Supplementary Information

SARS-CoV-2 RNAemia and proteomic biomarker trajectory inform
prognostication in COVID-19 patients admitted to intensive care

Clemens Gutmann\textsuperscript{1}\textsuperscript{*}, Kaloyan Takov\textsuperscript{1}\textsuperscript{*}, Sean A. Burnap\textsuperscript{1}, Bhawana Singh\textsuperscript{1}, Konstantinos Theofilatos\textsuperscript{1}, Ella Reed\textsuperscript{1}, Maria Hasman\textsuperscript{1}, Adam Nabeebaccus\textsuperscript{1,2}, Matthew Fish\textsuperscript{3,4}, Mark J.W. McPhail\textsuperscript{2,5,6}, Kevin O’Gallagher\textsuperscript{1,2}, Lukas E. Schmidt\textsuperscript{1}, Christian Cassel\textsuperscript{1}, Marieke Rienks\textsuperscript{1}, Xiaoke Yin\textsuperscript{1}, Georg Auzinger\textsuperscript{2}, Salvatore Napoli\textsuperscript{5}, Salma F. Mujib\textsuperscript{6}, Francesca Trovato\textsuperscript{2,5,6}, Barnaby Sanderson\textsuperscript{4}, Blair Merrick\textsuperscript{7}, Umar Niazi\textsuperscript{8}, Mansoor Saqi\textsuperscript{8}, Konstantina Dimitrakopoulou\textsuperscript{8}, Silke Braun\textsuperscript{9}, Romy Kronstein-Wiedemann\textsuperscript{10}, Katie J. Doores\textsuperscript{3}, Jonathan D. Edgeworth\textsuperscript{3,7}, Ajay M. Shah\textsuperscript{1}, Stefan R. Bornstein\textsuperscript{11,12}, Torsten Tonn\textsuperscript{10,13}, Adrian C. Hayday\textsuperscript{3,14}, Manu Shankar-Hari\textsuperscript{3,4,15}, Manuel Mayr\textsuperscript{1,11,15}.

\textsuperscript{1} King's College London British Heart Foundation Centre, School of Cardiovascular Medicine and Sciences, London, UK.
\textsuperscript{2} King's College Hospital NHS Foundation Trust, London, UK.
\textsuperscript{3} Department of Infectious Diseases, School of Immunology and Microbial Sciences, King's College London, London, UK.
\textsuperscript{4} Department of Intensive Care Medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK.
\textsuperscript{5} Department of Inflammation Biology, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK.
\textsuperscript{6} Institute of Liver Studies, King’s College Hospital, London, UK.
\textsuperscript{7} Clinical Infection and Diagnostics Research group, Department of Infection, Guy’s and St Thomas’ NHS Foundation Trust, London, UK.
Running title: SARS-CoV-2 RNAemia and Proteomics

To whom correspondence should be addressed:
Dr. Manu Shankar-Hari; manu.shankar-hari@kcl.ac.uk or Prof. Manuel Mayr; King’s British Heart Foundation Centre, King’s College London, 125 Coldharbour Lane, London, SE59NU UK; Phone: +44(0)2078485446; +44(0)2078485298; manuel.mayr@kcl.ac.uk.
**Supplementary Fig. 1: Study design.**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>COVID-19</th>
<th>Non-COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU patients</strong></td>
<td></td>
<td><strong>Pre-pandemic controls</strong></td>
</tr>
<tr>
<td>Plasma KCH</td>
<td>Patients: 16</td>
<td>Plasma GSTT</td>
</tr>
<tr>
<td>Patients: 78</td>
<td></td>
<td>Plasm</td>
</tr>
<tr>
<td>Samples: 55</td>
<td></td>
<td>Patients: 62</td>
</tr>
<tr>
<td><strong>Non-ICU patients</strong></td>
<td></td>
<td><strong>Pre-pandemic ICU sepsis patients</strong></td>
</tr>
<tr>
<td>SARS-CoV-2 RNAemia</td>
<td></td>
<td>Plasma GSTT</td>
</tr>
<tr>
<td>(Heparinase &amp; two-step RT-qPCR)</td>
<td></td>
<td>Patients: 12</td>
</tr>
<tr>
<td>(Immunoassays)</td>
<td></td>
<td>Samples: 60</td>
</tr>
<tr>
<td>SARS-CoV-2 antibodies</td>
<td></td>
<td>Proteomics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- COVID-19 vs sepsis vs controls</td>
</tr>
<tr>
<td>RAGE PTX3 LGALS3BP</td>
<td></td>
<td>- RNAemia and outcome association (DIA-MS &amp; PQ500)</td>
</tr>
<tr>
<td>(Immuoassays)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KCH: King’s College Hospital
GSTT: Guy’s and St Thomas’ NHS Foundation Trust
Supplementary Fig. 2: Pairwise Spearman correlation for continuous variables and point-biserial correlation for binary variables including SARS-CoV-2 RNAemia. Hierarchical clustering analysis and heat-map matrix illustrates positive and negative co-expression and clusters. Three distinct clusters emerge:

One comprising of albumin, hematocrit and hemoglobin, second cluster with urea, creatinine, hypertension, and type 2 diabetes and third cluster with sodium, WCC, neutrophils, FiO2 and CRP. White indicates no significant correlation (P value >0.05). Red indicates positive and blue negative correlation with P value <0.05. Abbreviations: Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, Bil: bilirubin, Crea: creatinine, CRP: C-reactive protein, DM: type 2 diabetes, Hct: hematocrit, Hb: hemoglobin, HR: heart rate, HTN: hypertension, Lymphoc: lymphocytes, MAP: mean arterial pressure, Monoc: monocytes, Neutroph: neutrophils, K: potassium, Resp. rate: respiratory rate, Na.: sodium, Temp: body temperature, WCC: white cell count.
Supplementary Fig. 3: COVID-19 plasma proteome signature, common to published reports. Plasma proteome profiling was conducted using a DIA-MS approach with spiked authentic heavy standards. 100 proteins were significantly different in the plasma proteome of COVID-19 ICU patients, when compared to control and sepsis ICU patients, and this panel was cross-referenced against two previously published proteomic studies, exploring circulating protein markers of COVID-19 severity, to generate a panel of 29 common proteins. These 29 common proteins are each individually represented to highlight their variation across disease phenotype. Significance was determined through the Kruskal-Wallis test with Benjamini and Hochberg’s FDR correction.
Supplementary Fig. 4: Comparison of the trajectories of individual proteins in COVID-19 ICU patients.

Listed are the proteins that show a significant interaction between survival and time of measurement (0 = ICU admission; 1 = first week after ICU admission; 2 = second week after ICU admission). Linear Mixed Models analysis was performed to calculate the P values, correcting for age and sex. Abbreviations: ApoB, apolipoprotein B; ApoC1, apolipoprotein C1; ApoE, apolipoprotein E; BTD, biotinidase; CFH, complement factor H; CSF1R, macrophage colony-stimulating factor 1 receptor; KNG1, kininogen; SELL, L-selectin.
**Supplementary Fig. 5: LGALS3BP enriched functional pathways.** Proteins that correlated with LGALS3BP levels as determined by proteomics with a greater than 0.6 Spearman coefficient were analyzed to determine enriched functional pathways. Gene ontology analysis revealed an enrichment of protein pathways related to the complement system, platelet degranulation, proteolysis and the innate immune response.
Supplementary Fig. 6: Existing biomarkers for ARDS and sepsis: RAGE (a) and PTX3 (b) were measured by ELISA. Comparisons of control (RAGE: n = 30, PTX3: n = 23), sepsis ICU (RAGE: n = 12, PTX3: n = 10) and COVID-19 ICU (RAGE: n = 74, PTX3: n = 13) patients using a Kruskal-Wallis and Dunn’s multiple comparisons test. Longitudinal comparisons at baseline, week 1 and week 2 after admission to ICU (n = 46). Red dots highlight patients who died, white dots represent patients who survived. Friedman test with Dunn’s multiple comparisons were used to determine statistical significance. Comparisons according to RNAemia status (n = 46 negative: “-ve”; n = 15 positive: “+ve”). Significance was determined by Mann-Whitney U test. Comparisons according to 28-day mortality (n = 13 died, n = 48 survived). Mann-Whitney U test were used for statistical comparisons.
Supplementary Fig. 7: Abundance of SARS-CoV-2 RNA in plasma or serum. Cq values of all samples in which SARS-CoV-2 RNA was detectable (Cq <40) are shown. Mann-Whitney U test. Red - died, white - survived.
Supplementary Fig. 8: Technical validation of machine learning model. a, Permutation test of SVM classifier performance: 10-fold cross-validation (CV) of the best predictor showing mean performance and standard error of mean. 10-fold CV is comparable with leave-one-out metrics shown in Supplementary table 4. Significance test of 10-fold CV performed using permutation test with 50 permutes i.e. repeating the classification procedure after random permuting of the outcome labels. This returned a significant P value i.e. <0.05, thus indicating that the classifier has found a real class structure (pattern) in the data. Hence, rejecting the null hypothesis that the classifier performance is by chance i.e. input variables and outcome labels are independent. b, Stability of feature importance under a Random Forest (RF) Model showing mean variable importance and standard error of mean across 100 resampling cycles of sensitivity analysis. Each resampling cycle takes equal proportions of the two outcome classes from the complete training data. Top 17 (of the 28) features are shown based on mean importance. The features with negative scores make the prediction worse and should be excluded from the model. The technical validation of feature importance stability using this
alternate machine learning method i.e. RF with resampling reinforces the importance of best predictor i.e. 'Age, RNAemia' that are ranked among the top 2 most important features. Abbreviations: CRP: C-reactive protein, HTN: Hypertension, MAP: Mean arterial pressure, K⁺: potassium, Temp: Body temperature.
### Supplementary Table 1: Baseline characteristics for COVID-19 ICU patients.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>COVID-19 ICU Patients (n = 78)</th>
<th>COVID-19 ‘Survivors’ (n = 60)</th>
<th>COVID-19 ‘Non-Survivors’ (n = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SARS-COV-2 RNAemia (%)</strong></td>
<td>23.08%</td>
<td>13.33%</td>
<td>55.56%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days POS until ICU Admission</td>
<td>7.00 (6.25, 10.00)</td>
<td>7.00 (6.00, 10.00)</td>
<td>9.50 (7.00, 14.00)</td>
<td>0.099</td>
</tr>
<tr>
<td>Days POS until Death</td>
<td>-</td>
<td>-</td>
<td>22.00 (19.00, 34.00)</td>
<td>-</td>
</tr>
<tr>
<td>Days from Admission to Death</td>
<td>-</td>
<td>-</td>
<td>13.50 (11.00, 15.50)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>54.00 (46.25, 64.01)</td>
<td>52.01 (44.00, 61.01)</td>
<td>65.01 (57.51, 77.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>71.79%</td>
<td>70.00%</td>
<td>77.78%</td>
<td>0.766</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.05 (24.71, 34.28)</td>
<td>28.10 (24.80, 34.90)</td>
<td>25.87 (24.55, 31.46)</td>
<td>0.252</td>
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<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COPD (%)</td>
<td>16.67%</td>
<td>15.00%</td>
<td>22.22%</td>
<td>0.483</td>
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<tr>
<td>Diabetes (%)</td>
<td>25.64%</td>
<td>25.00%</td>
<td>27.78%</td>
<td>0.769</td>
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<tr>
<td>Hypertension (%)</td>
<td>37.18%</td>
<td>33.33%</td>
<td>50.00%</td>
<td>0.267</td>
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<tr>
<td><strong>Acute Care Parameters</strong></td>
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<tr>
<td>APACHE II Score</td>
<td>15.00 (11.00, 19.00)</td>
<td>14.00 (11.00, 18.00)</td>
<td>17.00 (13.75, 20.50)</td>
<td>0.126</td>
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<tr>
<td>SOFA Score</td>
<td>6.00 (4.00, 8.00)</td>
<td>6.00 (4.00, 7.00)</td>
<td>8.00 (4.00, 9.00)</td>
<td>0.171</td>
</tr>
<tr>
<td>FiO₂ (Fraction of 1)</td>
<td>0.50 (0.35, 0.60)</td>
<td>0.47 (0.35, 0.56)</td>
<td>0.52 (0.50, 0.60)</td>
<td>0.113</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>96.01 (63.27, 112.49)</td>
<td>96.50 (63.01, 114.99)</td>
<td>93.00 (86.00, 101.51)</td>
<td>0.767</td>
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<tr>
<td>MAP (mmHg)</td>
<td>65.51 (61.09, 79.75)</td>
<td>65.17 (61.09, 80.75)</td>
<td>65.51 (61.33, 70.50)</td>
<td>0.749</td>
</tr>
<tr>
<td>Respiratory rate (bpm)</td>
<td>22.00 (16.25, 28.07)</td>
<td>20.7 (16.00, 28.00)</td>
<td>23.83 (22.00, 28.77)</td>
<td>0.138</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.19 (36.85, 39.07)</td>
<td>38.44 (36.95, 39.02)</td>
<td>37.94 (36.85, 38.97)</td>
<td>0.656</td>
</tr>
<tr>
<td><strong>Blood Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>30.00 (27.01, 33.00)</td>
<td>30.00 (27.01, 33.00)</td>
<td>29.50 (26.26, 30.28)</td>
<td>0.167</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>64.49 (48.99, 94.49)</td>
<td>64.49 (48.74, 97.24)</td>
<td>61.00 (50.25, 80.75)</td>
<td>0.981</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>36.01 (27.02, 51.92)</td>
<td>35.49 (25.02, 47.31)</td>
<td>41.68 (30.47, 55.86)</td>
<td>0.171</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>11.49 (8.00, 25.91)</td>
<td>10.99 (8.00, 21.89)</td>
<td>18.02 (8.00, 34.75)</td>
<td>0.313</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>94.49 (72.02, 170.03)</td>
<td>89.38 (69.77, 174.54)</td>
<td>124.03 (91.24, 153.75)</td>
<td>0.265</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>226.21 (143.02, 328.21)</td>
<td>237.71 (103.56, 336.98)</td>
<td>215.68 (167.97, 299.57)</td>
<td>0.981</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>115.63 (103.26, 123.75)</td>
<td>114.50 (100.51, 121.25)</td>
<td>120.00 (107.76, 125.74)</td>
<td>0.224</td>
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<tr>
<td>pH</td>
<td>7.36 (7.31, 7.41)</td>
<td>7.36 (7.31, 7.42)</td>
<td>7.32 (7.31, 7.38)</td>
<td>0.233</td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>4.50 (4.30, 4.80)</td>
<td>4.50 (4.30, 4.80)</td>
<td>4.35 (4.12, 4.85)</td>
<td>0.668</td>
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<tr>
<td>Sodium (mmol/L)</td>
<td>140.00 (137.00, 143.99)</td>
<td>140.00 (137.00, 143.24)</td>
<td>140.50 (137.25, 144.99)</td>
<td>0.426</td>
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<tr>
<td>Urea (mmol/L)</td>
<td>7.11 (5.01, 12.37)</td>
<td>6.55 (4.87, 10.77)</td>
<td>10.70 (6.36, 15.27)</td>
<td>0.039</td>
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<tr>
<td><strong>Cellular Evaluation</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Hematocrit (%)</td>
<td>37.20 (30.26, 39.82)</td>
<td>36.00 (29.71, 39.30)</td>
<td>39.30 (35.25, 41.10)</td>
<td>0.069</td>
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<tr>
<td>Lymphocytes (10⁹/l)</td>
<td>0.86 (0.63, 1.20)</td>
<td>0.88 (0.69, 1.20)</td>
<td>0.83 (0.45, 1.09)</td>
<td>0.498</td>
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<tr>
<td>Monocytes (10⁹/l)</td>
<td>0.40 (0.25, 0.50)</td>
<td>0.36 (0.28, 0.51)</td>
<td>0.40 (0.24, 0.48)</td>
<td>0.743</td>
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<tr>
<td>Neutrophils (10⁹/l)</td>
<td>7.38 (4.90, 9.68)</td>
<td>7.27 (4.90, 9.53)</td>
<td>7.50 (4.29, 9.83)</td>
<td>0.934</td>
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<tr>
<td>White cell count (10⁹/l)</td>
<td>8.50 (6.53, 11.28)</td>
<td>8.50 (6.60, 11.00)</td>
<td>8.53 (5.95, 12.12)</td>
<td>0.962</td>
</tr>
</tbody>
</table>
Continuous variables are presented as median (25th and 75th percentile). P value computed for survivors vs non-survivors using Mann-Whitney test for continuous variables and Fisher exact test for binary variables.

SARS-CoV-2 RNAemia: positive blood test within first six days of admission to ICU; Abbreviations: Days POS: days post onset of symptoms; APACHE II score: acute physiology and chronic health evaluation II score; SOFA score: the sequential organ failure assessment score; MAP: mean arterial pressure; ALP: alkaline phosphatase, ALT: alanine aminotransferase.
Supplementary Table 2: Baseline characteristics for non-ICU, hospitalized COVID-19 patients.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Non-ICU COVID-19 patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 RNAemia (%)</td>
<td>4.44%</td>
</tr>
<tr>
<td>Non-Survivors 28 days after hospitalization (%)</td>
<td>11.11%</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Non-ICU COVID-19 patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.82 (45.95, 71.58)</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>66.66%</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.32 (21.32, 31.50)</td>
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</table>

Comorbidities

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Non-ICU COVID-19 patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD – no. (%)</td>
<td>8 (17.77%)</td>
</tr>
<tr>
<td>Diabetes – no. (%)</td>
<td>12 (26.66%)</td>
</tr>
<tr>
<td>Hypertension – no. (%)</td>
<td>21 (46.66%)</td>
</tr>
</tbody>
</table>

Acute Care Parameters

<table>
<thead>
<tr>
<th>Acute Care Parameters</th>
<th>Non-ICU COVID-19 patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO₂ (Fraction of 1)</td>
<td>0.21 (0.21, 0.28)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>103 (87, 118)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.6 (36.85, 38.3)</td>
</tr>
</tbody>
</table>

Blood Biochemistry

<table>
<thead>
<tr>
<th>Blood Biochemistry</th>
<th>Non-ICU COVID-19 patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>37.00 (32.75, 40.00)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>30.50 (16.50, 52.00)</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>8 (4.5, 11)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>71 (62, 89)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>58 (29, 138)</td>
</tr>
</tbody>
</table>

Cellular Evaluation

<table>
<thead>
<tr>
<th>Cellular Evaluation</th>
<th>Non-ICU COVID-19 patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (10⁹/l)</td>
<td>1.05 (0.63, 1.30)</td>
</tr>
<tr>
<td>Monocytes (10⁹/l)</td>
<td>0.50 (0.40, 0.70)</td>
</tr>
<tr>
<td>Neutrophils (10⁹/l)</td>
<td>5.15 (3.33, 7.00)</td>
</tr>
<tr>
<td>Platelets (10⁹/l)</td>
<td>261.5 (192.0, 334.5)</td>
</tr>
<tr>
<td>White cell count (10⁹/l)</td>
<td>6.90 (4.65, 9.28)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (25th and 75th percentile). Abbreviations: ALT: alanine aminotransferase.
### Supplementary Table 3: Baseline characteristics for COVID-19 ICU patients with and without RNAemia.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>COVID-19 ICU Patients (n = 78)</th>
<th>RNAemia Negative (n = 60)</th>
<th>RNAemia Positive (n = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Survivors (%)</td>
<td>23.08%</td>
<td>13.33%</td>
<td>55.56%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days POS until ICU Admission</td>
<td>7.00 (6.25, 10.00)</td>
<td>7.00 (6.00, 10.00)</td>
<td>7.00 (6.25, 10.00)</td>
<td>0.690</td>
</tr>
<tr>
<td>Days POS until Death</td>
<td>22.00 (19.00, 34.00)</td>
<td>26.00 (19.00, 36.50)</td>
<td>21.50 (18.50, 25.25)</td>
<td>0.434</td>
</tr>
<tr>
<td>Days from Admission to Death</td>
<td>13.50 (11.00, 15.50)</td>
<td>13.00 (12.00, 17.00)</td>
<td>14.00 (11.00, 15.00)</td>
<td>0.641</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>54.00 (46.25, 64.01)</td>
<td>53.01 (45.75, 62.26)</td>
<td>61.01 (48.25, 66.01)</td>
<td>0.107</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>71.79%</td>
<td>71.67%</td>
<td>72.22%</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>28.05 (24.71, 34.28)</td>
<td>28.05 (24.65, 34.68)</td>
<td>29.38 (24.93, 31.70)</td>
<td>0.845</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD (%)</td>
<td>16.67%</td>
<td>15.00%</td>
<td>22.22%</td>
<td>0.483</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>25.64%</td>
<td>20.00%</td>
<td>44.44%</td>
<td>0.062</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>37.18%</td>
<td>28.33%</td>
<td>66.67%</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Acute Care Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>15.00 (11.00, 19.00)</td>
<td>14.50 (11.00, 17.75)</td>
<td>17.00 (11.75, 23.00)</td>
<td>0.114</td>
</tr>
<tr>
<td>SOFA Score</td>
<td>6.00 (4.00, 8.00)</td>
<td>5.00 (4.00, 8.00)</td>
<td>7.00 (4.00, 9.00)</td>
<td>0.363</td>
</tr>
<tr>
<td>FiO2 (Fraction of 1)</td>
<td>0.50 (0.35, 0.60)</td>
<td>0.50 (0.35, 0.60)</td>
<td>0.50 (0.46, 0.59)</td>
<td>0.306</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>96.01 (63.27, 112.49)</td>
<td>93.50 (62.76, 114.25)</td>
<td>99.50 (92.50, 108.25)</td>
<td>0.140</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>65.51 (61.09, 79.75)</td>
<td>63.50 (59.08, 80.08)</td>
<td>67.67 (65.34, 70.76)</td>
<td>0.057</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>22.00 (16.25, 28.07)</td>
<td>20.75 (13.80, 28.00)</td>
<td>26.00 (22.00, 30.00)</td>
<td>0.023</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.19 (36.85, 39.07)</td>
<td>38.29 (36.05, 39.09)</td>
<td>38.19 (37.75, 38.99)</td>
<td>0.622</td>
</tr>
<tr>
<td><strong>Blood Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>30.00 (27.01, 33.00)</td>
<td>30.50 (27.01, 33.00)</td>
<td>29.50 (27.01, 30.00)</td>
<td>0.178</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>64.49 (48.99, 94.49)</td>
<td>63.49 (48.99, 94.98)</td>
<td>65.51 (49.24, 88.49)</td>
<td>0.896</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>36.01 (27.02, 51.92)</td>
<td>33.00 (25.02, 43.31)</td>
<td>51.62 (41.02, 60.75)</td>
<td>0.003</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>11.49 (8.00, 25.91)</td>
<td>10.99 (8.00, 17.27)</td>
<td>30.47 (10.14, 44.17)</td>
<td>0.011</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>94.49 (72.02, 170.03)</td>
<td>93.49 (71.53, 166.00)</td>
<td>100.51 (81.03, 168.03)</td>
<td>0.817</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>226.21 (143.02, 328.21)</td>
<td>237.71 (138.78, 336.88)</td>
<td>189.52 (153.54, 320.12)</td>
<td>0.910</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>115.63 (103.26, 123.75)</td>
<td>113.85 (100.51, 121.25)</td>
<td>119.50 (114.00, 126.00)</td>
<td>0.104</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 (7.31, 7.41)</td>
<td>7.36 (7.31, 7.42)</td>
<td>7.32 (7.30, 7.38)</td>
<td>0.217</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.50 (4.30, 4.80)</td>
<td>4.40 (4.30, 4.72)</td>
<td>4.65 (4.27, 4.98)</td>
<td>0.118</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.00 (137.00, 143.99)</td>
<td>140.00 (137.00, 143.99)</td>
<td>139.50 (137.25, 144.49)</td>
<td>0.794</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>7.11 (5.01, 12.37)</td>
<td>6.55 (4.80, 11.77)</td>
<td>8.42 (6.63, 14.55)</td>
<td>0.141</td>
</tr>
<tr>
<td><strong>Cellular Evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>37.20 (30.26, 39.82)</td>
<td>36.00 (29.63, 39.30)</td>
<td>38.55 (35.85, 40.57)</td>
<td>0.078</td>
</tr>
<tr>
<td>Lymphocytes (10^9/l)</td>
<td>0.86 (0.63, 1.20)</td>
<td>0.80 (0.64, 1.19)</td>
<td>0.88 (0.62, 1.23)</td>
<td>0.784</td>
</tr>
<tr>
<td>Monocytes (10^9/l)</td>
<td>0.40 (0.25, 0.50)</td>
<td>0.40 (0.30, 0.59)</td>
<td>0.30 (0.21, 0.40)</td>
<td>0.064</td>
</tr>
<tr>
<td>Neutrophils (10^9/l)</td>
<td>7.38 (4.90, 9.68)</td>
<td>7.34 (4.90, 9.53)</td>
<td>7.69 (4.16, 10.27)</td>
<td>0.896</td>
</tr>
<tr>
<td>White cell count (10^9/l)</td>
<td>8.50 (6.53, 11.28)</td>
<td>8.50 (6.58, 11.00)</td>
<td>9.40 (5.36, 12.16)</td>
<td>0.995</td>
</tr>
</tbody>
</table>
Continuous variables are presented as median (25th and 75th percentile). P value computed for SARS-CoV-2 RNAemia positive vs negative patients within first six days of admission to ICU using Mann-Whitney U test for continuous variables and Fisher exact test for binary variables. Abbreviations: Days POS: days post onset of symptoms; APACHE II score: acute physiology and chronic health evaluation score; SOFA score: the sequential organ failure assessment score; MAP: mean arterial pressure; ALP: alkaline phosphatase, ALT: alanine aminotransferase.
**Supplementary Table 4: Baseline characteristics for non-COVID-19 ICU patients.**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Pre-pandemic non-COVID-19 ICU sepsis patients (n = 13)</th>
<th>Intra-pandemic non-COVID-19 ICU patients (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 RNAemia (%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Non-Survivors at day 28 (%)</td>
<td>0%</td>
<td>41.66%</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>64 (38, 73)</td>
<td>70 (59.25, 78)</td>
</tr>
<tr>
<td>Sex – % Male</td>
<td>53.85%</td>
<td>58.33%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.12 (23.88, 27.55)</td>
<td>30.30 (26.77, 34.09)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD (%)</td>
<td>3 (23.08%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>2 (15.39%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>7 (53.85%)</td>
<td>5 (41.66%)</td>
</tr>
<tr>
<td>Acute Care Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>16 (15, 21)</td>
<td>-</td>
</tr>
<tr>
<td>FiO₂ (Fraction of 1)</td>
<td>0.4 (0.27, 0.65)</td>
<td>0.28 (0.25, 0.31)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>115 (69, 136)</td>
<td>80 (78, 93)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>65.67 (60, 99.33)</td>
<td>81.5 (72, 85.75)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>23.50 (19.00, 28.75)</td>
<td>20.5 (19.75, 25.25)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>-</td>
<td>3.5 (1.75, 6.25)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.7 (35.8, 38.5)</td>
<td>36.9 (36.8, 37.0)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (25th and 75th percentile). Abbreviations: APACHE II score: acute physiology and chronic health evaluation II score, MAP: mean arterial pressure. SOFA score: sequential organ failure assessment score. Intra-pandemic, non-COVID-19 ICU patients repeatedly tested negative for nasopharyngeal SARS-CoV-2 by RT-qPCR. SARS-CoV-2 RNAemia was assessed in COVID-19-negative patients to determine assay specificity.
**Supplementary Table 5: Baseline characteristics for control patients before elective cardiac surgery.**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Non-COVID-19, non-ICU controls (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 RNAemia (%)</td>
<td>0%</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>70 (64.00, 74.75)</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>73.33%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.22 (25.02, 30.77)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>COPD (%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>7 (23.33%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>17 (56.66%)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (25th and 75th percentile). SARS-CoV-2 RNAemia was assessed in COVID-19-negative patients to determine assay specificity.
### Supplementary Table 6: External validation data based on proximity-extension assays.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Log2 Fold Change</th>
<th>Average Relative Quantity</th>
<th>P value</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTX3</td>
<td>0.89784</td>
<td>5.79471</td>
<td>&lt;0.00001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL17C</td>
<td>0.96308</td>
<td>2.67565</td>
<td>&lt;0.00001</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL6</td>
<td>1.42029</td>
<td>5.81313</td>
<td>&lt;0.00001</td>
<td>0.0003</td>
</tr>
<tr>
<td>PROC</td>
<td>-0.37773</td>
<td>3.21418</td>
<td>&lt;0.00001</td>
<td>0.0005</td>
</tr>
<tr>
<td>IL1RN</td>
<td>0.86502</td>
<td>2.69615</td>
<td>0.00001</td>
<td>0.001</td>
</tr>
<tr>
<td>CX3CL1</td>
<td>0.56603</td>
<td>4.56926</td>
<td>0.00003</td>
<td>0.002</td>
</tr>
<tr>
<td>IL1RL1</td>
<td>0.81686</td>
<td>2.75287</td>
<td>0.00004</td>
<td>0.003</td>
</tr>
<tr>
<td>CCL2</td>
<td>0.60728</td>
<td>6.13895</td>
<td>0.00007</td>
<td>0.003</td>
</tr>
<tr>
<td>IL15</td>
<td>0.47248</td>
<td>3.49095</td>
<td>0.00001</td>
<td>0.004</td>
</tr>
<tr>
<td>CXCL8</td>
<td>0.7077</td>
<td>3.27201</td>
<td>0.00014</td>
<td>0.004</td>
</tr>
<tr>
<td>CCL20</td>
<td>0.92856</td>
<td>5.23471</td>
<td>0.00032</td>
<td>0.007</td>
</tr>
<tr>
<td>IL4R</td>
<td>0.60584</td>
<td>3.31738</td>
<td>0.00054</td>
<td>0.009</td>
</tr>
<tr>
<td>IL19</td>
<td>0.67502</td>
<td>2.16278</td>
<td>0.00061</td>
<td>0.010</td>
</tr>
<tr>
<td>CXCL13</td>
<td>0.58454</td>
<td>3.52346</td>
<td>0.00094</td>
<td>0.013</td>
</tr>
<tr>
<td>CRLF1</td>
<td>0.31295</td>
<td>1.68468</td>
<td>0.00188</td>
<td>0.019</td>
</tr>
<tr>
<td>F7</td>
<td>-0.29250</td>
<td>3.56072</td>
<td>0.002</td>
<td>0.021</td>
</tr>
<tr>
<td>CXCL10</td>
<td>0.72777</td>
<td>7.41412</td>
<td>0.002</td>
<td>0.021</td>
</tr>
<tr>
<td>CCL7</td>
<td>0.76166</td>
<td>4.81714</td>
<td>0.003</td>
<td>0.025</td>
</tr>
<tr>
<td>CCL19</td>
<td>0.49678</td>
<td>3.5662</td>
<td>0.007</td>
<td>0.044</td>
</tr>
<tr>
<td>IL18R1</td>
<td>0.3364</td>
<td>6.64045</td>
<td>0.008</td>
<td>0.048</td>
</tr>
<tr>
<td>LBP</td>
<td>0.34828</td>
<td>4.96949</td>
<td>0.014</td>
<td>0.068</td>
</tr>
<tr>
<td>CD14</td>
<td>0.14460</td>
<td>7.28775</td>
<td>0.309</td>
<td>0.523</td>
</tr>
<tr>
<td>CDH5</td>
<td>0.06908</td>
<td>1.67967</td>
<td>0.343</td>
<td>0.554</td>
</tr>
<tr>
<td>ITIH3</td>
<td>-0.00439</td>
<td>2.16440</td>
<td>0.967</td>
<td>0.978</td>
</tr>
</tbody>
</table>

Differential expression analysis of proteins in survivors and non-survivors 28-days after hospitalization. This analysis was performed on a publicly available proximity-extension assay proteomics-based dataset (data provided by the MGH Emergency Department COVID-19 Cohort (Filbin, Goldberg, Hacohen) with Olink Proteomics: [https://www.olink.com/mgh-covid-study/](https://www.olink.com/mgh-covid-study/)). Only proteins that were also quantified in our study; reported in our main findings; and cytokines and interleukins significantly associated with 28-days mortality were analyzed. Statistical analysis was conducted using the Ebayes method of the limma package, correcting for age and adjusting for multiple testing using Benjamini and Hochberg’s FDR correction.
Supplementary Table 7: Plasma proteins binding to SARS-CoV-2 spike glycoprotein.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ctrl average</th>
<th>Spike average</th>
<th>Fold enrichment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIKE</td>
<td>3.35E+07</td>
<td>7.67E+09</td>
<td>228.8</td>
<td>0.00006</td>
</tr>
<tr>
<td>MYH9</td>
<td>2.37E+06</td>
<td>1.61E+07</td>
<td>6.7</td>
<td>0.0063</td>
</tr>
<tr>
<td>FLNA</td>
<td>1.10E+07</td>
<td>5.40E+07</td>
<td>4.9</td>
<td>0.015</td>
</tr>
<tr>
<td>C1QA</td>
<td>1.85E+07</td>
<td>7.78E+07</td>
<td>4.2</td>
<td>0.007</td>
</tr>
<tr>
<td>C1QC</td>
<td>4.29E+07</td>
<td>1.73E+08</td>
<td>4</td>
<td>0.004</td>
</tr>
<tr>
<td>LGALS3BP</td>
<td>1.27E+06</td>
<td>4.59E+06</td>
<td>3.6</td>
<td>0.008</td>
</tr>
<tr>
<td>C1QB</td>
<td>2.87E+07</td>
<td>1.00E+08</td>
<td>3.4</td>
<td>0.022</td>
</tr>
<tr>
<td>LSM4</td>
<td>2.46E+06</td>
<td>8.50E+06</td>
<td>3.4</td>
<td>0.015</td>
</tr>
<tr>
<td>C4BPB</td>
<td>2.27E+07</td>
<td>7.05E+07</td>
<td>3.1</td>
<td>0.022</td>
</tr>
<tr>
<td>APOD</td>
<td>6.18E+06</td>
<td>1.58E+07</td>
<td>2.5</td>
<td>0.037</td>
</tr>
<tr>
<td>ACTB</td>
<td>1.23E+08</td>
<td>2.86E+08</td>
<td>2.3</td>
<td>0.037</td>
</tr>
<tr>
<td>THAP5</td>
<td>1.72E+07</td>
<td>3.91E+07</td>
<td>2.2</td>
<td>0.028</td>
</tr>
<tr>
<td>C4BPA</td>
<td>3.89E+08</td>
<td>8.76E+08</td>
<td>2.2</td>
<td>0.045</td>
</tr>
<tr>
<td>KIF20B</td>
<td>7.46E+08</td>
<td>1.66E+09</td>
<td>2.2</td>
<td>0.011</td>
</tr>
<tr>
<td>APCS</td>
<td>1.03E+07</td>
<td>2.17E+07</td>
<td>2.1</td>
<td>0.022</td>
</tr>
<tr>
<td>KIF4B</td>
<td>8.84E+09</td>
<td>1.75E+10</td>
<td>1.9</td>
<td>0.03</td>
</tr>
<tr>
<td>SELENOP</td>
<td>1.00E+09</td>
<td>1.89E+09</td>
<td>1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>HIST2H2AC</td>
<td>5.42E+06</td>
<td>1.02E+07</td>
<td>1.8</td>
<td>0.021</td>
</tr>
<tr>
<td>HRG</td>
<td>4.48E+10</td>
<td>8.18E+10</td>
<td>1.8</td>
<td>0.038</td>
</tr>
<tr>
<td>ZW10</td>
<td>7.39E+07</td>
<td>1.35E+08</td>
<td>1.8</td>
<td>0.027</td>
</tr>
<tr>
<td>HABP2</td>
<td>2.02E+07</td>
<td>3.65E+07</td>
<td>1.8</td>
<td>0.017</td>
</tr>
<tr>
<td>CDA</td>
<td>2.12E+06</td>
<td>3.58E+06</td>
<td>1.6</td>
<td>0.021</td>
</tr>
<tr>
<td>ERP44</td>
<td>9.64E+05</td>
<td>1.48E+06</td>
<td>1.5</td>
<td>0.035</td>
</tr>
<tr>
<td>CPN1</td>
<td>3.04E+07</td>
<td>4.39E+07</td>
<td>1.4</td>
<td>0.024</td>
</tr>
</tbody>
</table>

List of the 24 non-immunoglobulin proteins detected at significantly higher levels by LC-MS/MS in pull-downs of His-tagged SARS-CoV-2 spike glycoprotein mixed with COVID-19 plasma. Control experiments were conducted to exclude: 1) co-isolates binding to the solid phase of the His-tagged pull-down metal affinity beads; 2) proteins present in the His-tagged SARS-CoV-2 preparation prior to mixing with plasma (i.e. carryover from HEK293 cells used for production of the recombinant Spike glycoprotein).
Supplementary Table 8: Comparison of plasma protein binding to SARS-CoV-2 spike glycoprotein in patients with and without COVID-19.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Non-COVID-19 average</th>
<th>COVID-19 average</th>
<th>Fold enrichment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGALS3BP</td>
<td>1.23E+06</td>
<td>4.59E+06</td>
<td>3.7</td>
<td>0.0025</td>
</tr>
<tr>
<td>APOD</td>
<td>4.95E+06</td>
<td>1.58E+07</td>
<td>3.1</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

Listed are the two non-immunoglobulin proteins detected at significantly higher levels by LC-MS/MS in pull-down samples of His-tagged spike glycoprotein mixed with plasma from COVID-19 compared to non-COVID-19 ICU patients.
### Supplementary Table 9: Machine learning signatures using the SVM RBF model.

<table>
<thead>
<tr>
<th>Single Signature</th>
<th>Accuracy</th>
<th>NPV</th>
<th>Specificity</th>
<th>PPV (A)</th>
<th>Sensitivity (B)</th>
<th>ROC AUC (C)</th>
<th>Average of A+B+C</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNAemia</td>
<td>79.49%</td>
<td>86.67%</td>
<td>86.67%</td>
<td>55.56%</td>
<td>55.56%</td>
<td>85.37%</td>
<td>65.49%</td>
</tr>
<tr>
<td>Age</td>
<td>73.08%</td>
<td>86.79%</td>
<td>76.67%</td>
<td>44.00%</td>
<td>61.11%</td>
<td>71.11%</td>
<td>58.74%</td>
</tr>
<tr>
<td>PTX3</td>
<td>78.21%</td>
<td>82.09%</td>
<td>91.67%</td>
<td>54.55%</td>
<td>33.33%</td>
<td>69.35%</td>
<td>52.41%</td>
</tr>
<tr>
<td>Urea</td>
<td>65.38%</td>
<td>78.95%</td>
<td>75.00%</td>
<td>28.57%</td>
<td>33.33%</td>
<td>54.63%</td>
<td>38.84%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Binary Signature</th>
<th>Accuracy</th>
<th>NPV</th>
<th>Specificity</th>
<th>PPV (A)</th>
<th>Sensitivity (B)</th>
<th>ROC AUC (C)</th>
<th>Average of A+B+C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, PTX3</td>
<td>87.18%</td>
<td>90.32%</td>
<td>93.33%</td>
<td>75.00%</td>
<td>66.67%</td>
<td>78.52%</td>
<td>73.40%</td>
</tr>
<tr>
<td>Age, RNAemia</td>
<td>83.33%</td>
<td>91.23%</td>
<td>86.67%</td>
<td>61.90%</td>
<td>72.22%</td>
<td>79.81%</td>
<td>71.31%</td>
</tr>
<tr>
<td>Age, FiO2</td>
<td>76.92%</td>
<td>90.38%</td>
<td>78.33%</td>
<td>50.00%</td>
<td>72.22%</td>
<td>78.70%</td>
<td>66.98%</td>
</tr>
<tr>
<td>Age, Albumin</td>
<td>82.05%</td>
<td>89.66%</td>
<td>86.67%</td>
<td>60.00%</td>
<td>66.67%</td>
<td>74.07%</td>
<td>66.91%</td>
</tr>
<tr>
<td>Age, ALT</td>
<td>82.05%</td>
<td>89.66%</td>
<td>86.67%</td>
<td>60.00%</td>
<td>66.67%</td>
<td>72.41%</td>
<td>66.36%</td>
</tr>
<tr>
<td>Age, Respiratory rate</td>
<td>80.77%</td>
<td>89.47%</td>
<td>85.00%</td>
<td>57.14%</td>
<td>66.67%</td>
<td>74.72%</td>
<td>66.18%</td>
</tr>
<tr>
<td>COPD, RNAemia</td>
<td>79.49%</td>
<td>86.67%</td>
<td>86.67%</td>
<td>55.56%</td>
<td>55.56%</td>
<td>86.39%</td>
<td>65.83%</td>
</tr>
<tr>
<td>Diabetes, RNAemia</td>
<td>79.49%</td>
<td>86.67%</td>
<td>86.67%</td>
<td>55.56%</td>
<td>55.56%</td>
<td>86.30%</td>
<td>65.80%</td>
</tr>
<tr>
<td>pH, RNAemia</td>
<td>73.08%</td>
<td>91.49%</td>
<td>71.67%</td>
<td>45.16%</td>
<td>77.78%</td>
<td>69.91%</td>
<td>65.30%</td>
</tr>
<tr>
<td>Hypertension, RNAemia</td>
<td>79.49%</td>
<td>86.67%</td>
<td>86.67%</td>
<td>55.56%</td>
<td>55.56%</td>
<td>82.13%</td>
<td>64.41%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triplet Signature</th>
<th>Accuracy</th>
<th>NPV</th>
<th>Specificity</th>
<th>PPV (A)</th>
<th>Sensitivity (B)</th>
<th>ROC AUC (C)</th>
<th>Average of A+B+C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, FiO2, RNAemia</td>
<td>84.62%</td>
<td>91.38%</td>
<td>88.33%</td>
<td>65.00%</td>
<td>72.22%</td>
<td>85.93%</td>
<td>74.38%</td>
</tr>
<tr>
<td>Age, RNAemia, PTX3</td>
<td>80.77%</td>
<td>90.91%</td>
<td>83.33%</td>
<td>56.52%</td>
<td>72.22%</td>
<td>82.59%</td>
<td>70.45%</td>
</tr>
<tr>
<td>Age, HR, Diabetes</td>
<td>87.18%</td>
<td>89.06%</td>
<td>95.00%</td>
<td>78.57%</td>
<td>61.11%</td>
<td>76.67%</td>
<td>72.12%</td>
</tr>
<tr>
<td>Age, FiO2, PTX3</td>
<td>83.33%</td>
<td>91.23%</td>
<td>86.67%</td>
<td>61.90%</td>
<td>72.22%</td>
<td>81.85%</td>
<td>71.99%</td>
</tr>
<tr>
<td>Age, Sodium, PTX3</td>
<td>87.18%</td>
<td>87.88%</td>
<td>96.67%</td>
<td>83.33%</td>
<td>55.56%</td>
<td>76.20%</td>
<td>71.70%</td>
</tr>
<tr>
<td>Age, Lymphocytes, RNAemia</td>
<td>84.62%</td>
<td>90.00%</td>
<td>90.00%</td>
<td>66.67%</td>
<td>66.67%</td>
<td>81.20%</td>
<td>71.51%</td>
</tr>
<tr>
<td>Age, CRP, RNAemia</td>
<td>83.33%</td>
<td>91.23%</td>
<td>86.67%</td>
<td>61.90%</td>
<td>72.22%</td>
<td>78.98%</td>
<td>71.04%</td>
</tr>
<tr>
<td>Age, HR, PTX3</td>
<td>85.90%</td>
<td>87.69%</td>
<td>95.00%</td>
<td>76.92%</td>
<td>55.56%</td>
<td>80.65%</td>
<td>71.04%</td>
</tr>
<tr>
<td>Age, pH, RNAemia</td>
<td>82.05%</td>
<td>91.07%</td>
<td>85.00%</td>
<td>59.09%</td>
<td>72.22%</td>
<td>81.67%</td>
<td>70.99%</td>
</tr>
<tr>
<td>Age, Bilirubin, Hb</td>
<td>83.33%</td>
<td>88.23%</td>
<td>86.67%</td>
<td>61.90%</td>
<td>72.22%</td>
<td>78.06%</td>
<td>70.73%</td>
</tr>
</tbody>
</table>

Single markers were filtered for prediction model based on statistical significance (P value < 0.05). The top 10 combinations were selected from 114 binary and 885 triplet combinations based on average score i.e. average of PPV, Sensitivity and ROC. Signatures are shown in descending order based on average score and using leave-one-out validation. Note that PTX3 levels are different in serum and plasma. The best triplet signature ‘Age, FiO2, RNAemia’ provides nominal gain in prediction probability as reflected in PPV with no uplift to specificity when compared to ‘Age, RNAemia’ suggesting the binary combination to be an optimal signature to choose. Abbreviations: NPV: negative predictive value; PPV: positive predicted value; Temp: body temperature; Hb: Hemoglobin, HR: Heart rate.
**Supplementary Table 10:** Isolation windows used in DIA-MS methods.

<table>
<thead>
<tr>
<th>Precursor ion [m/z]</th>
<th>Isolation Window [m/z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>360.5</td>
<td>61</td>
</tr>
<tr>
<td>405.5</td>
<td>31</td>
</tr>
<tr>
<td>431, 452, 473</td>
<td>22</td>
</tr>
<tr>
<td>492, 509, 526, 543, 560, 577, 594, 611, 628, 645</td>
<td>18</td>
</tr>
<tr>
<td>664, 685, 706, 727</td>
<td>22</td>
</tr>
<tr>
<td>752, 781, 810, 839</td>
<td>30</td>
</tr>
<tr>
<td>871</td>
<td>36</td>
</tr>
<tr>
<td>908, 947</td>
<td>40</td>
</tr>
<tr>
<td>991, 1040</td>
<td>50</td>
</tr>
<tr>
<td>1095</td>
<td>62</td>
</tr>
<tr>
<td>1162.5</td>
<td>75</td>
</tr>
</tbody>
</table>

**Supplementary Table 11:** Features with missing data in the combined COVID-19 ICU cohorts.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Missing Count</th>
<th>Missing %</th>
<th>Imputed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>1</td>
<td>1.3%</td>
<td>Yes</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>2</td>
<td>2.6%</td>
<td>Yes</td>
</tr>
<tr>
<td>Albumin</td>
<td>3</td>
<td>3.8%</td>
<td>Yes</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>4</td>
<td>5.1%</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3</td>
<td>3.8%</td>
<td>Yes</td>
</tr>
<tr>
<td>Monocytes</td>
<td>3</td>
<td>3.8%</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>3</td>
<td>3.8%</td>
<td>Yes</td>
</tr>
<tr>
<td>ALP (alkaline phosphatase)</td>
<td>3</td>
<td>3.8%</td>
<td>Yes</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>5</td>
<td>6.4%</td>
<td>Yes</td>
</tr>
<tr>
<td>White cell count</td>
<td>5</td>
<td>6.4%</td>
<td>Yes</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>5</td>
<td>6.4%</td>
<td>Yes</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7</td>
<td>9.0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Urea</td>
<td>9</td>
<td>11.5%</td>
<td>Yes</td>
</tr>
<tr>
<td>ALT (alanine aminotransferase)</td>
<td>16</td>
<td>20.5%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

List of features with missing data in the combined cohort i.e. GSTT and KCH cohort. Features with missing percentage less than 30% were imputed using KNN impute with $K=5$. Eosinophil counts and basophil counts with missing percentage greater than 30% were not imputed and excluded from data analysis.