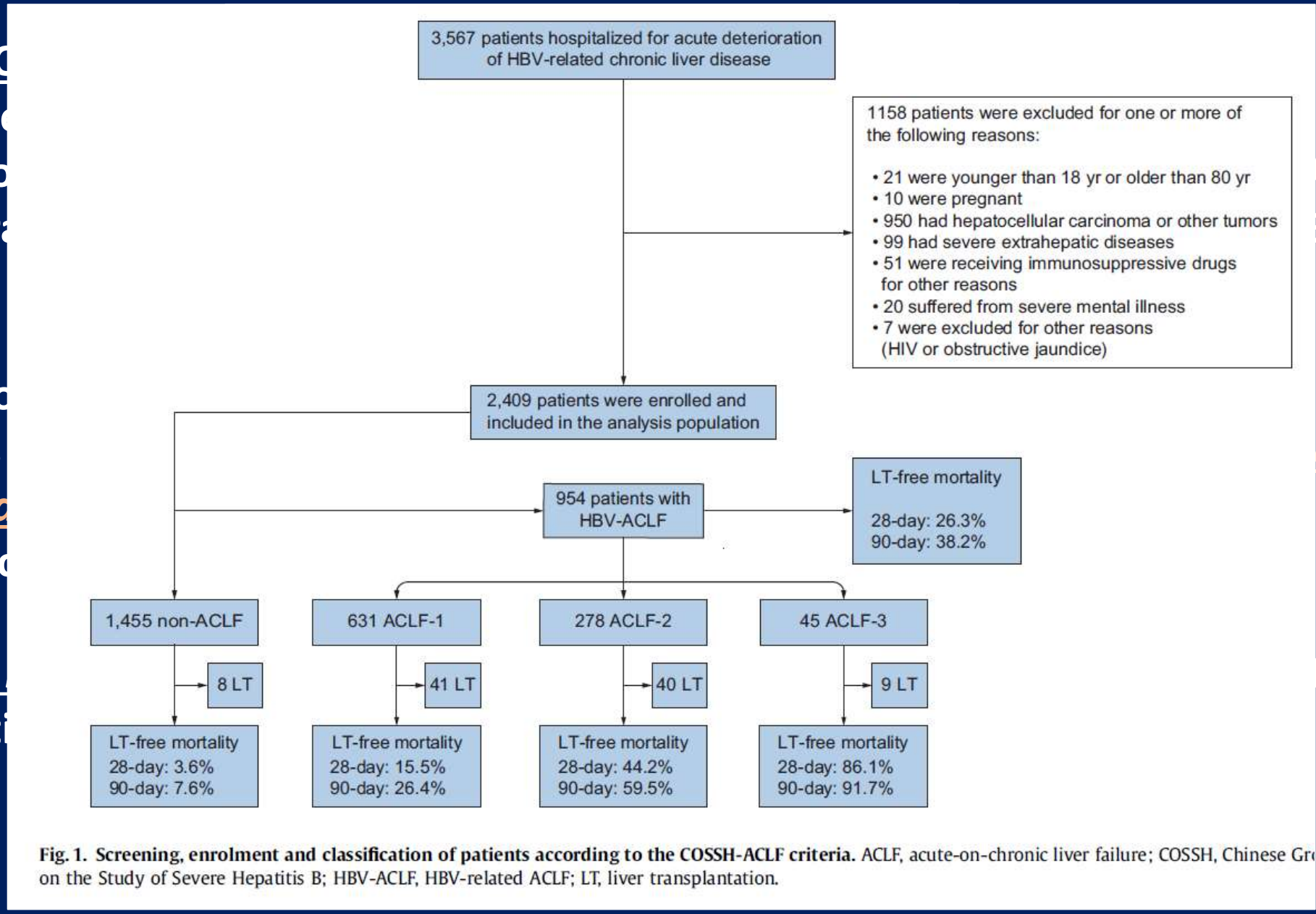

Fig. 1. Screening, enrolment and classification of patients according to the COSSH-ACLF criteria. ACLF, acute-on-chronic liver failure; COSSH, Chinese Gr… on the Study of Severe Hepatitis B; HBV-ACLF, HBV-related ACLF; LT, liver transplantation.

RESULTADOS

Table 1. Patient characteristics at enrolment.

Characteristic	Non-ACLF (n = 1,455)	ACLF (n = 954)	p^a value	ACLF-1 (n = 631)	ACLF-2 (n = 278)	ACLF-3 (n = 45)	p^b value
Male	1,180 (81.1%)	837 (87.7%)	<0.001	566 (89.7%)	233 (83.8%)	38 (84.4%)	0.035
Age (years)	49 ± 12	48 ± 12	0.098	48 ± 12	49 ± 12	49 ± 10	0.528
MAP (mmHg)	89 ± 88	89 ± 89	0.360	88 ± 88	91 ± 90	86 ± 86	0.070
Complications							
GIH	184 (12.6%)	54 (5.7%)	<0.001	31 (4.9%)	16 (5.8%)	7 (15.6%)	0.012
Ascites	795 (54.6%)	543 (56.9%)	0.271	342 (54.2%)	177 (63.7%)	24 (53.3%)	0.026
HE	52 (3.6%)	128 (13.4%)	<0.001	49 (7.8%)	50 (18.0%)	29 (64.4%)	<0.001
BI	332 (22.8%)	357 (37.4%)	<0.001	211 (33.4%)	127 (45.7%)	19 (42.2%)	0.002
HBV DNA level (IU/ml)			<0.001				0.386
$\leq 2\times10^2$	405 (27.8%)	145 (15.2%)		92 (14.6%)	41 (14.7%)	12 (26.7%)	
$2\times10^2 - 2\times10^6$	761 (52.3%)	559 (58.6%)		376 (59.6%)	161 (57.9%)	22 (48.9%)	
$>2\times10^6$	289 (19.9%)	250 (26.2%)		163 (25.8%)	76 (27.3%)	11 (24.4%)	
Organ failures							
Liver	212 (14.6%)	932 (97.7%)	<0.001	613 (97.1%)	274 (98.6%)	45 (100.0%)	0.243
Kidney	0	57 (6.0%)	<0.001	15 (3.4%)	21 (7.6%)	21 (46.7%)	<0.001
Coagulation	28 (1.9%)	289 (30.3%)	<0.001	2 (0.3%)	244 (87.8%)	43 (95.6%)	<0.001
Cerebral	12 (0.8%)	30 (3.1%)	<0.001	0	5 (1.8%)	25 (55.6%)	<0.001
Lungs	6 (0.4%)	13 (1.4%)	0.010	0	10 (3.6%)	3 (6.7%)	<0.001
Circulation	24 (1.6%)	7 (0.7%)	0.051	1 (0.2%)	2 (0.7%)	4 (8.9%)	<0.001
HE grade I or II	40 (2.7%)	98 (10.3%)	<0.001	49 (7.8%)	45 (16.2%)	4 (8.9%)	0.001
Renal dysfunction	15 (1.0%)	32 (3.4%)	<0.001	16 (2.5%)	14 (5.0%)	2 (4.4%)	0.143
1.5≤INR<2.5	433 (29.8%)	645 (67.6%)	<0.001	612 (97.0%)	31 (11.2%)	2 (4.4%)	<0.001
Severity scores							
COSSH-ACLFs	4.7 (4.4–5.1)	6.1 (5.6–6.8)	<0.001	5.8 (5.4–6.2)	6.9 (6.4–7.4)	8.3 (7.8–9.1)	<0.001
CLIF-C ACLFs	31.4 (27.2–36.0)	41.3 (36.9–46.2)	<0.001	38.9 (34.7–42.8)	45.3 (41.7–50.5)	53.4 (51.3–60.1)	<0.001
MELDs	13.1 (8.7–16.6)	23.4 (20.6–27.2)	<0.001	21.7 (19.9–23.7)	27.5 (25.1–30.6)	37.1 (29.6–41.9)	<0.001
MELD-Nas	14.7 (10.0–18.5)	24.8 (22.1–28.5)	<0.001	23.1 (21.1–25.4)	28.8 (26.1–32.2)	37.6 (30.0–41.8)	<0.001
LT-free mortality							
28-day	52 (3.6%)	232 (26.3%)	<0.001	94 (15.5%)	107 (44.2%)	31 (86.1%)	<0.001
90-day	110 (7.6%)	330 (38.2%)	<0.001	156 (26.4%)	141 (59.5%)	33 (91.7%)	<0.001

RESULTADOS

Characteristic	Non-ACLF (n = 1,455)	ACLF (n = 954)	p^a value	ACLF-1 (n = 631)	ACLF-2 (n = 278)	ACLF-3 (n = 45)	p^b value
Laboratory data							
Alb (g/L)	31.0 (27.0–35.3)	31.0 (28.2–33.9)	0.262	31.0 (28.3–33.8)	30.9 (27.8–34.0)	31.0 (28.6–34.1)	0.968
ALT (U/L)	68.0 (28.8–284.0)	263.0 (97.0–651.0)	<0.001	237.0 (89.0–544.0)	391.0 (121.8–873.0)	200.5 (88.3–719.8)	<0.001
AST (U/L)	85.0 (43.0–204.0)	200.0 (98.0–404.5)	<0.001	177.0 (92.0–351.0)	279.0 (122.0–538.5)	210.0 (112.5–399.0)	<0.001
ALP (U/L)	119.0 (86.0–159.0)	142.0 (116.0–177.0)	<0.001	140.0 (114.0–175.0)	149.0 (121.5–185.5)	132.0 (103.5–154.5)	0.013
TBA (μmol/L)	74.6 (23.2–171.0)	194.0 (145.4–240.8)	<0.001	190.0 (144.0–237.0)	199.2 (143.9–247.3)	205.0 (164.5–247.2)	0.186
TB (μmol/L)	89.0 (24.0–152.0)	341.0 (262.2–415.1)	<0.001	326.8 (251.2–403.9)	355.1 (278.0–429.7)	408.7 (321.0–503.6)	<0.001
GGT (U/L)	85.0 (38.0–154.0)	84.0 (58.0–128.0)	0.036	87.0 (59.0–130.0)	84.0 (54.0–125.0)	62.0 (40.0–93.5)	0.004
Cr (μmol/L)	69.0 (60.0–80.0)	68.0 (58.0–84.0)	0.596	68.0 (58.0–81.0)	67.1 (56.7–86.9)	150.0 (72.0–244.5)	<0.001
Serum urea (mmol/L)	4.7 (3.5–6.5)	4.1 (3.0–6.3)	<0.001	4.0 (3.1–5.8)	3.9 (2.7–6.9)	9.2 (3.7–16.7)	<0.001
TG (mmol/L)	1.1 (0.7–1.8)	1.2 (1.0–1.6)	<0.001	1.4 (1.1–1.8)	1.1 (0.8–1.3)	1.0 (0.8–1.1)	<0.001
Tch (mmol/L)	2.9 (2.3–3.6)	2.1 (1.6–2.7)	<0.001	2.3 (1.8–2.8)	1.9 (1.4–2.4)	1.5 (1.0–1.9)	<0.001
HDL-C (mmol/L)	0.6 (0.3–0.9)	0.2 (0.1–0.3)	<0.001	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.001
LDL-C (mmol/L)	1.6 (1.1–2.3)	1.1 (0.6–1.6)	<0.001	1.1 (0.5–1.7)	1.1 (0.6–1.5)	0.9 (0.4–1.3)	0.297
Glu (mmol/L)	4.9 (4.3–6.0)	4.5 (3.5–5.8)	<0.001	4.5 (3.7–5.8)	4.2 (3.2–5.9)	5.5 (3.5–7.2)	0.033
K (mmol/L)	4.0 (3.6–4.2)	4.1 (3.7–4.5)	<0.001	4.1 (3.7–4.4)	4.1 (3.7–4.5)	4.6 (4.1–5.0)	<0.001
Na (mmol/L)	138.0 (136.0–140.0)	137.0 (134.0–139.0)	<0.001	137.0 (134.9–139.0)	137.0 (134.0–139.0)	135.0 (133.0–139.5)	0.141
WBC (10^9/L)	4.6 (3.3–6.3)	6.7 (5.1–9.3)	<0.001	6.3 (4.8–8.6)	7.5 (5.7–10.0)	10.3 (7.3–13.4)	<0.001
Neutrophil (10^9/L)	2.8 (1.8–4.0)	4.5 (3.3–6.8)	<0.001	4.2 (3.1–5.9)	5.2 (3.7–7.9)	7.8 (5.4–11.4)	<0.001
Lymphocyte (10^9/L)	1.1 (0.7–1.6)	1.2 (0.8–1.6)	0.156	1.2 (0.8–1.6)	1.1 (0.8–1.5)	1.1 (0.7–1.6)	0.457
NLR	2.4 (1.6–3.9)	4.0 (2.6–6.6)	<0.001	3.6 (2.4–5.6)	5.0 (2.9–8.1)	7.6 (4.6–13.2)	<0.001
Hs-CRP (mg/L)	8.3 (4.0–14.8)	11.6 (8.0–17.2)	<0.001	11.8 (8.1–17.4)	11.0 (7.6–16.6)	10.7 (6.9–14.2)	0.351
Haemoglobin (g/L)	122.0 (101.0–138.0)	126.0 (112.0–139.0)	<0.001	127.0 (114.0–138.0)	126.0 (110.8–140.3)	115.0 (102.5–136.5)	0.087
Haematocrit (%)	35.8 (29.7–40.5)	36.2 (32.0–40.1)	0.026	36.2 (32.5–39.8)	36.5 (31.4–40.8)	32.0 (29.7–39.1)	0.053
PLT (10^9/L)	90.0 (58.0–142.0)	99.5 (68.8–139.3)	0.011	100.0 (66.0–137.0)	100.0 (70.0–153.5)	98.0 (67.0–152.0)	0.471
INR	1.3 (1.2–1.5)	2.0 (1.7–2.6)	<0.001	1.8 (1.6–2.1)	2.8 (2.6–3.2)	3.2 (2.8–4.1)	<0.001
Fib (g/L)	1.8 (1.3–2.4)	1.4 (1.1–1.7)	<0.001	1.5 (1.2–1.8)	1.2 (0.9–1.5)	0.9 (0.6–1.2)	<0.001
PT (s)	15.3 (13.7–17.3)	23.1 (19.2–28.8)	<0.001	20.5 (18.3–23.5)	31.1 (28.5–35.1)	35.6 (32.1–43.1)	<0.001
D dimer (ug/L)	503 (3–2042)	1,076 (5–3018)	<0.001	923 (5–2540)	1,336 (4–3624)	4,173 (1,639–6807)	<0.001
AFP (ng/ml)	21 (4–131)	79 (23–230)	<0.001	109 (34–270)	43 (15–151)	40 (9–78)	<0.001
Ferritin (ng/ml)	504 (106–1532)	2,537 (1,316–4198)	<0.001	2,169 (1,193–3635)	3,219 (1,694–5517)	3,548 (1,794–4749)	<0.001

NUEVO SCORE PRONÓSTICO

The new prognostic score for patients with HBV-ACLF fitted by multivariate competing risk regression was calculated using the following *formula*:

1.649 × ln(INR) + 0.457 × HE score (HE grade: 0/1, 1-2/2 and 3-4/3) + 0.425 × ln(neutrophil) (109/L) + 0.396 × ln(TB) (umol/L) + 0.576 × ln(serum urea) (mmol/L) + 0.033 × age.

COSSH-ACLF II score

RESULTADOS

A

The C-index of five scores for predicting 28-/90-day mortality

Model	COSSH-ACLF IIs C-index (95% CI)	COSSH-ACLFs C-index (95% CI)	CLIF-C ACLFs C-index (95% CI)	MELDs C-index (95% CI)	MELD-Nas C-index (95% CI)
Derivation group					
28-day mortality	0.826 (0.800-0.852)	0.793 (0.765-0.822)	0.792 (0.764-0.821)	0.731 (0.697-0.765)	0.730 (0.694-0.767)
*p value		<0.001	<0.001	<0.001	<0.001
90-day mortality	0.809 (0.786-0.833)	0.784 (0.759-0.809)	0.770 (0.745-0.796)	0.727 (0.698-0.757)	0.726 (0.695-0.757)
*p value		0.003	<0.001	<0.001	<0.001
Validation group					
28-day mortality	0.895 (0.860-0.931)	0.880 (0.829-0.931)	0.857 (0.803-0.910)	0.767 (0.683-0.851)	0.785 (0.686-0.885)
*p value		0.474	0.063	<0.001	0.004
90-day mortality	0.835 (0.788-0.884)	0.828 (0.775-0.881)	0.800 (0.745-0.856)	0.738 (0.665-0.810)	0.730 (0.645-0.815)
*p value		0.757	0.063	0.001	0.005

*p value for comparisons between COSSH-ACLF IIs and with four other scores in the patients with HBV-ACLF.

RESULTADOS

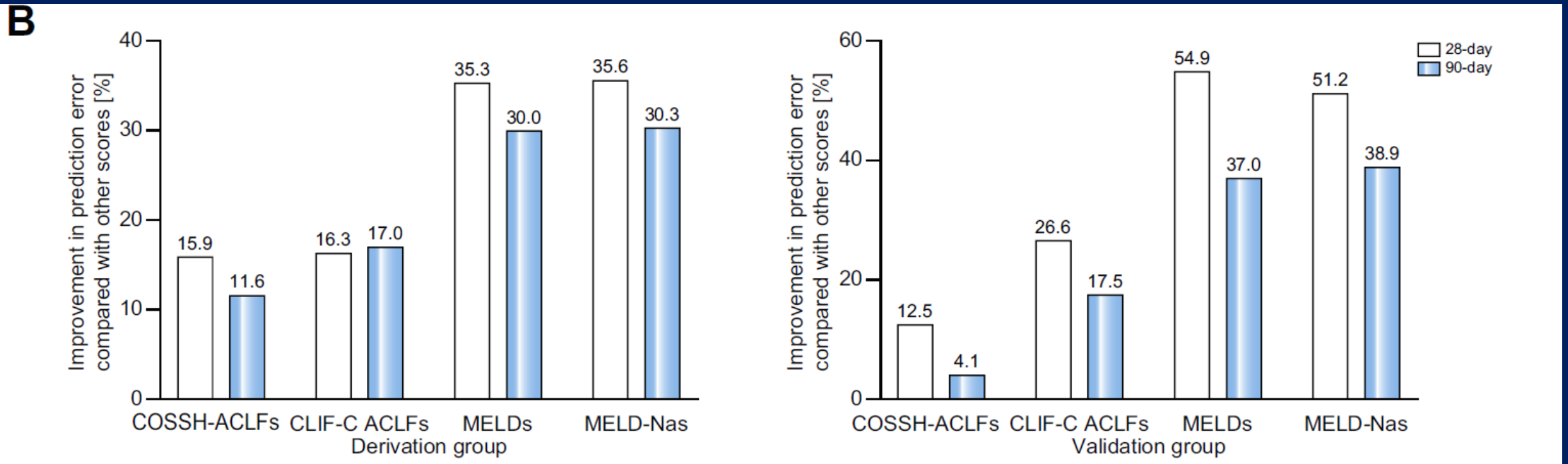

Fig. 2. Predictive discrimination ability of 5 scores. (A) The C-index of 5 scores for predicting 28-/90-day mortality (Z-score test). (B) Percent reduction in the prediction error rates of the COSSH-ACLF IIs compared to those of 4 other scores. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; COSSH-ACLFs, COSSH-ACLF score; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD-sodium score.

RESULTADOS

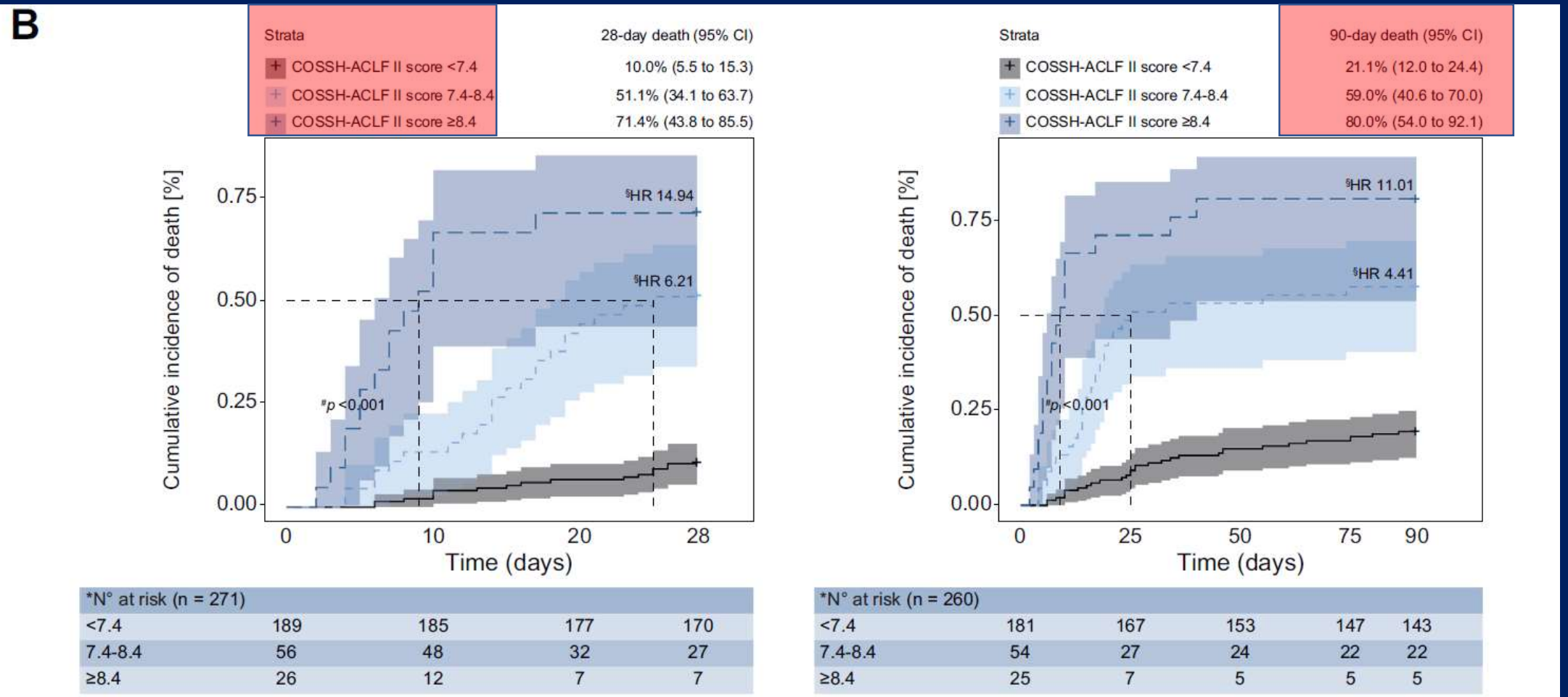

Fig. 6. Risk stratification of the COSSH-ACLF IIs. (A) The derivation group. (B) The validation group. Cumulative incidence of death at 28/90 days stratified according to the COSSH-ACLF IIs classification rule (low-/intermediate-/high-risk: COSSH-ACLF IIs <7.4/7.4-8.4/≥8.4). $^{\#}p$ <0.001 (Log-rank test) for comparisons of the cumulative incidence of death among 3 different risk strata; $^{\S}p$ <0.001 (Likelihood ratio test) for hazard ratios of death in the intermediate- and high-risk groups compared with those in the low-risk group. *Number of liver transplant-free patients. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score.

DISCUSIÓN

- En este estudio, los datos clínicos de la cohorte abierta multicéntrica y prospectiva del estudio COSSH se utilizaron para identificar las características clínicas de los pacientes con VHB-ACLF y desarrollar un nuevo score simplificado, los *COSSH-ACLF II*, que se pueden utilizar para predecir con precisión la mortalidad a *28 y 90 días* de estos pacientes.

- En el presente estudio, se seleccionaron *6 factores de riesgo independientes* (TB, INR, edad, neutrófilos, HE y urea) y desarrollamos una puntuación COSSH-ACLF II simplificada para la población con HBV-ACLF.

- Se demostró que la puntuación de pronóstico recientemente desarrollada fue *más simple y más precisa para predecir la gravedad* de la enfermedad de los pacientes con VHB-ACLF que la clasificación de grado basada en insuficiencia orgánica de las puntuaciones COSSH-ACLF y CLIF-C ACLF, como así también de MELD y MELD-Na.

LIMITACIONES

- **La nueva puntuación también requiere una *mayor validación en cohortes más grandes.***

- **Se debe *evaluar formalmente la utilidad clínica* de la nueva puntuación COSSH-ACLF II para priorizar a los candidatos para el trasplante de hígado.**

¡MUCHAS GRACIAS!