

1 **Supplementary**2 **The Aachen ACLF ICU score predicts ICU mortality in critically ill**
3 **patients with acute-on-chronic liver failure**

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21 **Suppl. Table S1: Additional baseline characteristics of ICU survivors vs. ICU**
22 **non-survivors**

	All Patients	ICU survivors	ICU non-survivors	p-Value
Characteristics				
Diabetes mellitus, yes (%)	55 (27)	26 (32)	29 (24)	0.186
Laboratory parameters				
WBC [n/nl], median (range)	13.7 (0.9 – 49.9)	11.94 (2.6 – 49.9)	14.9 (0.9 – 41.9)	0.004
Hb [g/dl], median (range)	8.97 (1.5 – 17.5)	8.94 (3.9 – 16.15)	8.98 (1.5 – 17.5)	0.643
PLT [n/nl], median (range)	94.13 (7.0 – 394.0)	101.7 (21 – 386)	89.1 (7 – 394)	0.166
AT III (%), median (range)	22.48 (2.0 – 65)	28.6 (4 – 59) n=41	20.2 (2 – 65) n=41	0.099
Fibrinogen [mg/dl], median (range)	138.46 (21.0 – 538.0)	132.2 (46 – 253)	140.7 (21 – 538)	0.823

eGFR [ml/min/1,73m ²], median (range)	40.0 (4.4 – 163.3)	45.9 (6.0 – 163.3)	36.05 (4.4 – 130.1)	0.240
AST [U/l], median (range)	653.3 (13 – 17398)	393.3 (13 – 16294)	827.6 (13 – 17398)	< 0.0001
ALT [U/l], median (range)	264.43 (5 – 6886)	186.38 (7 – 6886)	316.47 (5 – 6030)	0.021
Albumin [g/dl], median (range)	2.77 (1.10 – 5.10)	2.95 (1.70 – 5.10)	2.65 (1.1 – 4.7)	0.009
Ammonia [μmol/l], median (range)	88.7 (10 – 418)	78.6 (10 – 328)	94.8 (10 – 418)	0.078
LDH [U/l], median (range)	630.7 (68 – 12194)	448.5 (82 – 11585)	753.1 (68 – 12194)	0.004
Na ⁺ [mmol/l], median (range)	137 (108 – 163)	137 (123 – 156)	137 (108 – 163)	0.906
K ⁺ [mmol/l], median (range)	4.53 (2.7 – 7.7)	4.53 (3.1 – 7.7)	4.52 (2.7 – 6.6)	0.722
BNP [pg/ml], median (range)	6192.64 (8.3 – 43935.0)	6107.36 (25.3 – 43935.0)	6248.01 (8.3 – 42757.0)	0.048
CRP [mg/l], median (range)	56.6 (1.7 – 245.2)	49.1 (2.4 – 244.6)	61.6 (1.7 – 245.2)	0.060
PCT [ng/ml], median (range)	4.38 (0.07 – 64.42)	4.71 (0.07 – 63.18)	4.17 (0.09 – 64.42)	0.025
Il-6 [pg/ml], median (range)	4108 (9.6 – 136014.0)	1067.5 (9.6 – 15234.0)	6168.5 (20.63 – 136014.0)	0.007
Reason for decompensation of cirrhosis				
Bleeding, n (%)	48 (23)	24 (30)	24 (20)	0.099
Sepsis, n (%)	115 (56)	33 (40)	82 (66)	< 0.0001
SBP, n (%)	44 (22)	13 (16)	31 (25)	0.282
pulmonary, n (%)	47 (23)	10 (12)	37 (30)	0.003
ICU Data at the day of admission				
<i>Ventilation Data</i>				
mechanical ventilation, yes (%)	101 (49)	23 (28)	78 (63)	0.0001
RF [n/min], median (range)	19 (7 – 55)	18 (7- 29)	20 (11 – 33)	0.024
p _a O ₂ [mmHg], median (range)	87 (42 – 156)	89 (42 – 156)	85 (49 – 146)	0.421
PEEP [cm H ₂ O], median (range)	8.5 (5 – 15)	8.1 (5 – 15)	8.57 (5 – 15)	0.309
P _{insp} [mbar], median (range)	22 (8 – 32)	19 (8 – 30)	23 (12 – 32)	0.007
<i>Renal replacement data</i>				
Renal replacement therapy, yes (%)	87 (42)	24 (30)	63 (51)	0.002

- 1 Baseline patient characteristics at the time point of admission to ICU. For quantitative
- 2 variables median and range (in parentheses) are given. *Abbreviations are:* WBC, white
- 3 blood cell count; Hb, hemoglobin; PLT, platelet; AT III, antithrombin III; GFR,

1 glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine
 2 transaminase; LDH, lactic acid dehydrogenase; BNP, brain natriuretic peptide; CRP,
 3 C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; SBP, spontaneous bacterial
 4 peritonitis; RF, respiratory frequency; PEEP, positive end-expiratory pressure.

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 6 **Suppl. Table S2: Comparison of different decision tree models with logistic**
 7 **regression models**

	T a r g e t	CLIF – L1 - L2	Tree 1	Tree 2	Tree 3	Tree 4
Input featu res			all	R+C	All + CLIF-C ACLF	Model 6/7
Preci sion	1	0.91 (0.84- 0.96)	0.66 (0.60- 0.70)	0.81 (0.85- 0.79)	0.74 (0.69-0.77)	0.67 (0.59-0.72)
Sens itivit y	1	0.90 (0.94- 0.88)	0.67 (0.53- 0.76)	0.81 (0.65- 0.92)	0.74 (0.65-0.80)	0.67 (0.59-0.72)
F1- scor e	1	0.91 (0.89- 0.92)	0.66 (0.56- 0.73)	0.80 (0.73- 0.85)	0.74 (0.67-0.78)	0.67 (0.59-0.72)
Calib ratio n-in- the- large	0.6	0.5	0.64	0.67	0.62	0.61
AUR OC	1	0.95	0.64	0.8	0.71	0.67
Youd en's J		0.50	1.00	0.75	1.00	0.25
Num ber of used featu res		13	67	16	68	13

8 Evaluated tree models in comparison to the first logistic regression model. In the first
 9 step all features were evaluated, in the second step features related to organ failures
 10 were tested. *Abbreviations are:* CLIF, Chronic Liver Failure Consortium (CLIF-C) ACLF
 11 score; NOF, number of organ failures; L1, Lasso Regression; L2, Ridge Regression.

- 1 **Suppl. Table S3: Comparison of the performance of the generated logistic regression models.** Input features were related to
 2 organ failures, addition of the number of organ failures (NOF) was also tested.

Model number		Model 1	Model 2	Model 3	Model 4	Model 5 (ACICU Score)	Model 6	Model 7
Regularization		L1	L1 -> L2	L1	L2	L2	L1	L2
Precision	1	0.84 (0.75 – 0.91)	0.9 (0.88 – 0.92)	0.9 (0.88 – 0.92)	0.9 (0.88 – 0.92)	0.95 (0.94 – 0.96)	0.89 (0.80 – 0.95)	0.88 (0.76 – 0.95)
Sensitivity	1	0.83 (0.80 – 0.88)	0.9 (0.88 – 0.92)	0.9 (0.88 – 0.92)	0.9 (0.88 – 0.92)	0.95 (0.94 – 0.96)	0.88 (0.84 – 0.94)	0.86 (0.94 – 0.80)
F1-score	1	0.83 (0.81 – 0.85)	0.9 (0.88 – 0.92)	0.9 (0.88 – 0.92)	0.9 (0.88 – 0.92)	0.95 (0.94 – 0.96)	0.88 (0.86 – 0.89)	0.86 (0.84 – 0.87)
Calibration-in-the-large	0.6	0.57	0.6	0.5393	0.5952	0.58	0.535	0.50
Calibration intercept	0	0.03	- 0.04	0.2192	- 0.04	- 0.216	0.56	0.8833
Calibration slope	1	3.22	1.81	3.7	1.8095	2.7046	1.59	243.32
AUROC	1	0.93	0.95	0.94	0.95	0.96	0.91	0.95
Youden's J		0.49	0.47	0.53	0.47	0.54	0.41	0.50
Number of used features		8	5	5	5	5	13	13
Features		'd1_Horowitz', 'd1_FiO2', 'd1_paO2', 'd1_Ventilation',	'd1_CLIF_C_AC', 'LF', 'd1_Horowitz', 'd1_FiO2',	'd1_CLIF_C_AC', 'LF', 'd1_Horowitz', 'd1_FiO2',	'd1_CLIF_C_AC', 'LF', 'd1_Horowitz', 'd1_FiO2', 'd1_TPTD',	'd1_CLIF_C_AC', 'LF', 'Number_OF', 'd1_Horowitz',	'Number_OF', 'd1_AF', 'd1_Horowitz', 'd1_FiO2', 'd1_paO2', 'd1_Ventilation', 'cause of sepsis', 'd1_MAP',	'Number_OF', 'd1_AF', 'd1_Horowitz', 'd1_FiO2', 'd1_paO2',

	'd1_MAP', 'd1_TPTD', 'd1_RR_Sys', 'd1_Lactate'	'd1_TPTD, 'd1_ Lactate'	'd1_TPTD, 'd1_ Lactate'	'd1_Lactate'	'd1_FiO2', 'd1_ Lactate'	'd1_vasopressors', 'd1_ TPTD, 'd1_heart rate', 'd1_RR_Sys', 'd1_ Lactate'	'd1_Ventilatio n', cause of sepsis', 'd1_MAP', 'd1_vasopress os', 'd1_TPTD', 'd1_heart rate', 'd1_RR_Sys', 'd1_Lactate'
Coefficient s	-0.3472606 0.21422031 - 0.03058471 0.07092862 - 0.16473165 0.25087789 - 0.05219007 0.2849164	0.7937202 -0.30231107 0.28361903 0.44091147 0.29946303	0.49873336 -0.21536315 0.06984075 0.08288953 0.05421657	0.7937202 -0.30231107 0.28361903 0.44091147 0.29946303	0.65130518 0.14880095 -0.29750186 0.26440165 0.35542168	0.42208604 0.02775644 0.23321895 0.82631475 -0.5261933 0.3846778 0.05338636 -0.3745731 -0.20863558 0.37922956 0.08786658 -0.09197543 0.40577534	0.00247497 0.00097648 -0.00284844 0.00274555 -0.00052981 0.00226619 0.00126243 -0.00120199 0.00181572 0.00190038 0.00104307 -0.00096393 0.00204423

- 1 Used formula for logistic regression as described in Material and Methods. Performance and calibration of the validation cohort are
- 2 described in the upper part of the table. X_n refers to the features, β_n refers to the coefficients. *Abbreviations are:* CLIF, Chronic Liver

- 1 Failure Consortium (CLIF-C) ACLF score; NOF, number of organ failures; L1, Lasso Regression; L2, Ridge Regression; TPTD,
- 2 Transpulmonary Thermodilution

1 **Suppl. Table S4: Calculation of ACICU score in two exemplary patients**

	Patient 1	Patient 2
CLIF-C ACLFs	52	59
Horovitz [mmHg]	485	168
FiO₂ [%]	21	70
Number of Organ Failures	2	3
Lactate [mmol/l]	0.9	8.5
ACICU score	0.2	0.8
Risk group	Low risk	High risk
Estimated risk of ICU mortality [%]	24	82

2 Patient 1 representing a low risk patient, patient 2 representing a high risk patient with
3 ACLF. *Abbreviations are:* CLIF-C ACLFs, Chronic Liver Failure Consortium (CLIF-C)
4 ACLF score.

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6 **Suppl. Table S5: Correlation analysis of the features of the ACICU score**

	CLIF-C ACLF	NOF	Horovitz	FiO ₂	Lactate
CLIF-C ACLF	1.000000	0.618330	- 0.375265	0.367614	0.316619
NOF	0.618330	1.000000	- 0.354321	0.359048	0.242783
Horovitz	- 0.375265	- 0.354321	1.000000	- 0.822832	- 0.255031
FiO₂	0.367614	0.359048	- 0.822832	1.000000	0.339996
Lactate	0.316619	0.242783	- 0.255031	0.339996	1.000000

7 Correlation analysis showing pairwise the Pearson coefficients. *Abbreviations are:*
8 CLIF-C ACLF: CLIF, Chronic Liver Failure Consortium (CLIF-C) ACLF score; NOF,
9 number of organ failures

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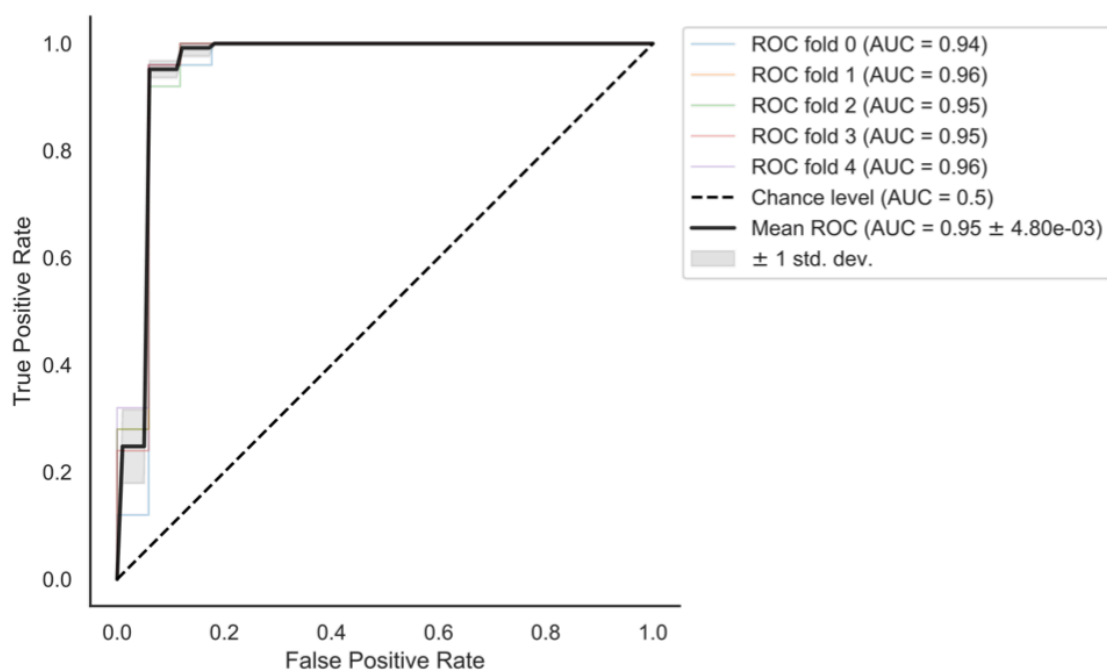
11 **Suppl. Table S6: Comparison of ACICU and CLIF-C ACLF score**

		ICU survivors (n=82) (%)	ICU non-survivors (n=124) (%)
CLIF-C ACLF ≥ 70	Yes (%)	4 (12.1)	29 (23.4)
	No (%)	78 (95.1)	95 (76.6)
ACICU ≥ 0.94	Yes (%)	0 (0)	9 (7.3)
	No (%)	82 (100)	115 (92.7)

1 Analysis of performance metrics of true and false classification of patients who do or
2 do not survive ICU by the respective thresholds of CLIF-C ACLFs of 70 and ACICU
3 score of 0.94. Percentages in the parentheses refer to the true survival status; number
4 and percentage of truly classified patients are in bold.

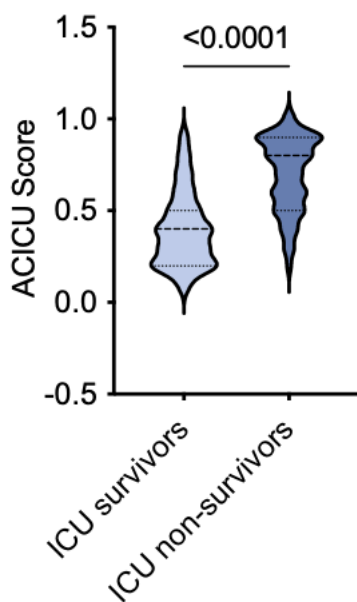
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1 **Suppl. Figure S1: ACICU score validation**



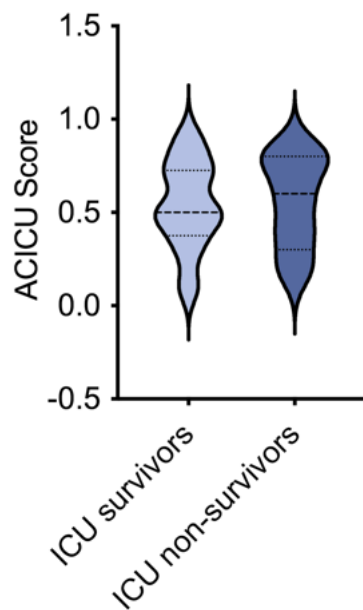
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3 Receiver operating characteristics of the ACICU score (mean AUROC=0.95) in 5-fold
4 cross- validation in test cohort.

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6 **Suppl. Figure S2: ACICU score in patients with ACLF without OLT**



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8 Comparison of ACICU score values between ICU survivors vs. ICU non-survivors after
9 exclusion of patients who received OLT (68 vs. 119 patients), $p < 0.0001$. An unpaired,
10 two-tailed t-test was used.

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2 **Suppl. Figure S3: ACICU score in patients with ACLF receiving OLT**

3

4 Comparison of ACICU score values between ICU survivors vs. ICU non-survivors after
5 OLT out of ACLF (10 vs. 5 patients), $p = 0.8849$. An unpaired, two-tailed t-test was
6 used.

7