Supplemental File 1

Clinical cohort:

From October 2011 to March 2020, we prospectively enrolled a convenience sample of mechanically-ventilated patients with ARF in Medical Intensive Care Units (ICUs) at the University of Pittsburgh Medical Center. We excluded patients unable to provide informed consent or if they were mechanically ventilated for >72 hours prior to enrollment. Informed consent was provided by all participants in accordance with local regulations. The study was approved by the University of Pittsburgh Institutional Review Board (protocol STUDY19050099). Under the same study protocol, from April 2020 to October 2020, we continued enrollment of patients with ARF during the COVID-19 pandemic. During this period, we enrolled both mechanically ventilated patients with COVID-19 ARDS as well as patients with severe COVID-19 pneumonia and ARF managed with high flow nasal cannula oxygen or non-invasive mechanical ventilation in the ICU. We recorded baseline demographics, comorbidities, mechanical ventilation and laboratory variables, and calculated sequential organ failure assessment (SOFA) scores.

Biomarker measurements:

We collected blood samples upon enrollment and measured 10 host-response biomarkers shown to have validated associations with ARDS and/or sepsis with a customized Luminex assay (R&D Systems, Minneapolis) (1). Host-response biomarkers were classified into markers of innate immune response (IL-6, IL-8, IL-10, fractalkine, TNFR-1, suppressor of tumorigenicity-2 [ST-2]), epithelial injury (receptor of advanced glycation end-products [RAGE]), endothelial injury (angiopoietin-2), and response to bacterial infections (procalcitonin and pentraxin-3). We also measured 1-3-beta-D-glucan (BDG), a fungal cell-wall constituent shown to correlate with inflammatory biomarkers, using the commercially available Fungitell® Limulus Amebocyte Lysate

(LAL) assay (Associates of Cape Cod, Inc, East Falmouth, MA, USA) at the manufacturer's facility (2).

Subphenotypic classifications:

In the derivation cohort, we combined baseline data from all six clinical categories of acute respiratory failure (ARF), namely a) ARDS per Berlin criteria (3), b) at-risk for ARDS, based on presence of an identifiable lung injury risk factor upon enrollment but not fulfilling ARDS criteria, c) cardiogenic pulmonary edema from congestive heart failure (CHF), d) acute on chronic respiratory failure (e.g. acute exacerbation of chronic obstructive pulmonary disease [COPD]), e) intubation for airway protection, and f) "multifactorial" category including cases for which the committee could not reach consensus for clinical classification into any of the categories above.

In the combined data set of 498 patients with ARF, we applied latent class analysis (LCA). First, we estimated the optimal number of classes that best fit our patient cohort, as subphenotyping analysis has not yet been performed in this population. LCA has been applied to several recent ARDS cohorts with the goal to identify subgroups of patients defined by a specific group of variables without consideration of clinical outcome. We considered both continuous and categorical clinical and biomarker variables similar to those used in previous LCA-derived models in ARDS trials (Supplemental Table S2). Similar to prior studies we standardized continuous variables to a common z-scale (mean value of 0, standard deviation value of 1) and coded categorical variables as 0 and 1. Data that were highly co-linear ($r>0.95$) were excluded from the model (e.g. systolic blood pressure was included instead of mean arterial pressure). Prior to performing the final LCA, we examined each continuous and categorical variable for discriminatory value, and selected only variables that were found to be discriminatory for consideration in development in the LCA model. Non-discriminatory variables were removed (defined as not significantly different from 0; $p\geq0.1$). Categorical variables were also compared graphically via Fisher exact tests with non-discriminatory variables being removed. Based off of

several prior studies(4, 5), we hypothesized that a two-class model would offer the best fit. Optimal fit was determined using 1) entropy to measure class separation (higher entropy values meaning better class separation), 2) a bootstrapped parametric likelihood ratio test with a level of significance at $p<0.05$, and 3) low frequency criterion for additional classes. Following selection of discriminatory variables (Table S1), a two class model vs. a single class model had a highly significant parametric likelihood ratio test (log-likelihood difference 1148, $p<0.0001$) and with entropy of 0.911. Addition of a third class did not improve entropy or the likelihood ratio and included a very small proportion of subjects in the third class (3.4%), considered clinically not useful, and therefore a two class model was considered as optimal fit for our dataset.

The continuous variables were graphically examined by plotting their standardized values to a common z-scale (mean of 0, standard deviation of 1). The continuous variables with higher discriminatory value can be viewed graphically in Supplementary Figure S3 at the extremes of distribution. LCA analyses were performed in MPlus 8.3(6).

We then developed a parsimonious logistic regression model based on a best subsets generalized linear model approach (*bestglm* R package) using Bayesian Information Criteria for selection of the minimal subset of the discriminatory variables that offered optimal predictions (7). We applied subphenotype classifications provided from the parsimonious model in the derivation cohort of patients with ARF to assess model performance, and then to the validation cohort to assess for differences in baseline clinical variables and outcomes between predicted subphenotypes. With an area under the curve (AUC) statistic, we examined for agreement between the predictions from our internal parsimonious model vs. an external predictive model by Famous et al in patients with ARDS that had utilized three biomarker variables (IL-8, bicarbonate, and TNFR-1) that were available in our dataset (8).

Clinical Outcomes:

Patients were followed prospectively for several clinical outcomes. These included 1) shock within the first week of enrollment (defined as need for vasopressors), 2) acute kidney injury (AKI, defined as absolute increase in serum creatinine concentration ≥0.3 mg/dL from baseline or a percentage increase in serum creatinine concentration of more than 50% within a 48 hour period; or oliguria of <0.5 mL/kg per hour for more than six hours), ICU length of stay, ventilator-free days (VFD) to 28 days(9), time-to-liberation from mechanical ventilation, and 30- and 90-day mortality. For subjects who died prior to day 28, zero VFDs were assigned.

Statistical analyses:

All analyses were performed with R v.3.5.1 except for the LCA analysis which was performed in MPlus 8.3(6, 10). We calculated descriptive statistics for baseline variables. Subphenotype comparisons were made with Wilcoxon test for continuous variables and Fisher's exact test for categorical variables. For the longitudinal outcomes of survival and time-to-liberation from mechanical ventilation, we performed time-to-event analyses with Kaplan-Meier curves and comparisons with a log-rank test. To assess for effects of subphenotype on each of these outcomes, we built Cox-proportional hazard models. For Cox models we tested the proportional hazard assumption. All of these models were adjusted for age and clinical categories of ARF.

Bibliography

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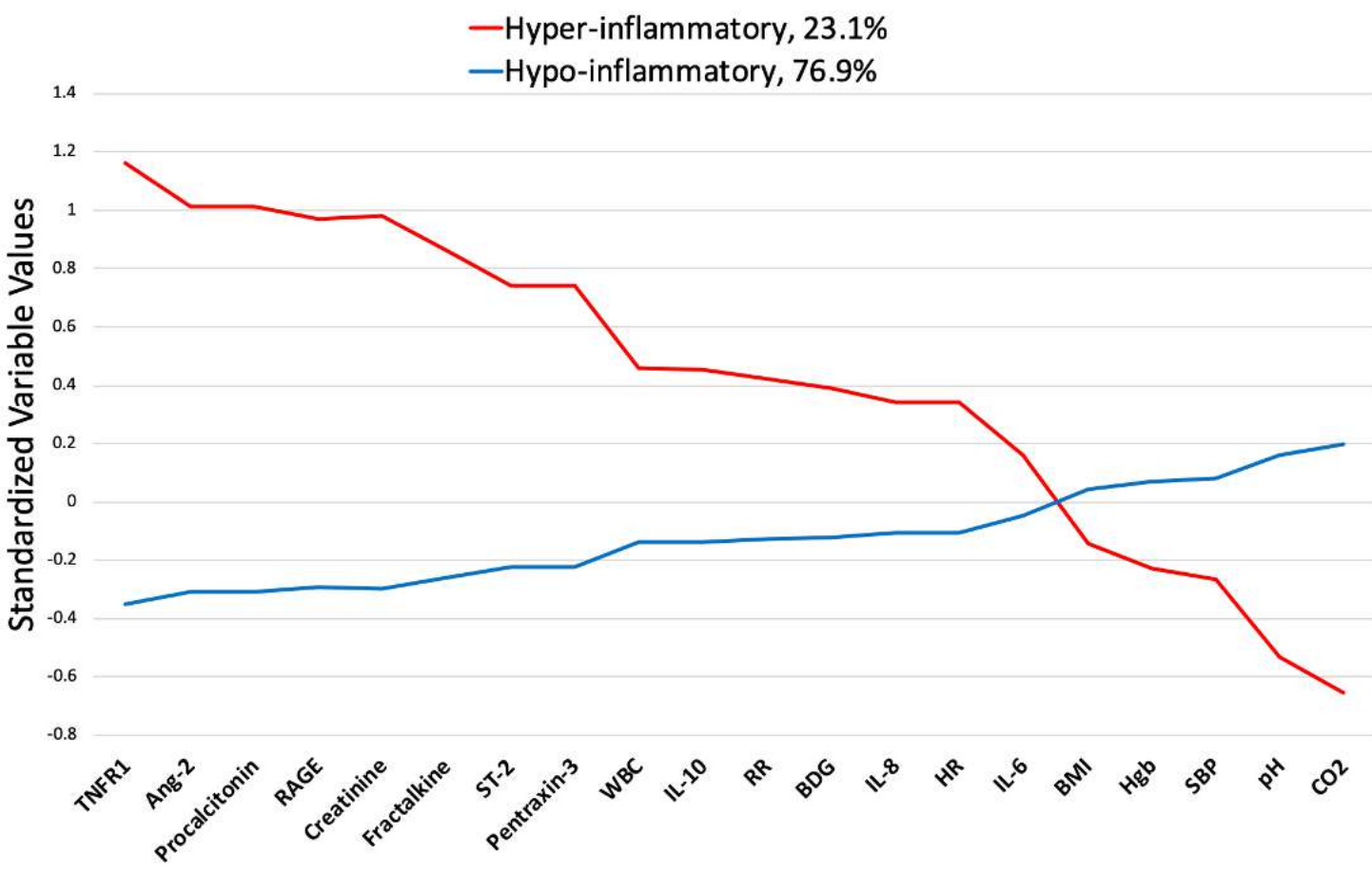
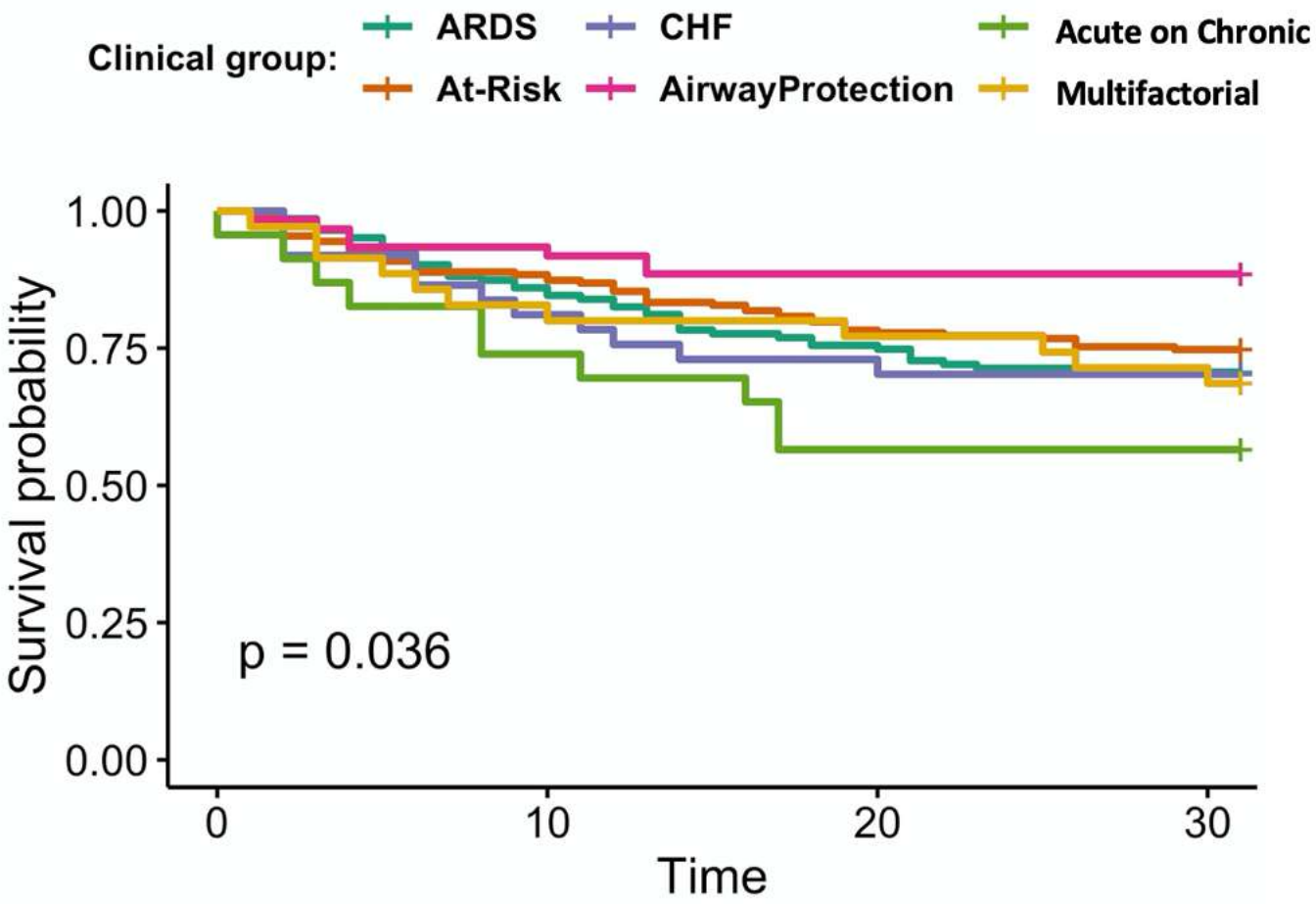
Continuous Variables	*Categorical Variables*
Age	Gender
BMI	Direct Lung Injury (Pneumonia or Aspiration)
Hemoglobin	Diabetes
Creatinine	COPD
Glucose	Immunosuppression
CO2	**Hypoalbuminemia**
PaO2:FIO2 ratio	Alcohol use
Heart rate	**Vasopressor usage**
SBP	
Temperature	
pHa	
WBC	
Platelets	
Respiratory Rate	
PEEP	
Peak inspiratory pressure	
Tidal Volume (per kg of PBW)	
IL-6	
IL-8	
IL-10	
TNFR-1	
Angiopoietin-2	
Pentraxin-3	
Fractalkine	
ST-2	
Procalcitonin	
RAGE	
BDG	

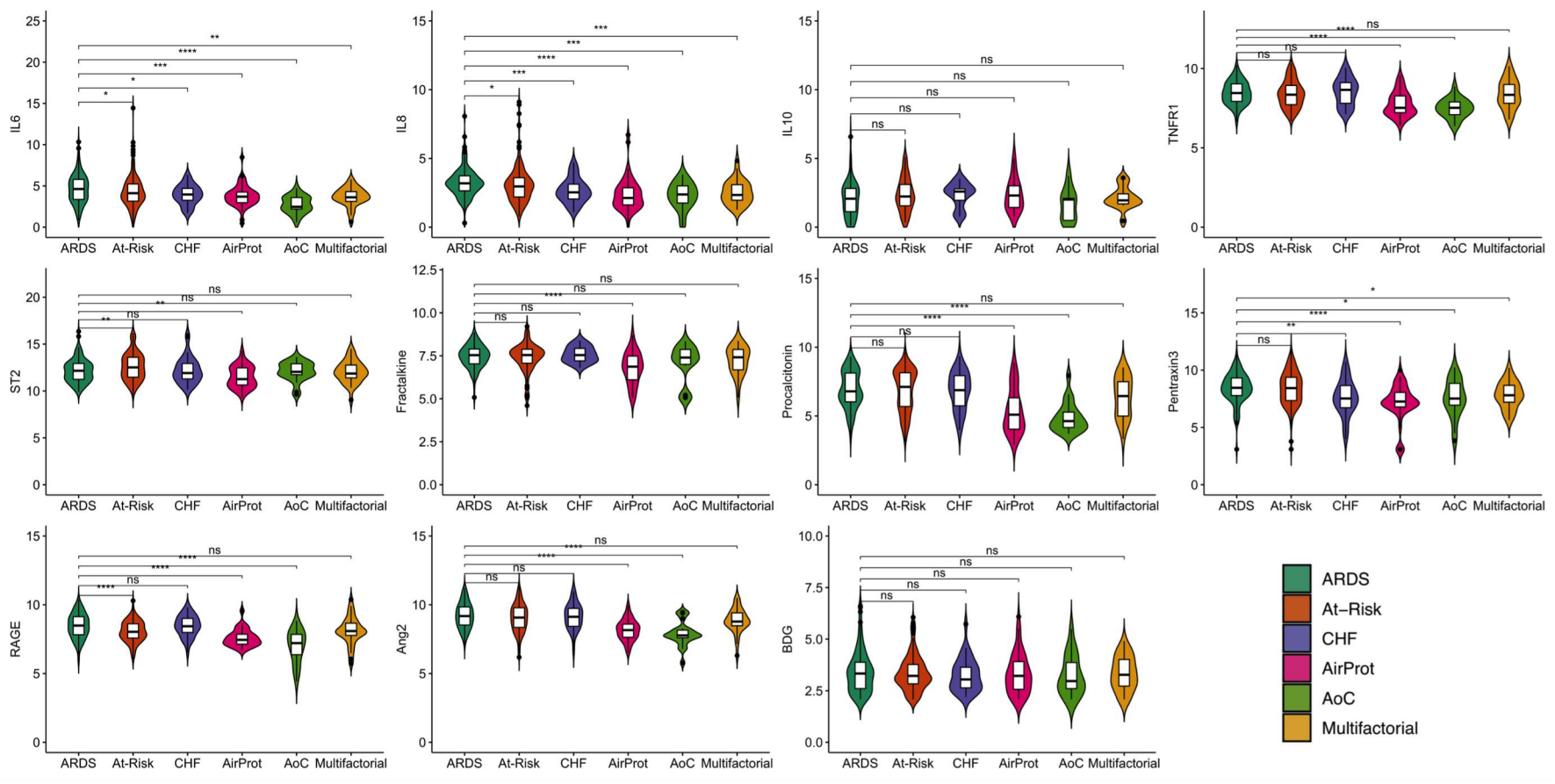

Hyper-inflammatory, 23.1%
Hypo-inflammatory, 76.9%
Standardized Variable Values
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
TNFR1
Ang-2
Procalcitonin
RAGE
Creatinine
Fractalkine
ST-2
Pentraxin-3
WBC
IL-10
RR
BDG
IL-8
HR
IL-6
BMI
Hgb
SBP
pH
CO2

Variable	ARDS	At Risk	CHF	Acute on Chronic	Airway Protection	Multifactorial	p-value
n	**143**	**198**	**37**	**23**	**61**	**35**	
Demographics							
Age (median [IQR])	55.4 [40.1, 65.1]	60.0 [49.6, 68.8]	64.5 [50.1, 69.5]	59.0 [53.5, 64.1]	54.9 [43.7, 62.5]	61.0 [50.0, 67.0]	**0.0037**
Male gender, N (%)	70 (49.0)	115 (58.1)	22 (59.5)	8 (34.8)	35 (57.4)	17 (48.6)	0.1971
BMI (median [IQR])	29.6 [25.1, 35.3]	29.3 [24.3, 35.7]	33.7 [27.1, 42.1]	28.4 [24.8, 34.9]	26.8 [24.4, 32.1]	28.5 [23.1, 36.8]	**0.0114**
Caucasian race, N (%)	136 (95.1)	184 (92.9)	29 (78.4)	20 (87.0)	55 (90.2)	32 (91.4)	**0.0330**
History of Chronic Disease, N (%)							
Diabetes	39 (27.3)	78 (39.4)	17 (45.9)	4 (17.4)	16 (26.2)	12 (34.3)	**0.0309**
COPD	27 (18.9)	52 (26.3)	6 (16.2)	14 (60.9)	7 (11.5)	8 (22.9)	**0.0001**
Immunosuppression	32 (22.4)	32 (16.2)	11 (29.7)	7 (30.4)	10 (16.4)	11 (31.4)	0.1078
Chronic kidney disease	16 (11.2)	33 (16.7)	15 (40.5)	0 (0.0)	7 (11.5)	12 (34.3)	**<0.0001**
Chronic cardiac failure	12 (8.4)	27 (13.6)	9 (24.3)	4 (17.4)	3 (4.9)	3 (8.6)	**0.0386**
Alcohol use	15 (10.5)	35 (17.7)	6 (16.2)	3 (13.0)	17 (27.9)	3 (8.6)	**0.0394**
Risk Factors for ARDS							
Pneumonia, N (%)	97 (67.8)	85 (42.9)	0 (0.0)	1 (4.3)	0 (0.0)	3 (8.6)	**<0.0001**
Aspiration, N (%)	26 (18.2)	56 (28.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	**<0.0001**
sepsis, N (%)	32 (22.4)	77 (38.9)	1 (2.7)	0 (0.0)	0 (0.0)	5 (14.3)	**<0.0001**
LIPS score (median [IQR])	6.5 [5.5, 8.0]	5.5 [4.5, 7.0]	4.0 [3.0, 5.0]	5.0 [3.0, 5.5]	3.0 [2.0, 4.0]	4.5 [3.5, 5.5]	**<0.0001**
Hemodynamic parameters							
HR (median [IQR])	90.0 [78.0, 106.5]	92.5 [78.0, 106.0]	90.0 [80.0, 96.0]	91.0 [72.5, 102.5]	91.0 [75.0, 99.0]	86.0 [78.0, 95.5]	0.4071
SBP (median [IQR])	113.0 [102.0, 128.0]	116.0 [102.0, 132.5]	117.0 [108.0, 137.0]	119.0 [105.0, 129.0]	128.0 [106.0, 145.0]	116.0 [103.0, 133.5]	**0.0416**
Laboratory parameters							
pHa (median [IQR])	7.4 [7.3, 7.4]	7.4 [7.3, 7.4]	7.4 [7.3, 7.4]	7.4 [7.3, 7.4]	7.4 [7.4, 7.4]	7.4 [7.4, 7.4]	0.2181
WBC (median [IQR])	12.7 [9.6, 18.4]	13.3 [9.4, 17.6]	10.9 [7.7, 15.9]	11.4 [8.0, 16.2]	10.3 [7.8, 14.7]	11.2 [7.3, 14.4]	**0.0451**
Creatinine (median [IQR])	1.4 [0.8, 2.5]	1.3 [0.8, 2.5]	2.2 [1.1, 3.4]	0.9 [0.7, 1.1]	0.9 [0.6, 1.2]	1.8 [0.9, 2.7]	**<0.0001**
Serum CO2 (median [IQR])	24.0 [21.0, 27.0]	23.0 [20.0, 26.0]	24.0 [22.0, 29.0]	30.0 [25.5, 35.0]	23.0 [22.0, 26.0]	25.0 [22.0, 28.0]	**<0.0001**

Illness severity/Clinical Outcomes							
Shock (vasopressor use), N (%)	95 (66.4)	108 (54.5)	22 (59.5)	12 (52.2)	11 (18.0)	18 (51.4)	**<0.0001**
SOFA score (median [IQR])	8.0 [5.0, 10.0]	7.0 [5.0, 9.0]	8.0 [6.0, 10.0]	6.0 [4.0, 6.0]	4.0 [4.0, 7.0]	7.0 [5.0, 9.8]	**<0.0001**
Acute kidney injury, N (%)	109 (76.2)	135 (68.2)	24 (64.9)	10 (43.5)	22 (36.1)	24 (68.6)	**<0.0001**
30-d mortality, N (%)	42 (29.4)	50 (25.3)	11 (29.7)	10 (43.5)	7 (11.5)	11 (31.4)	**0.0361**
90-d mortality, N (%)	50 (35.0)	52 (26.3)	12 (32.4)	10 (43.5)	8 (13.1)	12 (34.3)	**0.0176**
ICU length of stay (median [IQR])	12.0 [8.0, 21.0]	8.0 [5.0, 13.0]	6.0 [4.0, 10.0]	8.0 [4.0, 12.0]	5.0 [3.0, 9.0]	9.0 [6.0, 13.0]	**<0.0001**
Ventilator-free days (median [IQR])	12.0 [0.0, 21.0]	19.0 [0.0, 23.2]	22.0 [0.0, 24.0]	16.0 [0.0, 21.0]	24.0 [20.0, 26.0]	20.0 [0.0, 23.8]	**<0.0001**
Duration of mechanical ventilation, median [IQR], d	9.0 [5.5, 15.0]	6.0 [4.0, 12.0]	4.0 [3.0, 7.0]	7.0 [3.0, 9.0]	3.0 [2.0, 5.0]	5.5 [4.0, 9.5]	**<0.0001**
Mechanical Ventilation Parameters							
Worst PaO2:FiO2 ratio (median [IQR])	130.0 [84.0, 182.0]	188.0 [127.5, 266.0]	177.0 [132.0, 215.0]	143.0 [130.0, 193.5]	205.0 [164.0, 240.0]	164.0 [110.0, 205.0]	**<0.0001**
Peak Inspiratory pressure (median [IQR])	29.0 [25.5, 34.0]	22.5 [19.0, 29.0]	25.0 [21.0, 29.0]	30.0 [26.8, 35.5]	19.0 [15.0, 25.0]	27.0 [20.0, 32.0]	**<0.0001**
Tidal Volume (per kg of PBW), median [IQR], ml/kg	6.5 [5.8, 7.5]	6.8 [6.0, 7.6]	6.7 [6.0, 7.9]	7.2 [6.1, 8.3]	6.6 [6.0, 7.3]	6.8 [6.0, 8.0]	0.2849
Saturation, median [IQR], %	96.0 [95.0, 98.0]	98.0 [96.0, 99.8]	98.0 [96.0, 99.0]	97.0 [95.0, 99.0]	99.0 [97.0, 100.0]	97.0 [96.0, 100.0]	**<0.0001**
Biomarkers, median [IQR], pg/ml							
IL-6	102 [29, 327]	62 [23, 187]	52 [26. 111]	12 [7, 36]	40 [19.4, 70.3]	37 [23, 74]	**<0.0001**

IL-8	24 [14, 42]	19 [9, 37]	12 [8, 23]	11 [6, 20]	8 [5, 18]	10 [7, 22]	**<0.0001**
IL-10	0.9 [0.0, 7.5]	0.8 [0.0, 8.6]	0.1 [0.0, 2.3]	0.8 [0.1, 1.9]	0.1 [0.0, 2.1]	0.8 [0.0, 6.5]	0.1850
TNFR-1	4696 [2766, 8367]	4219 [2255, 7578]	5737 [2466, 9089]	1852 [1199, 2683]	1845 [1361, 3900]	4178 [2464, 8041]	**<0.0001**
Angiopoietin-2	9677 [5038, 18851]	8679 [4244, 17705]	9197 [4589, 16926]	2364 [2005, 3481]	3489 [2069, 5387]	6480 [4778, 12221]	**<0.0001**
Pentraxin-3	4710 [2388, 11087]	4314 [1435, 11718]	1848 [791, 5307]	1842 [1039, 6949]	1204 [644, 3012]	2435 [1066, 5686]	**<0.0001**
Fractalkine	1868 [1120, 2677]	1645 [735, 2445]	1521 [1025, 2464]	1427 [183, 2585]	767 [171, 1604]	1183 [643, 2452]	**0.0001**
ST-2	190540 [75604, 413621]	272451 [95811, 799828]	149453 [79700, 411553]	171886 [125476, 400924]	78043 [41646, 259535]	141460 [89086, 347590]	**<0.0001**
Procalcitonin	888 [413, 3355]	1232 [295, 3421]	973 [312, 2783]	102 [64, 196]	163 [57, 553]	631 [147, 1796]	**<0.0001**
Rage	4853 [2489, 9235]	3076 [1955, 5526]	4613 [2937, 8172]	1351 [585, 2572]	1713 [1255, 2589]	3256 [2373, 5782]	**<0.0001**
BDG	28 [14, 49]	25 [17, 44]	21 [14, 38]	20 [14, 49]	25 [13, 50]	27 [15, 56]	0.9331


Clinical group:
ARDS
CHF
Acute on Chronic
At-Risk
AirwayProtection
Multifactorial
1.00
0.75
0.50
0.25
0.00
Survival probability
p = 0.036
0
10
20
30
Time


IL6
IL8
IL10
TNFR1
ST2
Fractalkine
Procalcitonin
Pentraxin3
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ARDS
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AirProt
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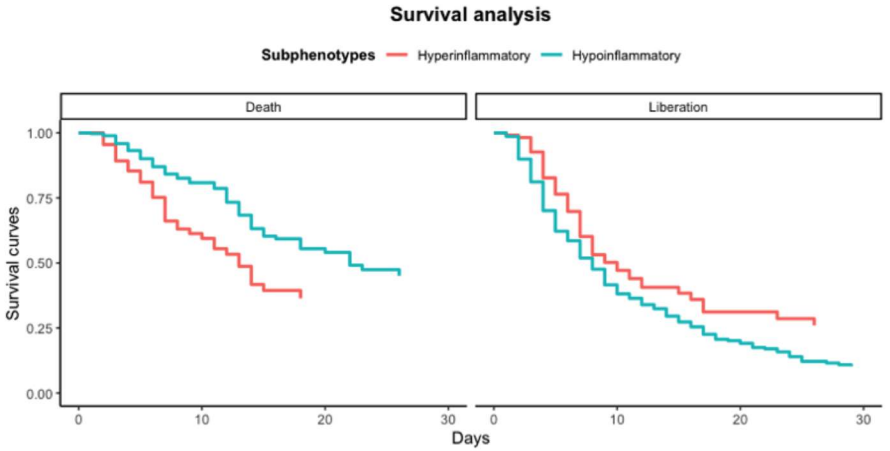
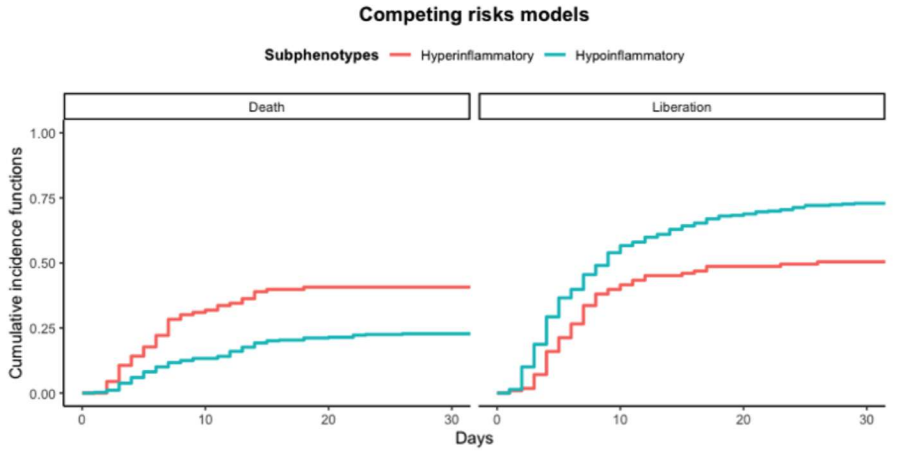
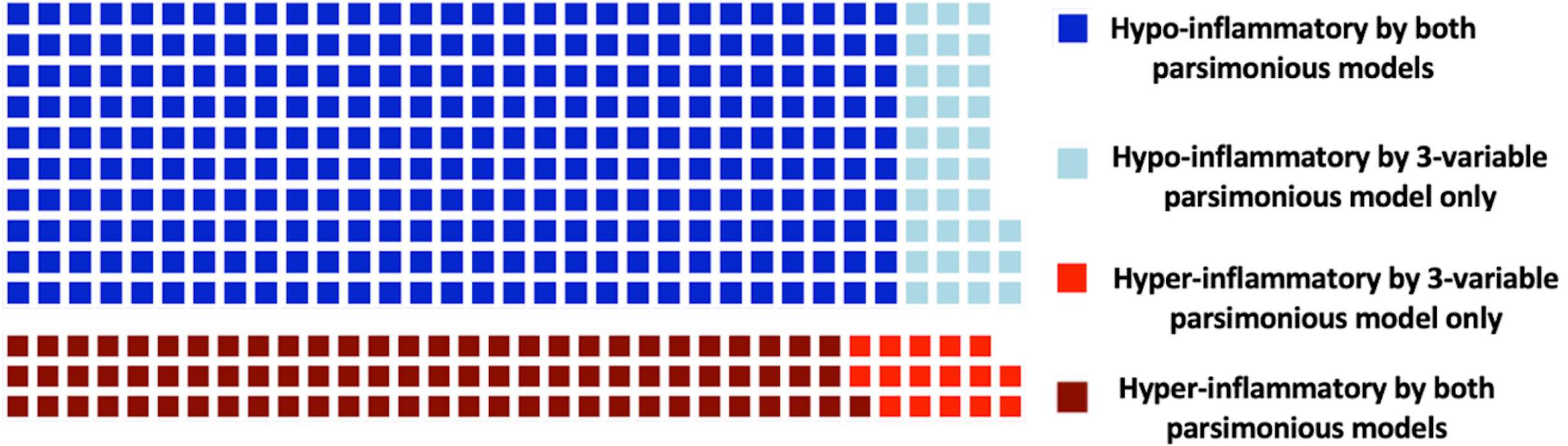


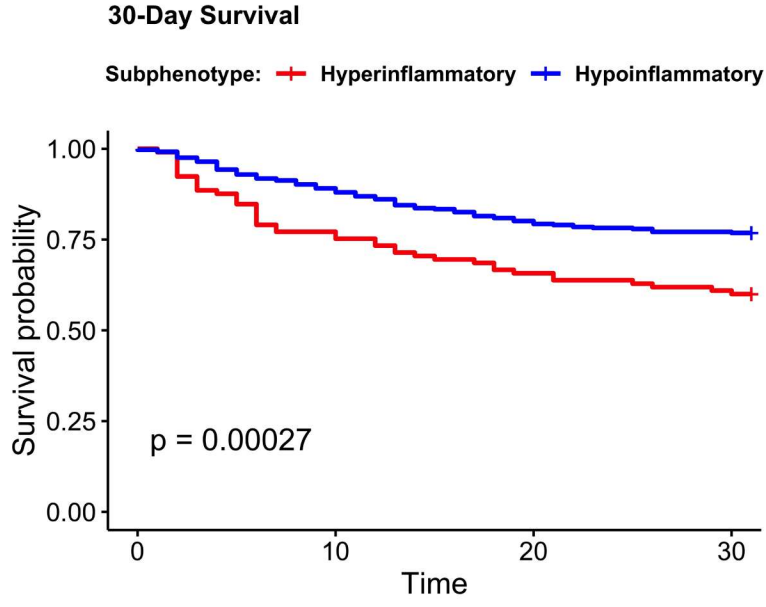


Competing risk likelihood ratio test for difference in time to liberation by subphenotypes: p=0.000031

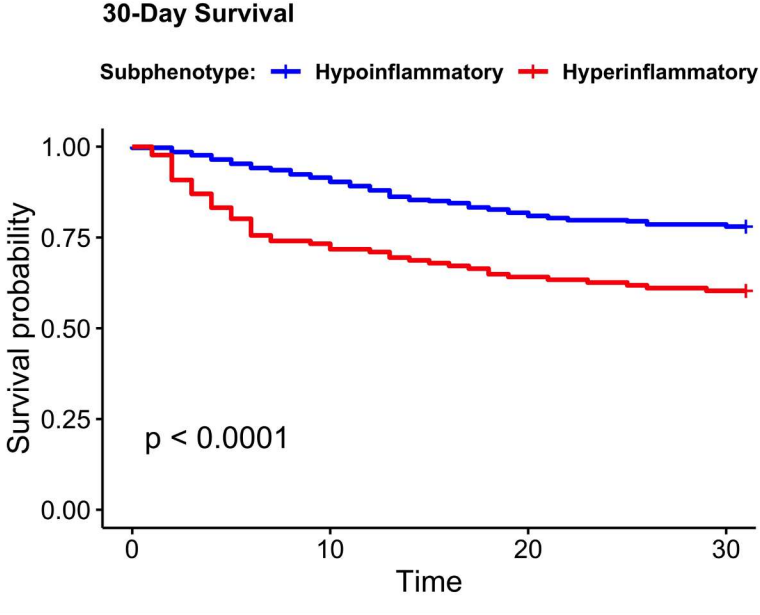
Subdistribution hazard ratio (95% confidence interval) for time to liberation of hyperinflammatory patients adjusted for the competing risk of death: 0.56 (0.43- 0.75), p= 0.000067


Hypo-inflammatory by both parsimonious models
Hypo-inflammatory by 3-variable parsimonious model only
Hyper-inflammatory by 3-variable parsimonious model only
Hyper-inflammatory by both parsimonious models

A. *4-variable internal parsimonious model predictions*

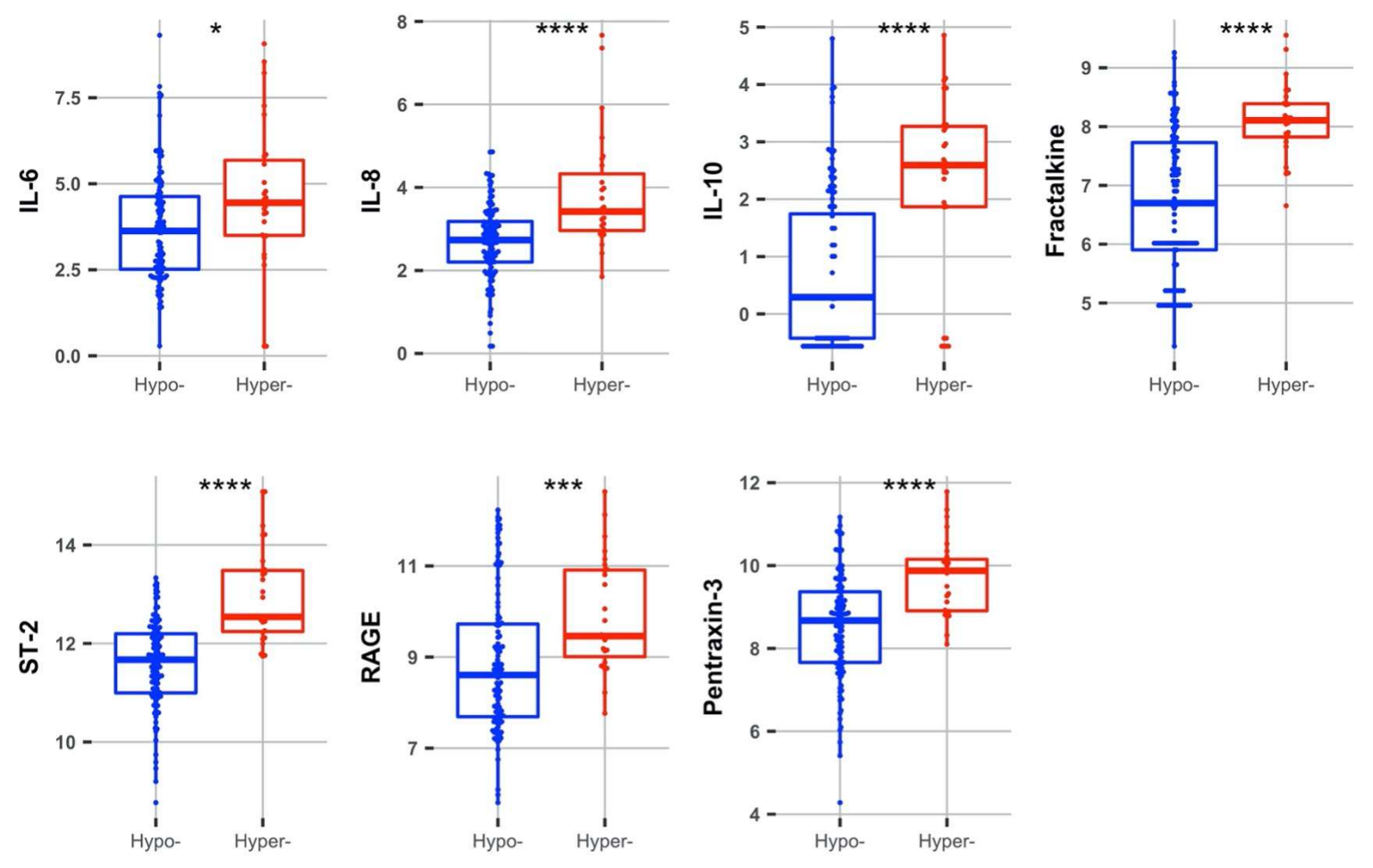


B. *3-variable external parsimonious model predictions*



Variable	Hypo-inflammatory	Hyper-inflammatory	p-value
n	**112**	**27**	
Demographics			
Age (median [IQR])	61.6 [52.0, 72.9]	63.0 [55.4, 70.3]	0.6490
Male gender, N (%)	68 (60.7)	16 (59.3)	1.0000
BMI (median [IQR])	31.1 [26.6, 37.7]	30.0 [26.8, 34.8]	0.4922
Caucasian race, N (%)	87 (77.7)	20 (74.1)	0.0594
COVID-19 positive, N (%)	66 (58.9%)	14 (51.9%)	0.6520
History of Chronic Disease			
Diabetes, N (%)	40 (35.7)	12 (44.4)	0.5353
COPD, N (%)	25 (22.3)	4 (14.8)	0.5499
Immunosuppression, N (%)	19 (17.0)	1 (3.7)	0.1452
Chronic kidney disease, N (%)	11 (9.8)	10 (37.0)	**0.0012**
Chronic cardiac failure, N (%)	14 12.5)	7 (25.9)	0.1473
Alcohol use, N (%)	10 (8.9)	2 (7.7)	1.0000
Hemodynamic parameters			
HR (median [IQR])	83.5 [69.0, 96.0]	92.0 [84.0, 109.0]	**0.0082**
SBP (median [IQR])	121.5 [106.2, 133.8]	120.5 [110.8, 146.2]	0.3161
Laboratory parameters			
pHa (median [IQR])	7.4 [7.3, 7.4]	7.3 [7.3, 7.4]	**0.0089**
WBC (median [IQR])	10.6 [7.2, 14.6]	11.8 [8.4, 21.6]	0.1942
Creatinine (median [IQR])	1.0 [0.7, 1.5]	3.2 [2.0, 4.1]	**<0.0001**
Serum CO2 (median [IQR])	26.0 [22.8, 29.0]	23.0 [19.5, 25.0]	**0.0009**
Mechanical Ventilation Parameters			
Worst PaO2:FiO2 ratio (median [IQR])	144.5 [88.5, 205.0]	144.5 [88.5, 205.0]	0.1261
Peak Inspiratory pressure (median [IQR])	25.0 [20.0, 30.0]	24.0 [21.0, 30.8]	0.5908
Severity of Illness and Clinical Outcomes			
Shock (vasopressor use), N (%)	50 (44.6)	20 (74.1)	**0.0114**
Acute kidney injury, N (%)	51 (45.5)	19 (70.4)	**0.0355**
30-d mortality, N (%)	33 (29.5)	12 (44.4)	0.2062
90-d mortality, N (%)	33 (29.5)	12 (44.4)	0.2062
ICU length of stay (median [IQR])	11.5 [6.0, 28.2]	11.5 [8.0, 19.2]	0.9091
Ventilator-free days (median [IQR])	17.0 [6.0, 23.0]	19.0 [12.0, 22.0]	0.5474
Duration of mechanical ventilation, median [IQR], d	11.0 [5.0, 22.0]	9.0 [6.0, 16.0]	0.5481
Biomarkers			
IL-6, median [IQR], pg/ml	38 [12, 102]	85 [33, 296]	**0.0128**
IL-8, median [IQR], pg/ml	15 [9, 24]	31 [19, 77]	**<0.0001**
IL-10, median [IQR], pg/ml	1 [1, 6]	13 [7, 26]	**<0.0001**
TNFR-1, median [IQR], pg/ml	3562 [2477, 5314]	12872 [9395, 20216]	**<0.0001**
Angiopoietin-2, median [IQR], pg/ml	5881 [3112, 12168]	26153 [12149, 51946]	**<0.0001**
Pentraxin-3, median [IQR], pg/ml	5847 [2130, 11706]	19450 [7410, 25708]	**<0.0001**
Fractalkine, median [IQR], pg/ml	812 [366, 2270]	3313 [2497, 4396]	**<0.0001**
ST-2, median [IQR], pg/ml	117071 [59692, 198230]	279570 [207407, 717116]	**<0.0001**

Procalcitonin, median [IQR], pg/ml	248 [128, 656]	3780 [1582, 4041]	**<0.0001**
Rage, median [IQR], pg/ml	5469 [2187, 16732]	12855 [8242, 54802]	**0.0005**


IL-6
*
7.5
5.0
2.5
0.0
Hypo-
Hyper-
IL-8
****
8
6
4
2
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Hypo-
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IL-10
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Fractalkine
****
9
8
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ST-2
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14
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Hypo-
Hyper-
RAGE
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11
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7
Hypo-
Hyper-
Pentraxin-3
****
12
10
8
6
4
Hypo-
Hyper-