Stratification of sepsis patients on admission into the Intensive Care Unit according to differential plasma metabolic phenotypes

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Quantification of Plasma Lipoproteins

A total of 112 lipoprotein parameters were quantified based on 1D NMR experiments as part of Bruker's IVDr experiment suite for blood plasma. This approach is termed Bruker's IVDr lipoprotein class and subclass Analysis (B.I.-LISA™) and lipid analytes include cholesterol, free cholesterol, phospholipids, triglycerides, apolipoproteins A1/A2/B100 and ratio B100/A1, in total plasma concentration and resolved for main lipoprotein classes and subclasses. Main classes of plasma-lipoproteins were defined as: high-density lipoprotein (HDL, density 1.063–1.210 kg/L), low-density lipoprotein (LDL, density 1.019–1.063 kg/L), intermediate-density lipoprotein (IDL, density 1.006–1.019 kg/L) and very low-density lipoprotein (VLDL, 0.950–1.006 kg/L). The main lipoprotein classes HDL, LDL, VLDL are further divided into different lipoprotein subclasses: (LDL1: 1.019–1.031 kg/L, LDL2: 1.031–1.034 kg/L, LDL3: 1.034–1.037 kg/L, LDL4: 1.037–1.040 kg/L, LDL5: 1.040–1.044 kg/L, LDL6: 1.044–1.063 kg/L), and the HDL subfractions into four density classes (HDL1 1.063–1.100 kg/L, HDL2 1.100–1.125 kg/L, HDL3 1.112–1.125 kg/L, and HDL4 1.125–1.210 kg/L), the VLDL sub-fractions divided into 5 density classes.

Table S1- Annotation of the keys used by the Bruker IVDr Lipoprotein Subclass Analysis (B.I.-LISA™) method. Abbreviations: LDL – low-density lipoprotein; HDL – high-density lipoprotein; VLDL – very low-density lipoprotein; IDL – intermediate-density lipoprotein.

Key	Class/subclass	Compound	Concentration unit
TPTG	Total Plasma	Triglycerides	mg/dL
TPCH	Total Plasma	Cholesterol	mg/dL
LDCH	LDL	Cholesterol	mg/dL
HDCH	HDL	Cholesterol	mg/dL
TPA1	Total Plasma	Apolipoprotein-A1	mg/dL
TPA2	Total Plasma	Apolipoprotein-A2	mg/dL
TPAB	Total Plasma	Apolipoprotein-B100	mg/dL
LDHD	Ratio LDL and HDL Cholesterol	LDL Cholesterol / HDL Cholesterol	-/-
ABA1	Ratio of Apolipoproteins A1 and B100	Apolipoprotein-A1 / Apolipoprotein-B100	-/-
TBPN	Apolipoprotein-B100 carrying particles	Particle Number	nmol/L
VLPN	VLDL	Particle Number	nmol/L
IDPN	IDL	Particle Number	nmol/L
LDPN	LDL	Particle Number	nmol/L
L1PN	LDL1	Particle Number	nmol/L
L2PN	LDL2	Particle Number	nmol/L
L3PN	LDL3	Particle Number	nmol/L
L4PN	LDL4	Particle Number	nmol/L
L5PN	LDL5	Particle Number	nmol/L
L6PN	LDL6	Particle Number	nmol/L
VLTG	VLDL Class	Triglycerides	mg/dL

IDTG	IDL Class	Triglycerides	mg/dL
LDTG	LDL Class	Triglycerides	mg/dL
HDTG	HDL Class	Triglycerides	mg/dL
VLCH	VLDL Class	Cholesterol	mg/dL
IDCH	IDL Class	Cholesterol	mg/dL
LDCH	LDL Class	Cholesterol	mg/dL
HDCH	HDL Class	Cholesterol	mg/dL
VLFC	VLDL Class	Free Cholesterol	mg/dL
IDFC	IDL Class	Free Cholesterol	mg/dL
LDFC	LDL Class	Free Cholesterol	mg/dL
HDFC	HDL Class	Free Cholesterol	mg/dL
VLPL	VLDL Class	Phospholipids	mg/dL
IDPL	IDL Class	Phospholipids	mg/dL
LDPL	LDL Class	Phospholipids	mg/dL
HDPL	HDL Class	Phospholipids	mg/dL
HDA1	HDL Class	Apolipoprotein-A1	mg/dL
HDA2	HDL Class	Apolipoprotein-A2	mg/dL
VLAB	VLDL Class	Apolipoprotein-B100	mg/dL
IDAB	IDL Class	Apolipoprotein-B100	mg/dL
LDAB	LDL Class	Apolipoprotein-B100	mg/dL
V1TG	VLDL1 Subclass	Triglycerides	mg/dL
V2TG	VLDL2 Subclass	Triglycerides	mg/dL
V3TG	VLDL3 Subclass	Triglycerides	mg/dL
V4TG	VLDL4 Subclass	Triglycerides	mg/dL
V5TG	VLDL5 Subclass	Triglycerides	mg/dL
V1CH	VLDL1 Subclass	Cholesterol	mg/dL
V2CH	VLDL2 Subclass	Cholesterol	mg/dL
V3CH	VLDL3 Subclass	Cholesterol	mg/dL
V4CH	VLDL4 Subclass	Cholesterol	mg/dL
V5CH	VLDL5 Subclass	Cholesterol	mg/dL
V1FC	VLDL1 Subclass	Free Cholesterol	mg/dL
V2FC	VLDL2 Subclass	Free Cholesterol	mg/dL
V3FC	VLDL3 Subclass	Free Cholesterol	mg/dL
V4FC	VLDL4 Subclass	Free Cholesterol	mg/dL
V5FC	VLDL5 Subclass	Free Cholesterol	mg/dL
V1PL	VLDL1 Subclass	Phospholipids	mg/dL
V2PL	VLDL2 Subclass	Phospholipids	mg/dL
V3PL	VLDL3 Subclass	Phospholipids	mg/dL
V4PL	VLDL4 Subclass	Phospholipids	mg/dL
V5PL	VLDL5 Subclass	Phospholipids	mg/dL
L1TG	LDL1 Subclass	Triglycerides	mg/dL

L2TG	LDL2 Subclass	Triglycerides	mg/dL
L3TG	LDL3 Subclass	Triglycerides	mg/dL
L4TG	LDL4 Subclass	Triglycerides	mg/dL
L5TG	LDL5 Subclass	Triglycerides	mg/dL
L6TG	LDL6 Subclass	Triglycerides	mg/dL
L1CH	LDL1 Subclass	Cholesterol	mg/dL
L2CH	LDL2 Subclass	Cholesterol	mg/dL
L3CH	LDL3 Subclass	Cholesterol	mg/dL
L4CH	LDL4 Subclass	Cholesterol	mg/dL
L5CH	LDL5 Subclass	Cholesterol	mg/dL
L6CH	LDL6 Subclass	Cholesterol	mg/dL
L1FC	LDL1 Subclass	Free Cholesterol	mg/dL
L2FC	LDL2 Subclass	Free Cholesterol	mg/dL
L3FC	LDL3 Subclass	Free Cholesterol	mg/dL
L4FC	LDL4 Subclass	Free Cholesterol	mg/dL
L5FC	LDL5 Subclass	Free Cholesterol	mg/dL
L6FC	LDL6 Subclass	Free Cholesterol	mg/dL
L1PL	LDL1 Subclass	Phospholipids	mg/dL
L2PL	LDL2 Subclass	Phospholipids	mg/dL
L3PL	LDL3 Subclass	Phospholipids	mg/dL
L4PL	LDL4 Subclass	Phospholipids	mg/dL
L5PL	LDL5 Subclass	Phospholipids	mg/dL
L6PL	LDL6 Subclass	Phospholipids	mg/dL
L1AB	LDL1 Subclass	Apolipoprotein-B100	mg/dL
L2AB	LDL2 Subclass	Apolipoprotein-B100	mg/dL
L3AB	LDL3 Subclass	Apolipoprotein-B100	mg/dL
L4AB	LDL4 Subclass	Apolipoprotein-B100	mg/dL
L5AB	LDL5 Subclass	Apolipoprotein-B100	mg/dL
L6AB	LDL6 Subclass	Apolipoprotein-B100	mg/dL
H1TG	HDL1 Subclass	Triglycerides	mg/dL
H2TG	HDL2 Subclass	Triglycerides	mg/dL
H3TG	HDL3 Subclass	Triglycerides	mg/dL
H4TG	HDL4 Subclass	Triglycerides	mg/dL
H1CH	HDL1 Subclass	Cholesterol	mg/dL
H2CH	HDL2 Subclass	Cholesterol	mg/dL
H3CH	HDL3 Subclass	Cholesterol	mg/dL
H4CH	HDL4 Subclass	Cholesterol	mg/dL
H1FC	HDL1 Subclass	Free Cholesterol	mg/dL
H2FC	HDL2 Subclass	Free Cholesterol	mg/dL
H3FC	HDL3 Subclass	Free Cholesterol	mg/dL
H4FC	HDL4 Subclass	Free Cholesterol	mg/dL

H1PL	HDL1 Subclass	Phospholipids	mg/dL
H2PL	HDL2 Subclass	Phospholipids	mg/dL
H3PL	HDL3 Subclass	Phospholipids	mg/dL
H4PL	HDL4 Subclass	Phospholipids	mg/dL
H1A1	HDL1 Subclass	Apolipoprotein-A1	mg/dL
H2A1	HDL2 Subclass	Apolipoprotein-A1	mg/dL
H3A1	HDL3 Subclass	Apolipoprotein-A1	mg/dL
H4A1	HDL4 Subclass	Apolipoprotein-A1	mg/dL
H1A2	HDL1 Subclass	Apolipoprotein-A2	mg/dL
H2A2	HDL2 Subclass	Apolipoprotein-A2	mg/dL
H3A2	HDL3 Subclass	Apolipoprotein-A2	mg/dL
H4A2	HDL4 Subclass	Apolipoprotein-A2	mg/dL
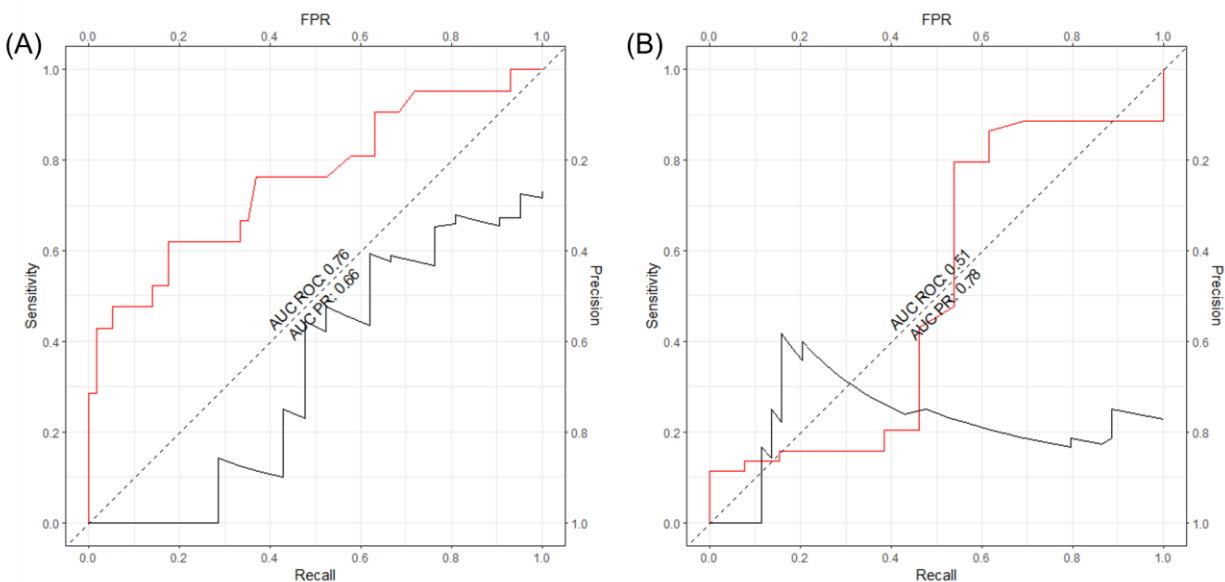
Figure S1 - (A) Area under the ROC (red) and area under the PR curves (black) for no sepsis vs sepsis and septic shock patients using only C-reactive protein. (B) Area under the ROC (red) and area under the PR curves (black) for sepsis vs septic shock patients using only C-reactive protein. Samples included only up to 48 hours admission into ICU.
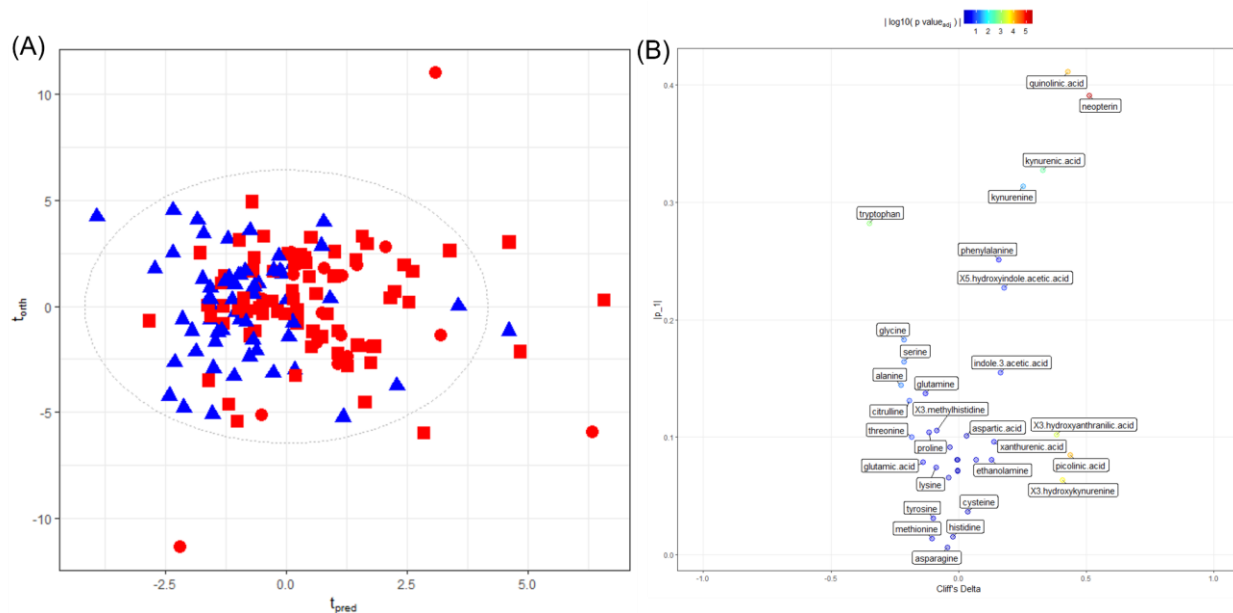
Figure S2 - (A) O-PLS-DA for non sepsis patients (blue triangle) versus sepsis (red square) and septic shock patients (red circle) for the amino acid and tryptophan pathway intermediates ($R^2X=0.13$, CV-AUROC=0.66) and eruption plot. Eruption plots are formed from the Cliff's delta (abscissa) and O-PLS-DA loadings (ordinate). Coloured by significance. Samples collected within 48 hours of admission only.

Table S2 - OPLS loadings, Cliff's delta and adjusted *p*-values for the amino acid and tryptophan pathway intermediates for no sepsis versus sepsis and septic shock. Ordered by Cliff's delta, only the significant metabolites are shown.

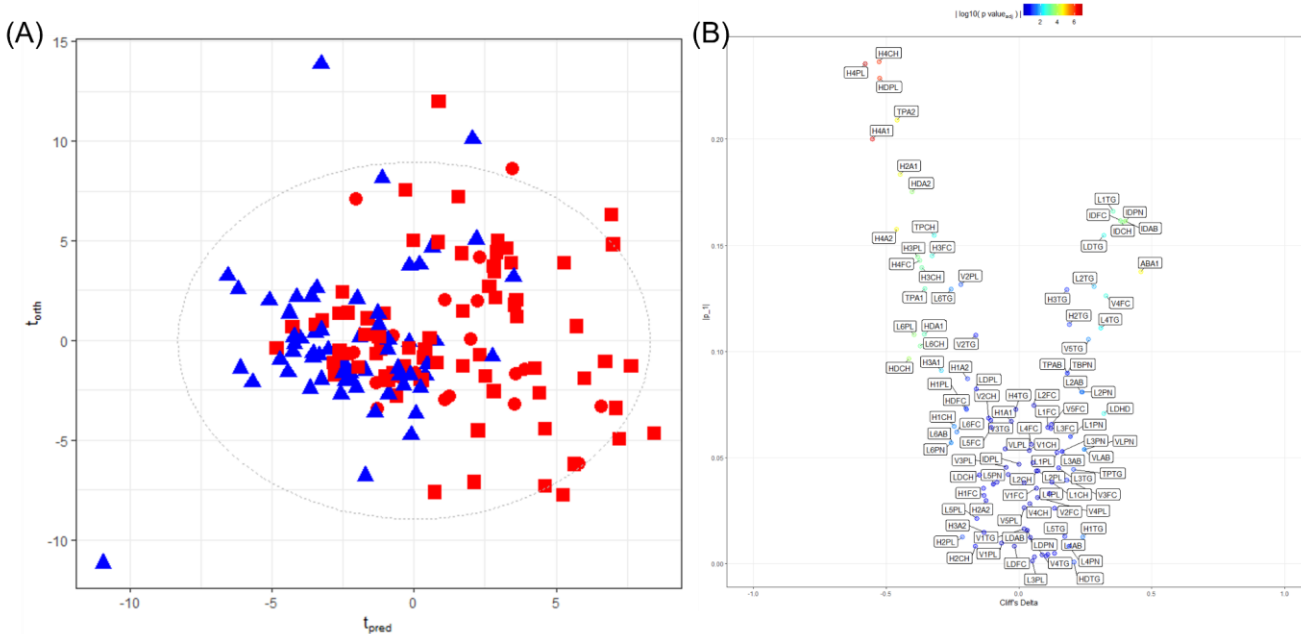| Metabolite	OPLS loadings	Cliff's delta	Adjusted *p*-value
Neopterin	0.391	0.51	3.13×10^{-6}
Picolinic acid	0.085	0.44	8.85×10^{-5}
Quinolinic acid	0.411	0.43	9.27×10^{-5}
3-hydroxykynurenine	0.064	0.41	1.98×10^{-4}
3-hydroxyanthranilic acid	0.102	0.38	4.48×10^{-4}
Tryptophan	0.282	-0.35	1.52×10^{-3}
Kynurenic acid	0.327	0.33	2.97×10^{-3}
Kynurenine	0.313	0.25	3.70×10^{-2}

Figure S3 - (A) O-PLS-DA for no sepsis patients (blue triangle) versus sepsis (red square) and septic shock patients (red circle) for the lipoproteins and (B) eruption plot. (R²X=0.13, CV-AUROC=0.78). Eruption plots are formed from the Cliff's delta (abscissa) and O-PLS-DA loadings (ordinate). Coloured by significance. Samples collected within 48 hours of admission only.

Table S3 - OPLS loadings, Cliff's delta and adjusted *p*-values for the lipoproteins for no sepsis versus sepsis and septic shock. Ordered by Cliff's delta, only the significant metabolites are shown.

Metabolite	OPLS loadings	Cliff's delta	Adjusted *p*-value
H4PL	0.235	-0.58	1.09×10^{-7}
H4A1	0.200	-0.55	3.30×10^{-7}
HDPL	0.229	-0.53	8.84×10^{-7}
H4CH	0.237	-0.53	8.84×10^{-7}
TPA2	0.209	-0.46	2.23×10^{-5}
ABA1	0.138	0.46	2.23×10^{-5}
H4A2	0.158	-0.46	2.23×10^{-5}
H2A1	0.182	-0.45	3.21×10^{-5}
HDCH	0.097	-0.41	1.55×10^{-4}
HDA2	0.175	-0.40	2.32×10^{-4}
IDPN	0.161	0.40	2.33×10^{-4}
IDAB	0.161	0.40	2.33×10^{-4}
L6PL	0.108	-0.39	2.58×10^{-4}
IDCH	0.161	0.39	3.50×10^{-4}
IDFC	0.162	0.38	2.33×10^{-4}
H3PL	0.145	-0.38	4.03×10^{-4}

L6CH	0.103	-0.37	5.03×10^{-4}
H4FC	0.143	-0.37	5.06×10^{-4}
H3CH	0.139	-0.37	6.52×10^{-4}
TPA1	0.130	-0.35	9.85×10^{-4}
HDA1	0.108	-0.36	9.85×10^{-4}
L1TG	0.166	0.35	1.02×10^{-3}
V4FC	0.126	0.33	2.61×10^{-3}
H3FC	0.145	-0.33	2.61×10^{-3}
TPCH	0.155	-0.32	3.26×10^{-3}
LDTG	0.155	0.32	3.26×10^{-3}
LDHD	0.071	0.32	3.26×10^{-3}
L4TG	0.111	0.31	4.60×10^{-3}
H3A1	0.091	-0.29	7.91×10^{-3}
L2TG	0.130	0.28	1.08×10^{-2}
V5TG	0.106	0.26	2.15×10^{-2}
L6PN	0.057	-0.26	2.33×10^{-2}
L6TG	0.129	-0.26	2.33×10^{-2}
L6AB	0.057	-0.26	2.33×10^{-2}
VLPN	0.054	0.25	2.95×10^{-2}
VLAB	0.054	0.25	2.95×10^{-2}
H1CH	0.065	-0.25	2.95×10^{-2}
H1TG	0.013	0.24	3.36×10^{-2}
L2PN	0.081	0.24	3.51×10^{-2}
L6FC	0.062	-0.24	3.51×10^{-2}
L2AB	0.081	0.24	3.51×10^{-2}
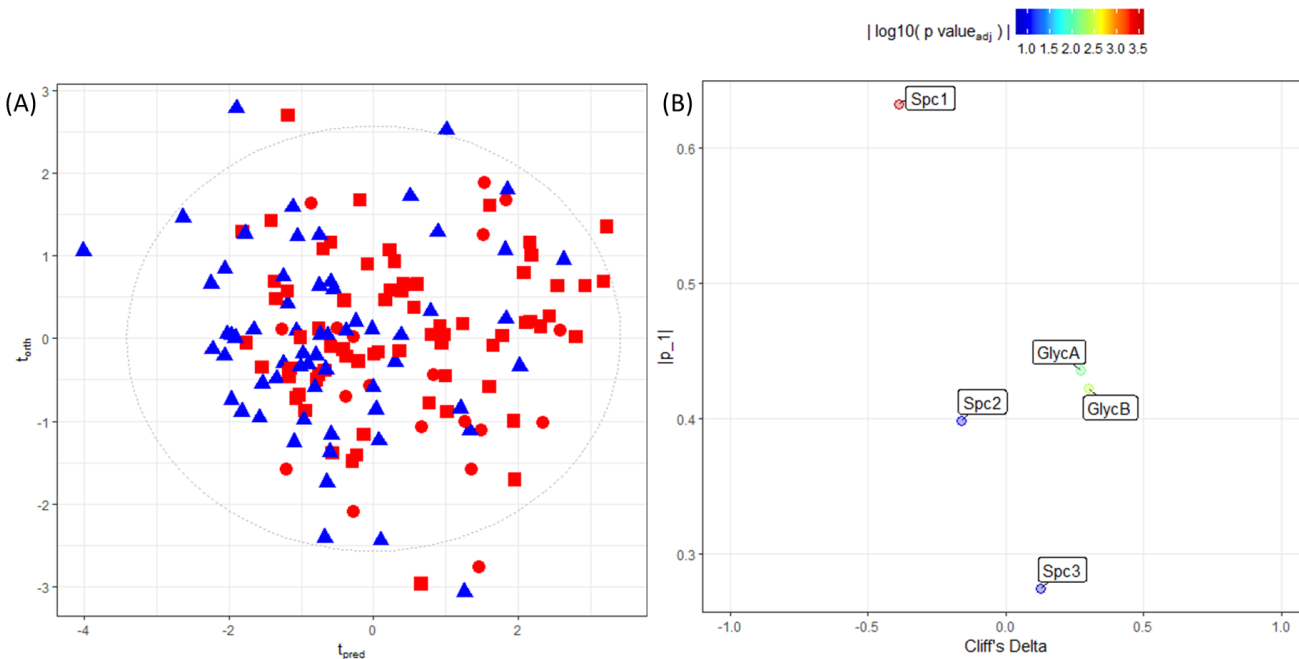
Figure S4 - (A) O-PLS-DA for non sepsis patients (blue triangle) versus sepsis (red square) and septic shock patients (red circle) for the inflammatory markers (glycoproteins and SPC). (R^2X=0.56, CV-AUROC=0.68) (B) Eruption plot of the O-PLS-DA model. Eruption plots are formed from the Cliff's delta (abscissa) and O-PLS-DA loadings (ordinate). Coloured by significance. Samples collected within 48 hours of admission only.

Table S4 - OPLS loadings, Cliff's delta and adjusted *p*-values for the Glycoprotein and SPC for no sepsis versus sepsis and septic shock. Ordered by Cliff's delta.

Metabolite	OPLS loadings	Cliff's delta	Adjusted *p*-value
SPC1	0.632	-0.39	2.45×10^{-4}
GlycB	0.422	0.30	4.04×10^{-3}
GlycA	0.435	0.27	7.65×10^{-3}
SPC2	0.398	-0.16	0.11
SPC3	0.274	0.13	0.18
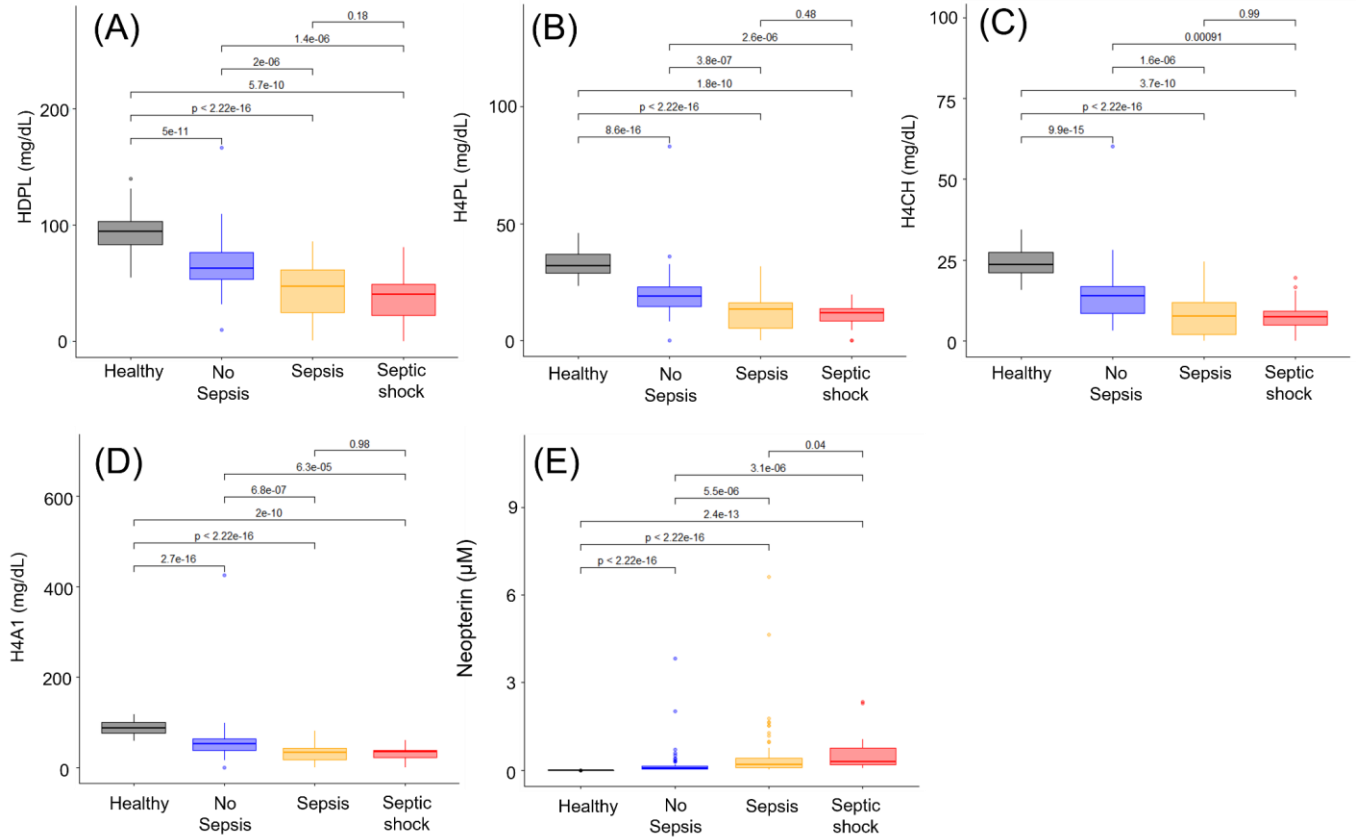
Figure S5 - Box plots of healthy controls (black), patients with no sepsis (blue), patients with sepsis (yellow) and patients with septic shock (red) for the model 1 lipoproteins and neopterin from samples collected within 48 hours of admission into ICU. Significance levels from Mann Whitney-U tests between the groups are shown above the corresponding plots.
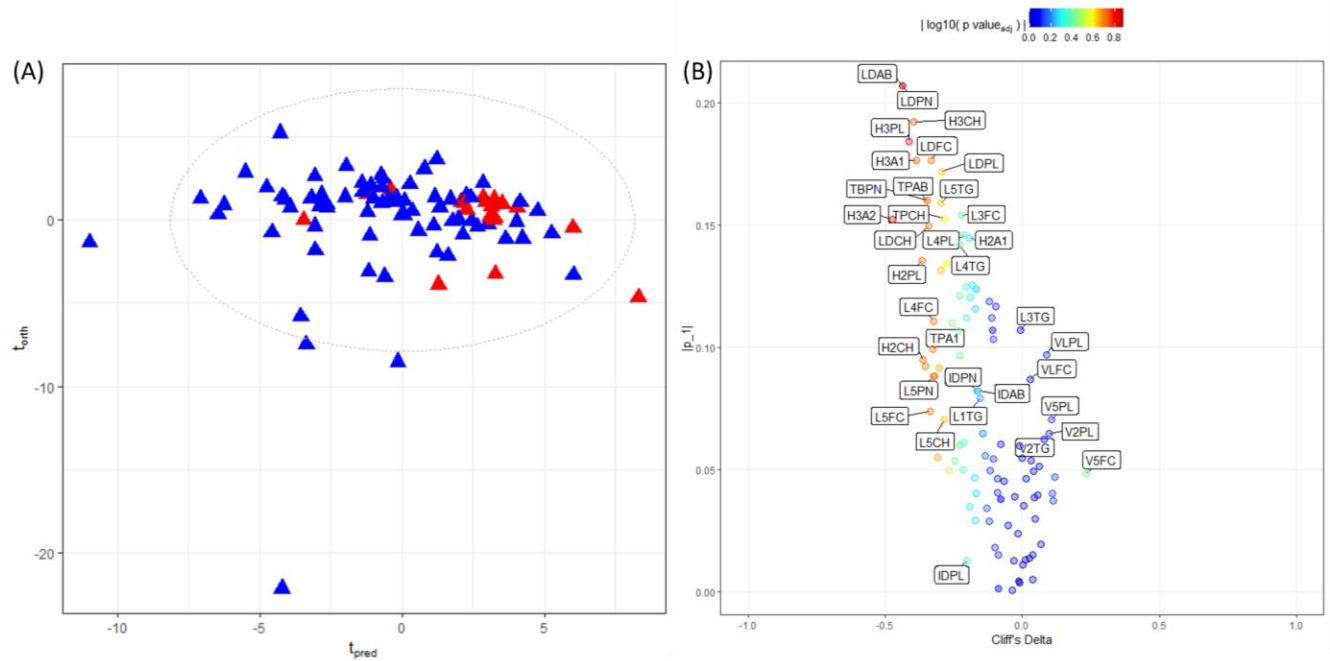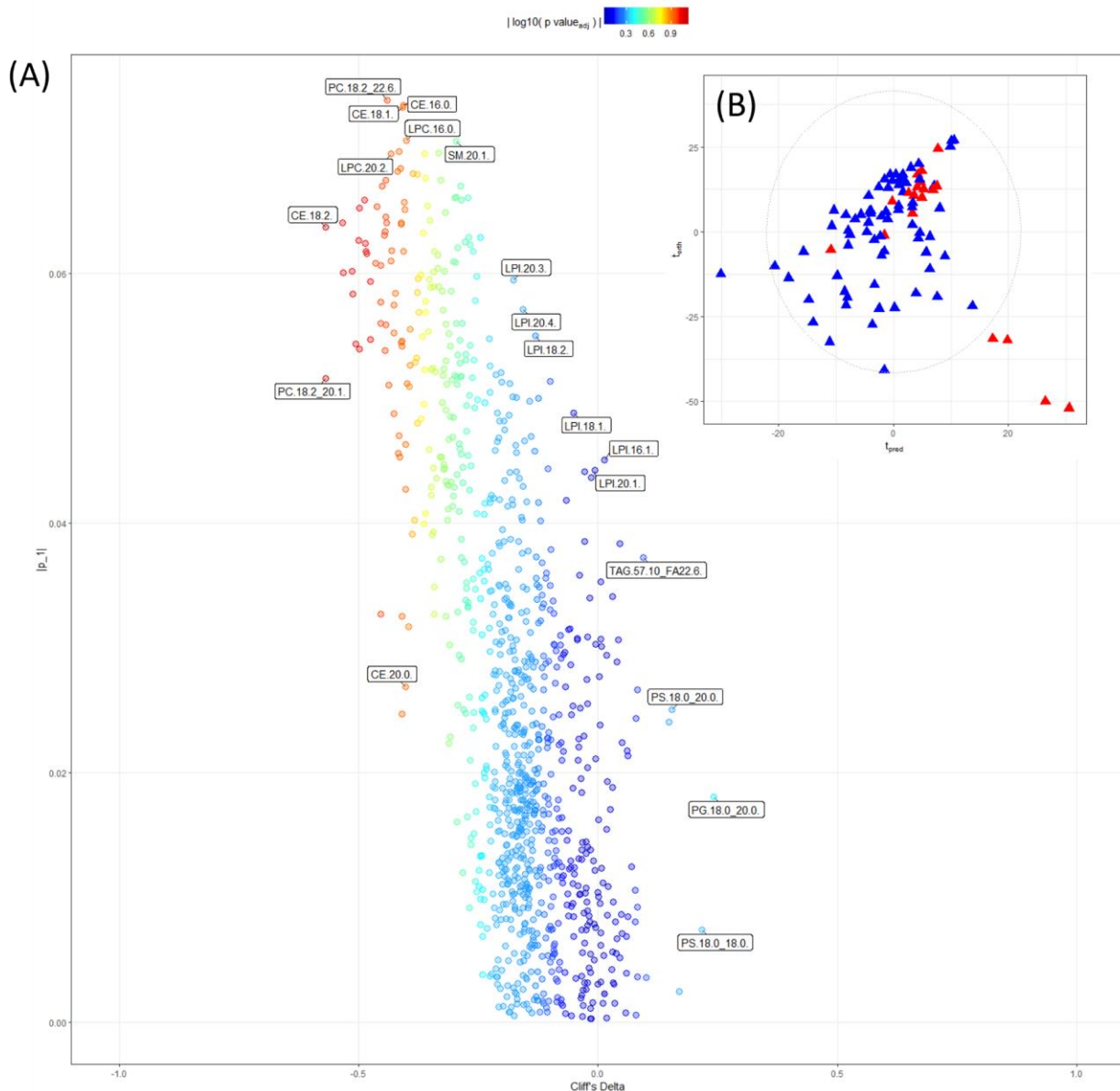
Figure S6 - (A) O-PLS-DA for sepsis patients (blue) versus septic shock patients (red) for the lipoproteins. (R²X=0.15, AUROC=0.60) (B) Eruption plot of the O-PLS-DA model. Eruption plots are formed from the Cliff's delta (abscissa) and O-PLS-DA loadings (ordinate). Coloured by significance. Samples collected within 48 hours of admission only.

Table S5 - OPLS loadings, Cliff's delta and adjusted *p*-values for the lipoproteins of sepsis patients vs septic shock patients at baseline. Only those lipoproteins with a Cliff's delta below 0.25 are shown.

Metabolite	OPLS loadings	Cliff's delta	Adjusted *p*-value
H3A2	0.152	-0.47	1.30×10^{-1}
LDAB	0.207	-0.44	1.30×10^{-1}
LDPN	0.207	-0.44	1.30×10^{-1}
H3PL	0.184	-0.41	1.62×10^{-1}
H3CH	0.192	-0.40	1.84×10^{-1}
H3A1	0.177	-0.39	1.84×10^{-1}
H2PL	0.136	-0.36	1.96×10^{-1}
H2CH	0.095	-0.36	1.96×10^{-1}
HDA1	0.092	-0.36	1.96×10^{-1}
TPAB	0.160	-0.35	1.96×10^{-1}
TBPN	0.160	-0.35	1.96×10^{-1}
LDCH	0.150	-0.34	1.96×10^{-1}
L5FC	0.074	-0.34	1.96×10^{-1}
LDFC	0.177	-0.33	1.96×10^{-1}
TPA1	0.099	-0.33	1.96×10^{-1}
L5PN	0.088	-0.32	1.96×10^{-1}

L4FC	0.111	-0.32	1.96×10^{-1}
L5AB	0.088	-0.32	1.96×10^{-1}
H3TG	0.055	-0.31	2.20×10^{-1}
L5PL	0.092	-0.30	2.20×10^{-1}
L5TG	0.159	-0.30	2.29×10^{-1}
H3FC	0.131	-0.30	2.29×10^{-1}
LDPL	0.172	-0.30	2.29×10^{-1}
TPCH	0.153	-0.29	2.55×10^{-1}
L5CH	0.070	-0.28	2.29×10^{-1}
L4AB	0.134	-0.28	2.67×10^{-1}
L4PN	0.134	-0.28	2.67×10^{-1}
H2TG	0.050	-0.27	2.97×10^{-1}
H2FC	0.110	-0.25	3.47×10^{-1}
HDTG	0.054	-0.25	3.80×10^{-1}

Figure S7 – (B) O-PLS-DA for sepsis patients (blue) versus septic shock patients (red) for the lipids. ($R^2X=0.18$, AUROC=0.68) (A) Eruption plot of the O-PLS-DA model. Eruption plots are formed from the Cliff's delta (abscissa) and O-PLS-DA loadings (ordinate). Coloured by significance. Samples collected within 48 hours of admission only.

Table S6 – OPLS loadings, Cliff's delta and adjusted *p*-values for the lipids of sepsis patients vs septic shock patients at baseline. Only those lipids with a Cliff's delta below -0.4 are shown.

Metabolite	OPLS loadings	Cliff's delta	Adjusted *p*-value
CE (18:2)	0.064	-0.57	7.30×10^{-2}
PC (18:2/20:1)	0.052	-0.57	7.30×10^{-2}
CE (20:3)	0.064	-0.53	8.56×10^{-2}

PC (16:0/20:2)	0.060	-0.53	8.56×10^{-2}
PC (20:0/20:3)	0.060	-0.51	8.56×10^{-2}
PE.P (18:0/20:5)	0.058	-0.51	8.56×10^{-2}
DCER (26:1)	0.054	-0.51	8.56×10^{-2}
PC (18:2/20:3)	0.063	-0.50	8.56×10^{-2}
CE (18:0)	0.054	-0.50	8.56×10^{-2}
PC (18:0/20:3)	0.065	-0.50	8.56×10^{-2}
PI (20:0/18:2)	0.066	-0.49	8.98×10^{-2}
CE (20:2)	0.062	-0.49	8.98×10^{-2}
PE.P (18:0/20:3)	0.062	-0.48	8.98×10^{-2}
PC (16:0/20:3)	0.062	-0.48	8.98×10^{-2}
PE.O (16:0/20:5)	0.055	-0.48	9.33×10^{-2}
PE.P (18:1/20:3)	0.061	-0.46	1.06×10^{-1}
SM (24:1)	0.065	-0.46	1.06×10^{-1}
CE (20:5)	0.056	-0.45	1.06×10^{-1}
PC (20:0/20:2)	0.058	-0.45	1.06×10^{-1}
PE.P (18:0/20:4)	0.061	-0.45	1.06×10^{-1}
PG (18:2/20:4)	0.033	-0.45	1.06×10^{-1}
PC (18:0/20:2)	0.067	-0.45	1.06×10^{-1}
PC (18:1/22:5)	0.063	-0.45	1.06×10^{-1}
PC (18:1/20:5)	0.054	-0.44	1.06×10^{-1}
PC (18:2/22:5)	0.063	-0.44	1.06×10^{-1}
CE (22:5)	0.065	-0.44	1.06×10^{-1}
PC (18:1/22:6)	0.067	-0.44	1.06×10^{-1}
PC (20:0/20:4)	0.056	-0.44	1.06×10^{-1}
PC (18:2/20:4)	0.064	-0.44	1.06×10^{-1}
PC (18:2/22:6)	0.074	-0.44	1.06×10^{-1}
CER (26:0)	0.051	-0.44	1.10×10^{-1}
LPC (20:2)	0.070	-0.43	1.13×10^{-1}
PC (20:0/22:5)	0.061	-0.43	1.14×10^{-1}
CE (18:3)	0.062	-0.43	1.14×10^{-1}
PC (14:0/20:5)	0.057	-0.43	1.15×10^{-1}
PE.P (16:0/20:5)	0.055	-0.43	1.15×10^{-1}
PI (20:0/18:1)	0.049	-0.43	1.15×10^{-1}
PC (18:2/20:5)	0.058	-0.42	1.17×10^{-1}
LPC (14:0)	0.068	-0.42	1.17×10^{-1}
PE (18:2/16:1)	0.046	-0.42	1.17×10^{-1}
CE (14:0)	0.047	-0.42	1.17×10^{-1}
LPC (18:0)	0.070	-0.42	1.17×10^{-1}
PS (18:0/20:4)	0.045	-0.41	1.17×10^{-1}

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LPC (20:0)	0.068	-0.41	1.17×10^{-1}
PC (18:2/18:2)	0.064	-0.41	1.17×10^{-1}
PE.P (18:0/22:5)	0.054	-0.41	1.17×10^{-1}
SM (24:0)	0.064	-0.41	1.17×10^{-1}
CE (24:0)	0.033	-0.41	1.17×10^{-1}
DAG (20:0/20:0)	0.025	-0.41	1.17×10^{-1}
PE.P (16:0/20:3)	0.055	-0.41	1.17×10^{-1}
PS (20:0/20:5)	0.054	-0.41	1.17×10^{-1}
CE (18:1)	0.073	-0.41	1.18×10^{-1}
CE (16:0)	0.073	-0.41	1.18×10^{-1}
PE.P (16:0/20:1)	0.062	-0.41	1.18×10^{-1}
LPC (20:3)	0.066	-0.41	1.19×10^{-1}
PI (20:0/20:4)	0.065	-0.40	1.20×10^{-1}
CE (20:0)	0.027	-0.40	1.20×10^{-1}
PC (18:0/18:2)	0.046	-0.40	1.20×10^{-1}
PE.P (14:0/18:1)	0.043	-0.40	1.20×10^{-1}
LPC (16:0)	0.071	-0.40	1.20×10^{-1}
CE (16:1)	0.051	-0.40	1.21×10^{-1}
CE (22:0)	0.032	-0.40	1.30×10^{-1}
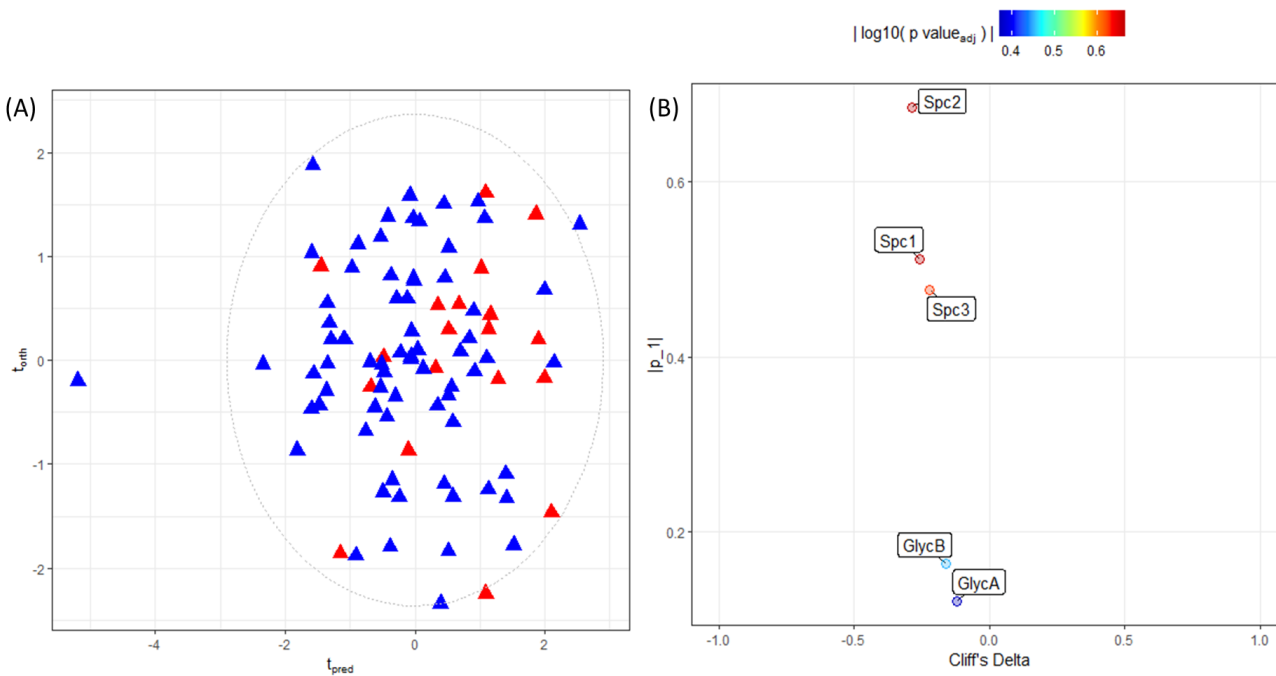
Figure S8 – (A) O-PLS-DA for sepsis patients (blue) versus septic shock patients (red) for the glycoproteins and SPC. ($R^2X=0.46$, AUROC=0.63) (B) Eruption plot of the O-PLS-DA model. Eruption plots are formed from the

Cliff's delta (abscissa) and O-PLS-DA loadings (ordinate). Coloured by significance. Samples collected within 48 hours of admission only.

Table S7 - OPLS loadings, Cliff's delta and adjusted *p*-values for the glycoproteins and SPC of sepsis patients vs septic shock patients at baseline.

Metabolite	OPLS loadings	Cliff's delta	Adjusted *p*-value
SPC2	0.685	-0.29	0.24
SPC1	0.512	-0.26	0.22
SPC3	0.477	-0.22	0.24
GlycB	0.163	-0.16	0.35
GlycA	0.121	-0.12	0.43
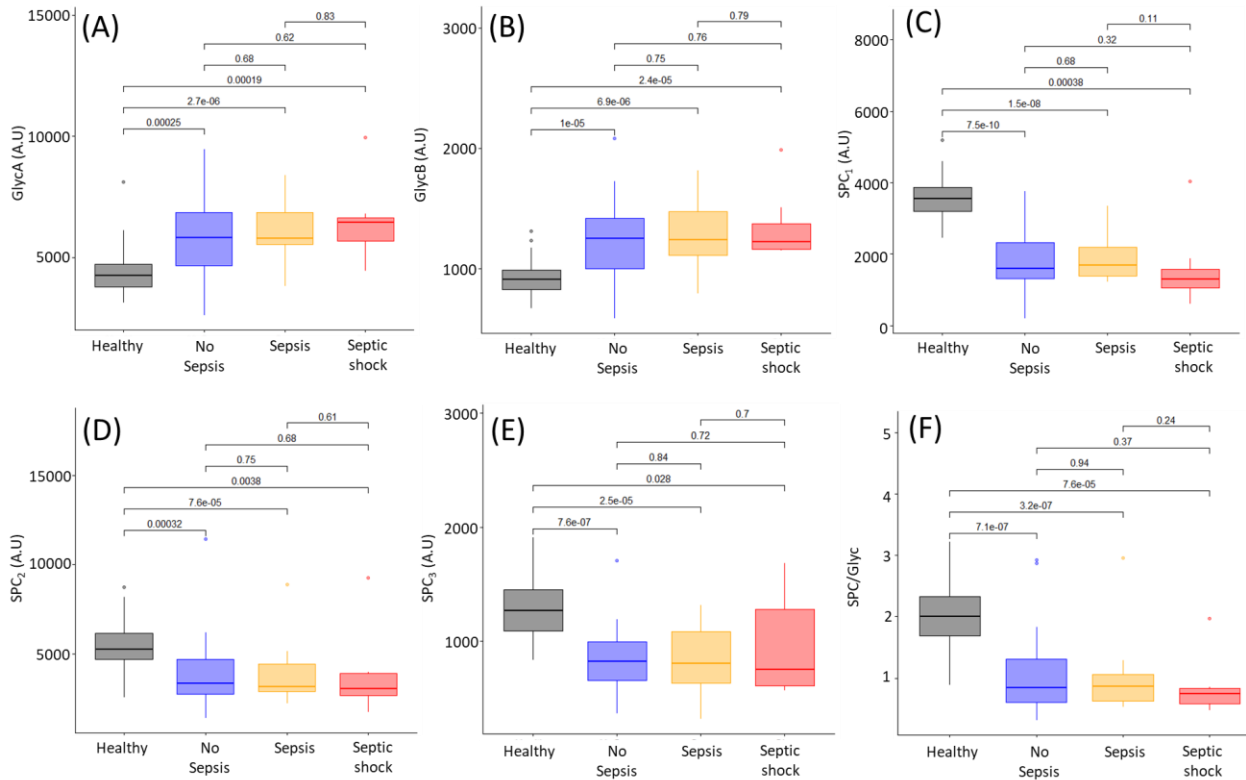
Figure S9 - Box plots of healthy controls (black), patients with no sepsis (blue), patients with sepsis (yellow) and patients with septic shock (red) for the glycoproteins and SPC at 7 days post ICU admission. Significance levels from Mann Whitney-U tests between the groups are shown above the corresponding plots.
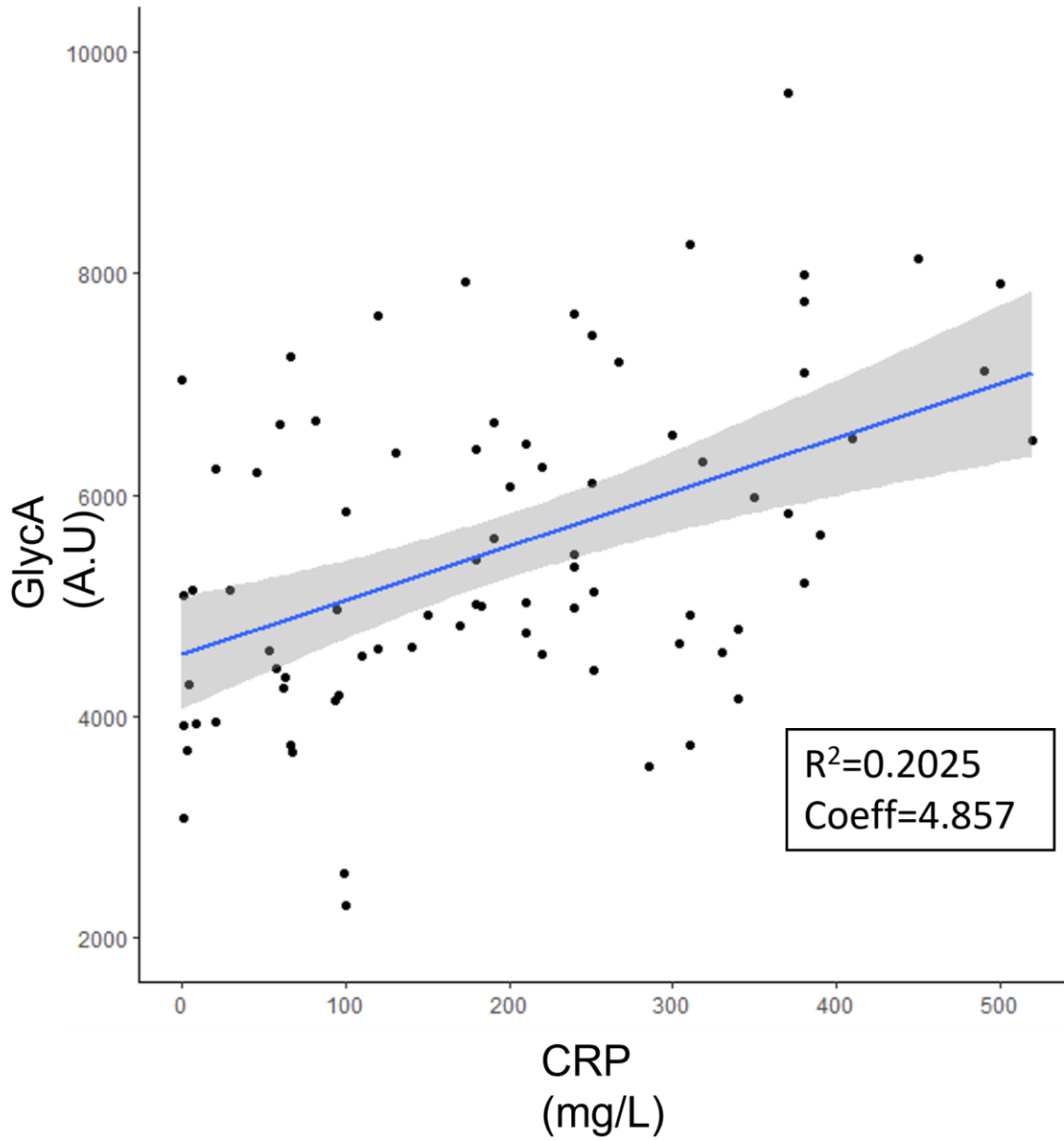
Figure S10 - CRP and GlycA correlation. Samples collected within 48 hours of admission into ICU only.