Supplementary information

An inflammatory cytokine signature predicts COVID-19 severity and survival

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SUPPLEMENTARY TABLES

COMPETING RISK MODEL			
VARIABLES		HR (95% CI)	**Overall P-value**
TNF-α	High	1.63 (1.17, 2.26)	**0.004**
	Low	Ref	
IL-6	High	2.95 (2.11, 4.13)	**<.0001**
	Low	Ref	
IL-8	High	1.80 (1.34, 2.42)	**0.0001**
	Low	Ref	
IL-1β	High	1.01 (0.77, 1.32)	0.9519
	Low	Ref	
SEX	Female	1.36 (1.03, 1.79)	**0.0282**
	Male	Ref	
AGE	50-70	2.18 (1.30, 3.67)	**<.0001**
	>70	3.95 (2.30, 6.77)	
	<50	Ref	
RACE/ETHNICITY	NH African American	0.86 (0.57, 1.31)	0.7740
	Hispanic	1.04 (0.73, 1.50)	
	Other	1.00 (0.62, 1.61)	
	NH White	Ref	
DIABETES	Yes	0.98 (0.70, 1.37)	0.8984
	No	Ref	
HYPERTENSION	Yes	0.90 (0.65, 1.24)	0.5103
	No	Ref	
SMOKING STATUS	Active smoker	1.34 (0.69, 2.60)	0.6852
	Quit	1.04 (0.73, 1.49)	
	Unknown	0.89 (0.62, 1.27)	
	Non-smoker	Ref	
CKD	Yes	1.42 (0.92, 2.18)	0.1159
	No	Ref	
ASTHMA	Yes	0.93 (0.49, 1.76)	0.8274
	No	Ref	
COPD	Yes	0.83 (0.41, 1.66)	0.5925
	No	Ref	
CHF	Yes	0.60 (0.29, 1.24)	0.1668
	No	Ref	
ATRIAL FIBRILLATION	Yes	1.31 (0.86, 1.99)	0.2105
	No	Ref	
CANCER	Yes	1.19 (0.80, 1.78)	0.3923
	No	Ref	
SLEEP APNEA	Yes	1.32 (0.71, 2.46)	0.3843
	No	Ref	
BMI	BMI>30	1.37 (1.01, 1.84)	**0.0149**
	Unknown	2.11 (1.19, 3.74)	
	BMI<=30	Ref	

Supplementary Table S1. Competing risk model with four cytokines, demographics and co-morbidities (n=1,097). After adjustments, IL-6, IL-8, and TNF-α remain significantly predictive. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; BMI: body mass index.

COX SURVIVAL MODEL			
VARIABLES		**HR (95% CI)**	**Overall P-value**
TNF-α	High	1.73 (1.18, 2.55)	**0.0049**
	Low	Ref	
IL-6	High	2.58 (1.72, 3.87)	**<.0001**
	Low	Ref	
IL-8	High	1.41 (1.00, 2.00)	**0.0491**
	Low	Ref	
IL-1β	High	0.90 (0.65, 1.24)	0.5279
	Low	Ref	
CRP	High	1.31 (0.90, 1.90)	0.1643
	Low	Ref	
D-DIMER	High	1.03 (0.69, 1.54)	0.8858
	Low	Ref	
FERRITIN	High	0.89 (0.64, 1.24)	0.5056
	Low	Ref	
SEX	Female	1.47 (1.06, 2.05)	**0.0219**
	Male	Ref	
AGE	50-70	1.95 (1.06, 3.59)	**0.0001**
	>70	3.24 (1.75, 6.02)	
	<50	Ref	
RACE/ETHNICITY	NH African American	0.67 (0.40, 1.12)	0.1791
	Hispanic	1.07 (0.71, 1.61)	
	Other	0.78 (0.45, 1.36)	
	NH White	Ref	
DIABETES	Yes	0.82 (0.55, 1.21)	0.3121
	No	Ref	
HYPERTENSION	Yes	1.12 (0.75, 1.66)	0.5930
	No	Ref	
SMOKING STATUS	Active smoker	1.24 (0.60, 2.57)	0.6208
	Quit	1.18 (0.78, 1.79)	
	Unknown	0.85 (0.55, 1.30)	
	Non-smoker	Ref	
CKD	Yes	1.45 (0.88, 2.38)	0.1489
	No	Ref	
ASTHMA	Yes	1.09 (0.53, 2.23)	0.8171
	No	Ref	
COPD	Yes	0.92 (0.46, 1.87)	0.8239
	No	Ref	
CHF	Yes	0.61 (0.28, 1.35)	0.2245
	No	Ref	
ATRIAL FIBRILLATION	Yes	1.06 (0.66, 1.70)	0.8136
	No	Ref	
CANCER	Yes	1.14 (0.73, 1.77)	0.5681
	No	Ref	
SLEEP APNEA	Yes	1.41 (0.68, 2.92)	0.3525
	No	Ref	
BMI	BMI>30	1.04 (0.73, 1.47)	**<.0001**
	Unknown	4.63 (2.31, 9.27)	
	BMI<=30	Ref	

Supplementary Table S2. Cox survival model with four cytokines, demographics, co-morbidities, and inflammatory markers, including CRP, D-dimer, ferritin (n=863). After adjustments, IL-6, IL-8 and TNF-α remain significantly predictive. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; BMI: body mass index.

Competing risk model with multiple variable adjustments			
Variables	**Levels**	**HR (95% CI)**	**Overall P-value**
TNF-α	High	2.01 (1.32, 3.07)	**0.0012**
	Low	Ref	
IL-6	High	2.29 (1.47, 3.55)	**0.0002**
	Low	Ref	
IL-8	High	1.40 (0.97, 2.01)	0.0706
	Low	Ref	
IL-1β	High	0.89 (0.64, 1.24)	0.4923
	Low	Ref	
CRP	High	1.38 (0.93, 2.05)	0.1113
	Low	Ref	
D-DIMER	High	0.90 (0.57, 1.42)	0.6371
	Low	Ref	
FERRITIN	High	0.90 (0.63, 1.29)	0.5677
	Low	Ref	
SEX	Female	1.27 (0.90, 1.80)	0.1713
	Male	Ref	
AGE	50-70	1.95 (1.05, 3.61)	**<.0001**
	>70	3.46 (1.83, 6.56)	
	<50	Ref	
RACE/ETHNICITY	NH African American	0.74 (0.43, 1.28)	0.6492
	Hispanic	1.00 (0.65, 1.52)	
	Other	0.94 (0.53, 1.67)	
	NH White	Ref	
BMI	BMI>30	0.99 (0.67, 1.46)	**0.0005**
	Unknown	3.27 (1.75, 6.11)	
	BMI<=30	Ref	
DIABETES	Yes	0.84 (0.56, 1.25)	0.3834
	No	Ref	
HYPERTENSION	Yes	1.04 (0.68, 1.58)	0.8743
	No	Ref	
SMOKING STATUS	Active smoker	1.32 (0.58, 2.99)	0.4607
	Quit	1.41 (0.90, 2.20)	
	Unknown	1.03 (0.67, 1.59)	
	Non-smoker	Ref	
CKD	Yes	1.90 (1.10, 3.31)	**0.0221**
	No	Ref	
ASTHMA	Yes	1.02 (0.42, 2.46)	0.9640
	No	Ref	
CHF	Yes	0.75 (0.26, 2.17)	0.5911
	No	Ref	
COPD	Yes	0.90 (0.35, 2.30)	0.8308
	No	Ref	
SLEEP APNEA	Yes	1.65 (0.73, 3.72)	0.2253
	No	Ref	
ATRIAL FIBRILLATION	Yes	0.84 (0.49, 1.45)	0.5304
	No	Ref	
CANCER	Yes	1.76 (1.06, 2.93)	**0.0282**
	No	Ref	
SEVERITY SCORE	Severe	4.05 (2.57, 6.37)	**<.0001**
	Severe with EOD	6.20 (3.67, 10.46)	
	Moderate	Ref	

Supplementary Table S3. Competing risk model with four cytokines, demographics, co-morbidities, and laboratory measurements (n=802). After adjustments, IL-6 and TNF-α remain significantly predictive. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; BMI: body mass index.

Competing risk models adjusting for multiple variables (Overall P-value)					
Effect	**IL-6**	**IL-8**	**TNF-α**	**IL-1β**	**All cytokines**
IL-6	**<.0001**				**0.0038**
IL-8		**<.0001**			0.1090
TNF-α			**<.0001**		**0.0152**
IL-1β				0.4816	0.1409
SEX	0.3162	0.4602	0.5325	0.4293	0.3749
AGE	**0.0005**	**0.0005**	**0.0008**	**0.0003**	**0.0012**
RACE / ETHNICITY	0.6348	0.4411	0.4363	0.468	0.666
DIABETES	**0.0251**	0.1868	0.093	0.0709	0.0947
HYPERTENSION	0.3552	0.8798	0.934	0.7853	0.7574
SMOKING STATUS	0.6322	0.7500	0.6498	0.8288	0.5121
CKD	**0.0073**	**0.0132**	0.0515	**0.0179**	**0.0353**
ASTHMA	0.38	0.5425	0.6684	0.5363	0.4956
COPD	0.542	0.3782	0.4989	0.3675	0.6134
CHF	0.8534	0.9471	0.7073	0.7922	0.8496
ATRIAL FIBRILLATION	**0.0437**	**0.0429**	0.0712	0.0738	**0.0422**
CANCER	0.0687	0.0658	**0.0399**	0.0679	0.0664
SLEEP APNEA	**0.0172**	**0.0083**	**0.0068**	**0.0086**	**0.0115**
SEVERITY SCORE	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**
BMI	**0.0042**	**0.0027**	**0.0036**	**0.0087**	**0.0021**
SYSTOLIC BP MAX	**0.0027**	**0.0003**	**0.0009**	**0.0003**	**0.0021**
O2 SATURATION MIN	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**
D-DIMER	0.0753	0.0818	0.1557	0.2163	**0.0404**
ALBUMIN	**0.0001**	**0.0002**	**0.0004**	**0.0002**	**0.0001**
CALCIUM	0.0627	0.1742	0.2577	0.2785	0.0537
CHLORIDE	**0.004**	**0.0114**	**0.0035**	**0.0068**	**0.0052**
PLATELET	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**

Supplementary Table S4. Type 3 test of competing risk survival analysis for cytokine tested in ELLA and adjusted for comorbidities and laboratory/clinical metrics. After adjustment, IL-6 and TNF-α remain significantly predictive of survival based on a competing risk model. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; BMI: body mass index.

Stratification	Effect	HR (95% CI)	P-value
O$_2$ saturation	**TNF-α**	**2.17 (1.50, 3.15)**	**<.0001**
	IL-6	**2.06 (1.35, 3.14)**	**0.0008**
	IL-8	**1.45 (1.01, 2.08)**	**0.0409**
	IL-1β	1.20 (0.86, 1.68)	0.2930
Age Group	**TNF-α**	**1.99 (1.34, 2.87)**	**0.0002**
	IL-6	**2.13 (1.41, 3.22)**	**0.0003**
	IL-8	1.42 (0.99, 2.04)	0.0542
	IL-1β	1.18 (0.84, 1.64)	0.3404
Severity Score (moderate, severe, severe with end organ damage)	**TNF-α**	**2.07 (1.44, 2.97)**	**<.0001**
	IL-6	**2.14 (1.42, 3.24)**	**0.0003**
	IL-8	1.43 (1.00, 2.05)	0.0526
	IL-1β	1.17 (0.84, 1.63)	0.3502
SOFA Severity Score[#] (≤1, >1)	**TNF-α**	**1.71 (1.14, 2.55)**	**0.0090**
	IL-6	**2.58 (1.63, 4.10)**	**<.0001**
	IL-8	**1.65 (1.09, 2.49)**	**0.0173**
	IL-1β	1.42 (0.99, 2.03)	0.0580

*Each model includes one cytokine (n=802)

*Covariates: sex, age, race/ethnicity, diabetes, hypertension, smoking status, chronic kidney disease (CKD), asthma, congestive heart failure (CHF), atrial fibrillation, chronic obstructive pulmonary disease (COPD), cancer, severity score, body mass index (BMI), systolic blood pressure max, O$_2$ saturation min, D-dimer, albumin, calcium, chloride, platelets.

*O$_2$ saturation min is not in the covariates of the model stratified by O$_2$ saturation

*Age is not in the covariates of the model stratified by age group

*Severity score is not in the covariates of the model stratified by Severity Score

[#]For SOFA severity, cutoff chosen based on median, and only 663 patients were available (O$_2$ saturation and age group had similar significance in this subset, not shown).

Supplementary Table S5.
After stratification by the most predictive variables (O$_2$ saturation, age group, and severity score), the independent predictive value of IL-6 and TNF-α remains, and IL-8 returns to significance. The estimates were obtained using SAS PHREG procedure and STRATA statement.