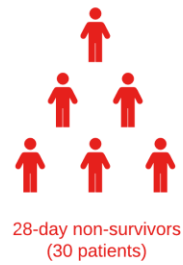**Supplementary Figure 1**. Abbreviated inclusion criteria and study flow diagram. Patients with vasopressor dependent septic shock from the Rapid Administration of Carnitine in Sepsis (RACE) trial were considered. Patients randomized to receive saline placebo and who had at least one serum sample available for analysis were included in this secondary analysis. Longitudinal serum samples were analyzed for acylcarnitines by liquid chromatography – mass spectrometry (LC-MS), small polar metabolites by nuclear magnetic resonance (NMR), and protein markers of the host response by immunoassays.
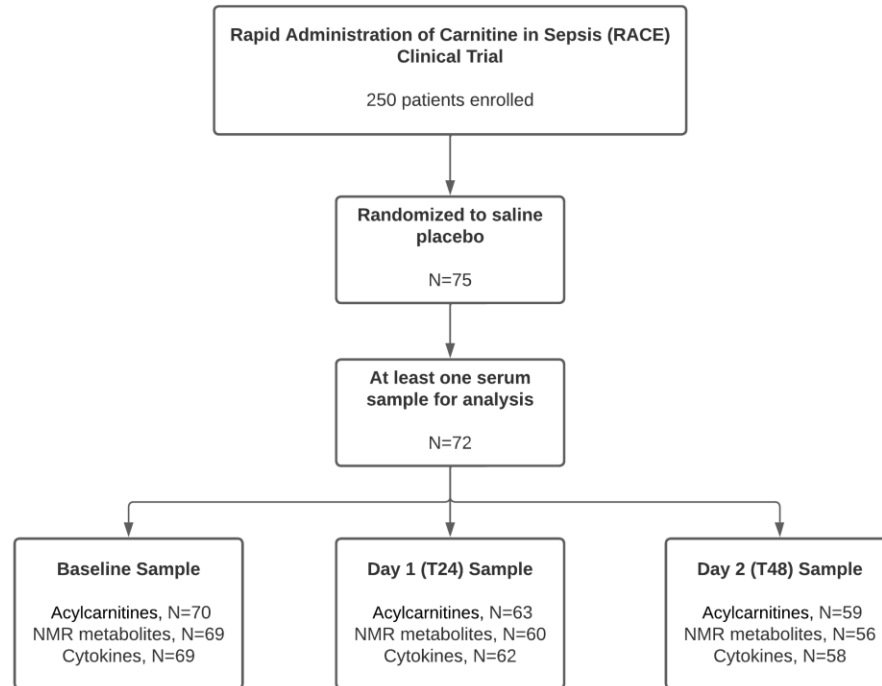
A)

28-day survivors
(42 patients)

Abbreviated Inclusion Criteria

1.) Enrollment within 24-hours of septic shock

2.) Vasopressor depedence

3.) Blood lactate exceeding 18 mg/dL

28-day non-survivors
(30 patients)

B)

Rapid Administration of Carnitine in Sepsis (RACE) Clinical Trial

250 patients enrolled

Randomized to saline placebo

N=75

At least one serum sample for analysis

N=72

Baseline Sample

Acylcarnitines, N=70
NMR metabolites, N=69
Cytokines, N=69

Day 1 (T24) Sample

Acylcarnitines, N=63
NMR metabolites, N=60
Cytokines, N=62

Day 2 (T48) Sample

Acylcarnitines, N=59
NMR metabolites, N=56
Cytokines, N=58

Supplementary Figure 2. Clustering performance using dimensionality reduced or full metabolomics data. We used the k-means algorithm with Euclidean distance to cluster baseline metabolomics data into distinct subgroups. We tested performance with k varying from 1 to 10 and selected the optimal number of clusters by maximizing the average Silhouette width. Clustering was first performed with a dataset subject to principal component analysis (PCA) to reduce dimensionality and reduce the risk of overfitting. We also considered clustering performance on the full metabolomics dataset. **A**) The optimal number of clusters in the after PCA dimensionality reduction. **B**) The optimal number of clusters using the full metabolomics dataset. **C**) Contingency table highlighting that patients were consistently placed into the same cluster regardless of whether the reduced or full dataset was used.
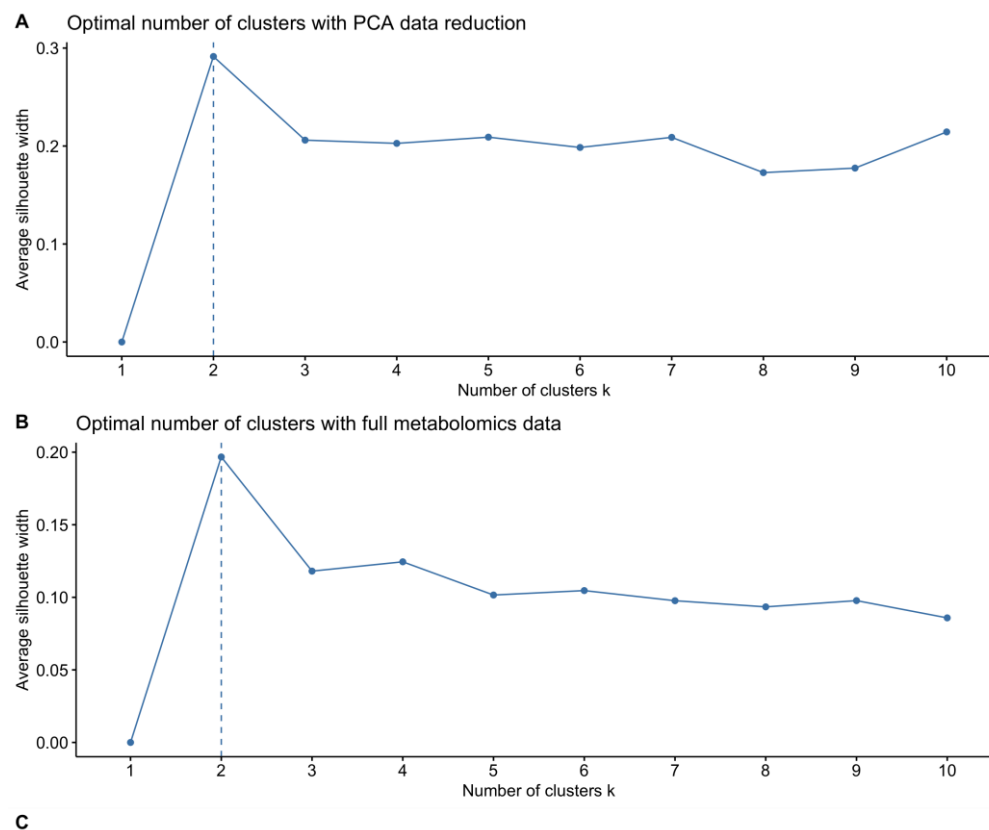
	Assigned to Cluster 1 with PCA Dimensionality Reduction	Assigned to Cluster 2 with PCA Dimensionality Reduction
Assigned to Cluster 1 with Full Metabolomics Data	28	0
Assigned to Cluster 2 with Full Metabolomics Data	0	41

Supplementary Table 1: Linear mixed model results for measured metabolite and protein analytes. For each analyte a fixed vs. interaction model was selected as described in the methods. The overall p-value was determined by comparing the selected model to a null model, which only included a patient-level intercept and covariates. Resulting p-values were corrected for multiple comparisons according to Benjamini and Hochberg and are reported as q values. Model coefficients for time, mortality, and their interaction are reported with their 95% confidence interval. Blue coefficients indicate a negative slope significantly different from zero, while red coefficients indicate a positive slope significantly different from zero.

Metabolite/Protein	Platform	Model Selected	Q-Value	Time	Mortality	Interaction
C6	LC-MS	Fixed Effects Only Model	8.10e-05	-0.196 (-0.284, -0.107)	0.433 (0.027, 0.839)	
C2 (Acetylcarnitine)	LC-MS	Fixed Effects Only Model	2.76e-04	-0.093 (-0.173, -0.014)	0.779 (0.382, 1.176)	
C8	LC-MS	Fixed Effects Only Model	2.76e-04	-0.115 (-0.193, -0.037)	0.667 (0.28, 1.055)	
C16	LC-MS	Interaction Model	3.02e-04	0.167 (0.068, 0.267)	0.958 (0.498, 1.418)	-0.275 (-0.448, -0.103)
C4	LC-MS	Fixed Effects Only Model	3.05e-04	-0.154 (-0.234, -0.074)	0.497 (0.07, 0.924)	
C20.1	LC-MS	Interaction Model	4.36e-04	0.163 (0.059, 0.267)	0.972 (0.508, 1.437)	-0.194 (-0.375, -0.014)
C14.1	LC-MS	Interaction Model	4.66e-04	0.074 (-0.02, 0.169)	1.026 (0.57, 1.482)	-0.225 (-0.39, -0.061)
C12	LC-MS	Fixed Effects Only Model	6.19e-04	-0.056 (-0.138, 0.027)	0.869 (0.439, 1.299)	
C16.1	LC-MS	Interaction Model	6.97e-04	0.072 (-0.022, 0.166)	0.98 (0.533, 1.428)	-0.216 (-0.38, -0.053)
C12.1	LC-MS	Interaction Model	1.08e-03	0.057 (-0.03, 0.144)	0.98 (0.522, 1.438)	-0.18 (-0.332, -0.028)
C18.1	LC-MS	Fixed Effects Only Model	1.28e-03	-0.023 (-0.094, 0.048)	0.848 (0.422, 1.273)	
C14	LC-MS	Interaction Model	1.42e-03	0.023 (-0.083, 0.128)	0.919 (0.475, 1.363)	-0.19 (-0.372, -0.008)
C18.2	LC-MS	Interaction Model	1.85e-03	0.02 (-0.069, 0.109)	0.848 (0.374, 1.323)	-0.207 (-0.362, -0.052)
C10.1	LC-MS	Fixed Effects Only Model	2.64e-03	-0.002 (-0.073, 0.07)	0.776 (0.368, 1.183)	
C3	LC-MS	Fixed Effects Only Model	2.77e-03	-0.067 (-0.148, 0.015)	0.705 (0.282, 1.128)	
C8.1	LC-MS	Fixed Effects Only Model	3.00e-03	-0.178 (-0.276, -0.081)	0.146 (-0.294, 0.586)	
C20.2	LC-MS	Interaction Model	3.93e-03	0.056 (-0.046, 0.157)	0.913 (0.437, 1.389)	-0.189 (-0.365, -0.013)
C20	LC-MS	Fixed Effects Only Model	4.07e-03	0.103 (0.022, 0.184)	0.607 (0.156, 1.059)	
C10	LC-MS	Fixed Effects Only Model	5.15e-03	-0.028 (-0.113, 0.058)	0.689 (0.289, 1.09)	
C18	LC-MS	Interaction Model	6.18e-03	0.142 (0.025, 0.259)	0.817 (0.339, 1.295)	-0.207 (-0.41, -0.004)
L-carnitine	LC-MS	Fixed Effects Only Model	1.18e-02	-0.097 (-0.17, -0.025)	0.38 (-0.073, 0.833)	

C5	LC-MS	Fixed Effects Only Model	2.37e-02	-0.025 (-0.098, 0.048)	**0.591 (0.175, 1.008)**	
C20.4	LC-MS	Fixed Effects Only Model	2.26e-01	0.062 (-0.052, 0.176)	-0.272 (-0.657, 0.112)	
C20.3	LC-MS	Fixed Effects Only Model	2.67e-01	-0.028 (-0.188, 0.132)	0.291 (-0.057, 0.639)	
Lactate	NMR	Fixed Effects Only Model	1.72e-09	**-0.456 (-0.583, -0.33)**	0.309 (-0.045, 0.664)	
Pyruvate	NMR	Interaction Model	2.39e-09	**-0.53 (-0.683, -0.377)**	0.089 (-0.336, 0.515)	**0.287 (0.023, 0.551)**
Isoleucine	NMR	Fixed Effects Only Model	7.82e-06	**0.346 (0.223, 0.469)**	0.144 (-0.28, 0.567)	
Lysine	NMR	Fixed Effects Only Model	7.82e-06	**0.293 (0.187, 0.399)**	0.336 (-0.073, 0.745)	
Propylene glycol	NMR	Fixed Effects Only Model	5.66e-05	**-0.274 (-0.398, -0.15)**	**0.401 (0.033, 0.769)**	
Methionine	NMR	Fixed Effects Only Model	3.53e-04	**0.263 (0.138, 0.389)**	**0.402 (0.026, 0.779)**	
Valine	NMR	Fixed Effects Only Model	3.96e-04	**0.28 (0.156, 0.405)**	0.132 (-0.279, 0.543)	
C2 (Acetylcarnitine)	NMR	Fixed Effects Only Model	4.66e-04	**-0.113 (-0.221, -0.005)**	**0.679 (0.312, 1.046)**	
L-carnitine	NMR	Fixed Effects Only Model	1.19e-03	**-0.179 (-0.31, -0.047)**	**0.533 (0.153, 0.914)**	
3-Hydroxybutyrate	NMR	Fixed Effects Only Model	2.80e-03	**-0.182 (-0.325, -0.039)**	**0.45 (0.094, 0.807)**	
Leucine	NMR	Fixed Effects Only Model	4.07e-03	**0.21 (0.093, 0.327)**	0.18 (-0.243, 0.602)	
Ornithine	NMR	Fixed Effects Only Model	5.37e-03	**0.223 (0.095, 0.351)**	-0.033 (-0.461, 0.395)	
Creatinine	NMR	Fixed Effects Only Model	6.16e-03	**-0.172 (-0.275, -0.069)**	0.133 (-0.289, 0.555)	
Glycine	NMR	Fixed Effects Only Model	1.33e-02	**0.115 (0.019, 0.21)**	**0.443 (0.05, 0.835)**	
2-Hydroxybutyrate	NMR	Fixed Effects Only Model	3.20e-02	-0.092 (-0.195, 0.011)	**0.425 (0.012, 0.837)**	
Alanine	NMR	Fixed Effects Only Model	3.32e-02	-0.083 (-0.186, 0.021)	**0.44 (0.035, 0.846)**	
Tyrosine	NMR	Fixed Effects Only Model	3.35e-02	0.077 (-0.024, 0.179)	**0.521 (0.097, 0.945)**	
Citrate	NMR	Fixed Effects Only Model	5.51e-02	**0.128 (0.013, 0.243)**	0.317 (-0.105, 0.74)	
Betaine	NMR	Fixed Effects Only Model	1.12e-01	-0.085 (-0.176, 0.006)	0.229 (-0.176, 0.634)	
Glutamine	NMR	Fixed Effects Only Model	1.43e-01	-0.008 (-0.114, 0.098)	**0.422 (0.019, 0.826)**	
Phenylalanine	NMR	Fixed Effects Only Model	2.06e-01	0.093 (-0.018, 0.204)	0.234 (-0.204, 0.672)	
2-Oxoisocaproate	NMR	Fixed Effects Only Model	4.04e-01	-0.07 (-0.219, 0.078)	0.196 (-0.197, 0.59)	
Creatine	NMR	Fixed Effects Only Model	4.10e-01	0.026 (-0.048, 0.099)	0.29 (-0.164, 0.743)	

Proline	NMR	Fixed Effects Only Model	4.10e-01	0.02 (-0.095, 0.135)	0.278 (-0.121, 0.677)	
Glucose	NMR	Fixed Effects Only Model	5.74e-01	0.091 (-0.075, 0.258)	-0.015 (-0.366, 0.335)	
Histidine	NMR	Fixed Effects Only Model	6.16e-01	0.052 (-0.056, 0.16)	0.088 (-0.32, 0.495)	
Choline	NMR	Fixed Effects Only Model	9.47e-01	-0.024 (-0.167, 0.119)	-0.007 (-0.408, 0.395)	
IL-6	Protein Immunoassay	Interaction Model	2.10e-26	**-0.759 (-0.87, -0.647)**	-0.224 (-0.625, 0.177)	**0.228 (0.038, 0.419)**
IL-8	Protein Immunoassay	Interaction Model	9.56e-24	**-0.577 (-0.674, -0.48)**	**0.654 (0.231, 1.076)**	**0.185 (0.018, 0.352)**
TNFα	Protein Immunoassay	Interaction Model	1.80e-22	**-0.531 (-0.619, -0.444)**	-0.164 (-0.628, 0.301)	**0.17 (0.019, 0.322)**
IL-10	Protein Immunoassay	Fixed Effects Only Model	6.40e-19	**-0.456 (-0.535, -0.377)**	**0.496 (0.084, 0.909)**	
IL-12(p40)	Protein Immunoassay	Fixed Effects Only Model	1.57e-11	**-0.342 (-0.422, -0.263)**	0.001 (-0.455, 0.457)	
ANG2	Protein Immunoassay	Interaction Model	2.39e-09	**-0.327 (-0.412, -0.242)**	-0.194 (-0.636, 0.249)	**0.314 (0.165, 0.463)**
IL-1β	Protein Immunoassay	Fixed Effects Only Model	2.21e-08	**-0.252 (-0.326, -0.177)**	0.332 (-0.131, 0.796)	
Fractalkine	Protein Immunoassay	Fixed Effects Only Model	3.44e-06	**-0.221 (-0.299, -0.143)**	0.296 (-0.154, 0.746)	
IL-1α	Protein Immunoassay	Fixed Effects Only Model	1.08e-03	**-0.156 (-0.242, -0.07)**	0.403 (-0.045, 0.851)	
IL-18	Protein Immunoassay	Fixed Effects Only Model	1.63e-03	**-0.104 (-0.157, -0.052)**	0.025 (-0.491, 0.542)	