Supplementary Material

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: EMMANUEL WEISS, CARLOS DE LA PEÑA-RAMIREZ, FERRAN AGUILAR, et al.; Sympathetic Nervous Activity, Mitochondrial Dysfunction and Outcome in Acutely Decompensated Cirrhosis: The Metabolomic Prognostic Models**.** (124 characters with spaces)

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Results

Supplementary Table 1. Description of models and scores included in the current study

Model	Description
CLIF-C MET model 1	[0.02396·Age + 0.32981·$\log_2$(4-Hydroxy-3-methoxyphenylglycol sulphate) + 0.45602·$\log_2$(Hexanoylcarnitine) + 0.27226·$\log_2$(D-Galacturonic acid) – 18.1561] / 0.0965
CLIF-C MET model 2	[0.03432·Age + 0.34020·$\log_2$(4-Hydroxy-3-methoxyphenylglycol sulphate) + 0.50724·$\log_2$(Hexanoylcarnitine) + 0.04037·Serum Bilirubin + 0.34674·INR – 14.6517] / 0.1218
CLIF-C ACLF score	10·[0.33·CLIF-OFs* + 0.04·Age + 0.63·log(WBC count) – 2]
CLIF-C AD score	10·[0.03·Age + 0.66·log(Creatinine) + 1.71·log(INR) + 0.88·log(WBC) – 0.05·Sodium + 8]
MELD score	9.6·log(Creatinine) + 3.8·log(Bilirubin) + 11.2·log(INR) + 6.4
MELDNa score	MELD – Sodium – 0.025·MELD·(140 – Sodium) + 140

*Definition of the Chronic Liver Failure Consortium Organ Failure score (CLIF-OFs) can be found in Supplementary Table 2.

Supplementary Table 2. Description of the Chronic Liver Failure Consortium Organ Failure (CLIF-OF) score. *

Organ/System	Subscore = 1	Subscore = 2	Subscore = 3
Liver	Bilirubin < 6 mg/dL	Bilirubin ≥ 6 mg/dL and < 12 mg/dL	Bilirubin ≥ 12 mg/dL
Kidney	Creatinine < 2 mg/dL	Creatinine ≥ 2 mg/dL and < 3.5 mg/dL	Creatinine ≥ 3.5 mg/dL or renal replacement therapy
Brain (West-Haven grade for HE)	Grade 0	Grades 1-2	Grades 3-4[a]
Coagulation	INR < 2.0	INR ≥ 2.0 and < 2.5	INR ≥ 2.5
Circulatory	MAP ≥ 70 mmHg	MAP < 70 mmHg	Use of vasopressors
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2	 > 300 or > 357	 ≤ 300 and > 200 or ≤ 357 and > 214	 ≤ 200[b] or ≤ 214[b]

*Each organ system function receives a score ranging from 1 point (close to normal) to 3 points (abnormal). The dark-gray cells indicate the definition of each organ failure, and the light-gray cells the definition of each organ dysfunction. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4. Fio2 denotes fraction of inspired oxygen, INR international normalized ratio, MAP mean arterial pressure, Pao2 partial pressure of arterial oxygen, RRT renal-replacement therapy, and Spo2 oxygen saturation as measured by pulse oximetry. The shaded area highlights the criteria for diagnosing an organ failure. HE, hepatic encephalopathy; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; SpO_2, pulse oximetric saturation. [a]: A patient submitted to mechanical ventilation due to HE is considered as presenting a cerebral failure (brain subscore = 3). [b]: A patient enrolled in the study with mechanical ventilation is considered as presenting a respiratory failure (respiratory subscore = 3).

Supplementary Table 3. Correlation between the serum metabolome and the 28-day mortality*.

Metabolite	C-index	
	Discovery set: CANONIC study cohort	Validation set: PREDICT study cohort
4-Hydroxy-3-methoxyphenylglycol sulphate	0.822	0.760
Hexanoylcarnitine	0.799	0.721
L-Saccharopine	0.786	0.704
4-Acetamidobutanoic acid	0.783	0.515
N-Acetyl-aspartyl-glutamate	0.782	0.709
p-Hydroxyphenyllactic acid	0.777	0.733
D-Galacturonic acid	0.766	0.724
N-Acetyl-L-alanine	0.759	0.684
Butyrylcarnitine	0.759	0.681
Pentose alcohols	0.758	0.703
Cystathionine	0.757	0.711
Octanoylcarnitine	0.747	0.707
5'-Deoxy-5'-(methylthio)adenosine	0.747	0.707
β-Pseudouridine	0.746	0.664
Phenyllactic acid	0.742	0.699
N6,N6,N6-Trimethyl-L-lysine	0.742	0.719
N-Acetyl-L-tyrosine	0.741	0.687
D-Glucuronic acid	0.737	0.712
Pentose phosphates	0.736	0.726
N-Formyl-L-methionine	0.733	0.701
N-Acetylneuraminic acid	0.732	0.694
N-Acetyl-L-phenylalanine	0.729	0.713
D-Threitol	0.727	0.673
Quinolinic acid	0.727	0.688
Creatine	0.722	0.611
Succinic semialdehyde/2-Oxobutyric acid	0.721	0.649
Mevalonic acid	0.719	0.680
N8-Acetylspermidine	0.717	0.659
2-Hydroxycaproic acid	0.716	0.691
2,2'-Thiodiacetic acid	0.712	0.664
N-Acetyl-L-tryptophan	0.708	0.625
Succinate	0.705	0.552
L-Kynurenine	0.705	0.590
N-Acetyl-L-aspartic acid	0.704	0.637
Carnitine	0.702	0.601
Hexadecanedioic acid	0.701	0.687
Hexose alcohols	0.700	0.570
2-Oxovaleric acid	0.699	0.555

p-Anisic acid	0.697	0.598
2-Heptanone	0.696	0.595
Aconitic acid	0.694	0.639
Trisaccharides	0.693	0.605
Decanoylcarnitine	0.690	0.669
Lysine	0.690	0.639
D-Tartaric acid	0.688	0.526
Indolelactic acid	0.686	0.623
Orotidine	0.679	0.648
Adenine	0.675	0.618
Oxaloacetic acid	0.675	0.594
Androsterone sulphate	0.672	0.555
Citric acid/Isocitric acid	0.671	0.619
N6-Acetyl-L-lysine	0.667	0.633
2-Aminoisobutyric acid	0.666	0.524
Guanidinosuccinic acid	0.665	0.611
Pyruvic acid	0.663	0.569
Phenol	0.662	0.515
3-Methylcrotonyl glycine	0.661	0.561
Phenylalanine	0.660	0.621
Phenylacetyl-L-glutamine	0.658	0.641
Pantothenic acid	0.654	0.614
Dehydroisoandrosterone sulphate	0.654	0.519
Dihydrothymine	0.652	0.564
Methionine sulfoxide	0.647	0.504
DL-3-Aminoisobutyric acid	0.646	0.620
Lactic acid	0.644	0.609
Methylimidazoleacetic acid	0.642	0.576
N-Acetylglycine	0.642	0.555
Methylhippuric acids	0.633	0.519
Indoleacetic acid	0.630	0.625
Methionine	0.628	0.589
Allantoin	0.624	0.502
Arginine succinate	0.624	0.586
Threonic acid	0.620	0.524
Malic acid/Diglycolic acid	0.619	0.650
α-Ketoglutaric acid	0.619	0.592
Asparagine	0.616	0.565
4-Pyridoxic acid	0.613	0.550
Tyrosine	0.612	0.564
Histidine	0.610	0.626
N-Isobutyrylglycine	0.609	0.506
Benzoic acid/4-Hydroxybenzaldehyde	0.609	0.509
Alanines/Sarcosine	0.608	0.605
Glutamine	0.602	0.570
Hexoses	0.596	0.543

Ehtylmalonic acid	0.582	0.497
Proline	0.580	0.563
10-hydroxydecanoic acid/3-hydroxydecanoic acid	0.579	0.623
L-Citrulline	0.577	0.487
γ-Butyrolactone	0.576	0.613
D-Glyceric acid	0.575	0.539
Phenylpyruvic acid	0.575	0.525
Mesaconic acid/Glutaconic acid/Itaconic acid	0.573	0.560
L-Cystine	0.572	0.555
5-Hydroxylysine	0.569	0.596
Nonanoic acid	0.567	0.512
Pyroglutamic acid	0.552	0.564
Threonines	0.552	0.555
Indoxyl sulfate	0.551	0.584
Uric acid	0.546	0.571
2,5-Dihydroxybenzaldehyde/Salicylic acid	0.546	0.493
Methylhistidines	0.544	0.480
Hippuric acid	0.540	0.555
1α,25-Dihydroxyvitamin D3	0.539	0.461
Arginine	0.536	0.484
Caproic acid	0.521	0.458
Ornithine	0.519	0.467
N-Acetyl-ornithine	0.516	0.518
Quinic acid	0.512	0.495
Glycerol 3-phosphate	0.510	0.266
Perillic acid	0.506	0.459
Oxalic acid	0.504	0.409
Thymine	0.498	0.479
Tryptophan	0.490	0.467
4-Methyl-2-oxovaleric acid/3-Methyl-2-oxovaleric acid/2-Ketohexanoic acid	0.486	0.504
2,6-Dihydroxybenzoic acid	0.475	0.435
Allantoic acid	0.473	0.494
Taurine	0.469	0.529
Hypoxanthine	0.443	0.515
Inosine	0.440	0.483
Dimethyluric acids	0.429	0.484
Indole-3-propionic acid	0.427	0.511
Serine	0.412	0.402
Glutamic acid	0.412	0.501
Xanthine	0.411	0.510
Spermidine	0.399	0.504
Choline	0.397	0.460
1,5-Anhydro-D-sorbitol	0.391	0.449
Cotinine	0.371	0.489

Aspartic acid	0.350	0.443
Aspartylphenylalanine	0.315	0.431

* For each of the 130 metabolites and for each cohort, we estimated the Harrel's Concordance index (C-index) assessing the discriminating accuracy of the metabolite levels, expressed in relative units corresponding to chromatographic peak areas, in differentiating prognosis (considering death as the primary event and liver transplant as the competing risk). Metabolites are ranked according to the Canonic study results.

Supplementary Table 4. Twenty-five metabolites of the death-related metabolomic fingerprint (listed in bold text) were among the 38 metabolites of the ACLF-related metabolomic fingerprint reported by the CANONIC study (first column)[1].

ACLF-related metabolomic fingerprint	**Area Under the Curve**	**C-index**	
	CANONIC study cohort	**Discovery set: CANONIC study cohort**	**Validation set: PREDICT study cohort**
β-Pseudouridine	0.86	0.746	0.664
Pentose alcohols	0.86	0.758	0.703
Pentose phosphates	0.85	0.736	0.726
N-Acetyl-L-alanine	0.87	0.759	0.684
D-Galacturonic acid	0.85	0.766	0.724
N-Acetyl-aspartyl glutamate	0.85	0.782	0.709
D-Glucuronic acid	0.81	0.737	0.712
L-Kynurenine	0.81	0.705	0.590
4-hydroxy-3-methoxyphenylglycol sulphate	0.81	0.822	0.760
N-Acetyl-L-phenylalanine	0.79	0.729	0.713
Cystathionine	0.79	0.757	0.711
D-Threitol	0.84	0.727	0.673
4-Acetamidobutanoic acid	0.84	0.783	0.515
N-Acetylneuraminic acid	0.82	0.732	0.694
Quinolinic acid	0.83	0.727	0.688
Mevalonic acid	0.82	0.719	0.680
L-Saccharopine	0.81	0.786	0.704
Hydroxyphenylacetic acids	0.79	0.725	0.652
Phenyllactic acid	0.75	0.742	0.699
N-Acetyl-L-aspartic acid	0.76	0.704	0.637
Hexanoylcarnitine	0.77	0.799	0.721
p-Hydroxyphenyllactic acid	0.76	0.777	0.733
5'-Deoxy-5'-(methylthio)adenosine	0.78	0.747	0.707
N-Formyl-L-methionine	0.79	0.733	0.701
N-Acetyl-L-tyrosine	0.78	0.741	0.687
Related to Succinate*	0.76		
2-Heptanone	0.75	0.696	0.595
Kynurenic acid*	0.78		
N6,N6,N6-Trimethyl-L-lysine	0.76	0.742	0.719
Trisaccharides	0.77	0.693	0.605
2,2'-Thiodiacetic acid	0.75	0.712	0.664
Octanoylcarnitine	0.73	0.747	0.707

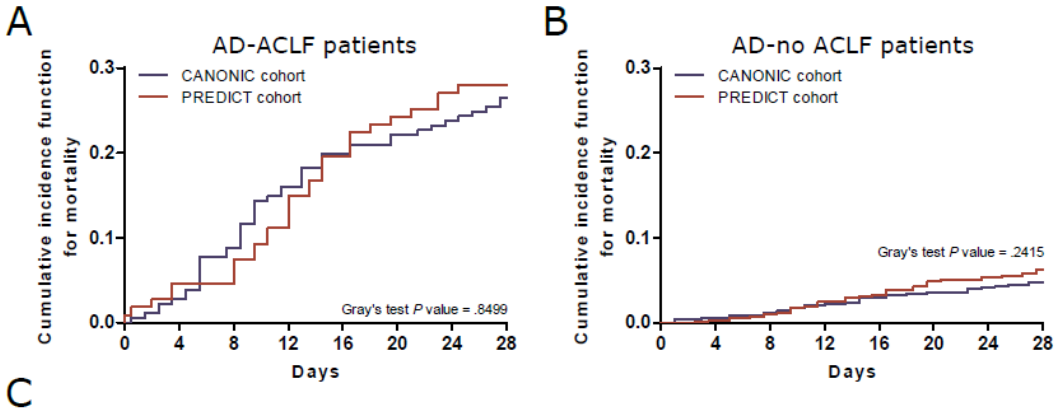
Pantothenic acid	0.75	0.654	0.614
Indolelactic acid	0.77	0.686	0.625
P-Anisic acid	0.78	0.697	0.598
Phenol	0.77	0.662	0.515
N-Acetyl-L-tryptophan	0.76	0.708	0.625
L-(+)-Tartaric acid*	0.74		

* Metabolites related to succinate, Kynurenic acid, and L-(+)-Tartaric acid were not detected in both studies, so they were not included in the current analysis.

Supplementary table 5. Coefficient of variation of CLIF-C MET model 1, CLIF-C MET model 2, MELD score and MELDNa score of 46 patients with stable decompensated cirrhosis of the first three visits within 90 days.

Model	Mean coefficient of variation
CLIF-C MET model 1	14.9%
CLIF-C MET model 2	13.1%
MELD score	18.4%
MELDNa score	21.9%

Supplementary figure 1. Mortality incidence behaves similarly in patients with or without ACLF in both study cohorts. Top half shows the cumulative incidence function for mortality for AD-ACLF patients (A) and for AD-no ACLF patients (B) with a time limit of 28 days. (C) Standard deviation of estimated C-indices at 28 days. Standard deviation has been estimated by jack-knife in each subgroup.



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Model	Standard deviation at 28 days	
	Discovery set: CANONIC study cohort	**Validation set: PREDICT study cohort**
AD-ACLF patients	*(n = 181)*	*(n = 109)*
Metabolomic model 1	0.0276	0.0476
Metabolomic model 2	0.0235	0.0428
CLIF-C ACLF score	0.0347	0.0487
MELDNa score	0.0340	0.0474
AD-no ACLF patients	*(n = 650)*	*(n = 742)*
Metabolomic model 1	0.0438	0.0373
Metabolomic model 2	0.0441	0.0377
CLIF-C AD score	0.0441	0.0389
MELDNa score	0.0471	0.0353

References

1. Moreau R, Clària J, Aguilar F, et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. J Hepatol 2020; 72:688–701.