Supplementary Appendix

Modulation of the Association between Age and Death by Risk Factor Burden in Critically Ill Patients with COVID-19

Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19

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Supplemental Methods

Multivariable Modeling of the Association of Age with 28-Day Mortality

We prespecified the variables below for inclusion in the multivariable models based on clinical knowledge, biologic plausibility, and completeness of data. All patient data were abstracted through manual chart review by study staff. To minimize missingness of laboratory and physiologic data, we selected the worst value on ICU day 1 or 2.

1. Age: 18-39 (ref); 40-49; 50-59; 60-69; 70-79; ≥80 years
2. Sex: Female (ref) vs Male
3. Race: White (ref) vs non-white
4. Hypertension: per chart review
5. Diabetes mellitus: per chart review
6. Body mass index: <25 (ref); 25-29; 30-34; 35-39.9; and ≥40 kg/m^2
7. Coronary artery disease: per chart review; includes any history of angina, myocardial infarction, or coronary artery bypass graft surgery
8. Congestive heart failure: per chart review; includes patients with heart failure with preserved or reduced ejection fraction
9. Chronic obstructive pulmonary disease: per chart review
10. Current smoking status: per chart review, does not include vaping or non-tobacco products
11. Active malignancy: active malignancy (other than non-melanoma skin cancer) treated in the past year. Defined as cancer of the lung, breast, colorectal, prostate, gastric, pancreatic, melanoma, ovarian, brain, or other
12. Days from symptom onset to ICU admission: ≤3 vs. >3
13. Lymphocyte count (lowest value on ICU day 1 or day 2): <1000 vs. ≥1000 per mm^3 (ref)
14. Shock on ICU days 1 or 2: defined as the simultaneous receipt of ≥2 vasopressors/inotropes
15. Number of hospital ICU beds: ≥100 (ref), 50–99, <50
16. Renal, liver, and coagulation components of the Sequential Organ Failure Assessment (SOFA) score:

SOFA Score Component	Categories				
	0	1	2	3	4
SOFA Renal[a]	Cr<1.2 mg/dL and UOP≥500	Cr 1.2-1.9 mg/dL and UOP≥500	Cr ≥2-3.4 mg/dL and UOP≥500	Cr 3.5-4.9 mg/dL or UOP<500	Cr≥5 mg/dL or UOP<200 or acute RRT or ESKD
SOFA Liver[b] (Bilirubin)	<1.2 mg/dL	1.2-1.9 mg/dL	≥2 mg/dL	---	---
SOFA Coagulation[b] (Platelets)	≥150 µL	100-149 µL	≤99 µL	---	---

[a]If the UOP was missing, the category was assigned according to the Cr

[b]Categories 3 and 4 were collapsed with category 2 due to the small number of patients with scores >2

Abbreviations: sequential organ failure score (SOFA), serum creatinine (Cr), urine output (UOP), renal replacement therapy (RRT), and end-stage kidney disease (ESKD)

Supplemental Table 1. Baseline characteristics of STOP-COVID patients

Characteristic	Age, years							
	All patients N = 5037 60.9 ± 14.7	**18-39 N = 474 32.0 ± 5.3**	**40 – 49 N = 592 45.1 ± 2.9**	**50 – 59 N = 1090 54.9 ± 2.9**	**60 – 69 N = 1413 64.5 ± 2.9**	**70 – 79 N = 985 74.0 ± 2.8**	**≥80 N = 483 84.6 ± 3.8**	***P***
Male	3179 (63.1)	310 (65.4)	411 (69.4)	715 (65.6)	892 (63.1)	573 (58.2)	278 (57.6)	<.001
Race/Ethnicity								
Non-Latino White	1315 26.1)	82 (17.3)	89 (15.0)	231 (21.2)	421 (29.8)	314 (31.9)	178 (36.9)	<.001
Non-Latino Black	1372 (27.2)	112 (23.6)	147 (24.8)	317 (29.1)	405 (28.7)	276 (28.0)	115 (23.8)	
Non-Latino Asian	274 (5.4)	28 (5.9)	30 (5.1)	49 (4.5)	78 (5.5)	53 (5.4)	36 (7.5)	
Latino	1176 (23.4)	172 (36.3)	218 (36.8)	292 (26.8)	269 (19.0)	155 (15.7)	70 (14.5)	
Body mass index, kg/m^2	31.9 ± 8.4	35.5 ± 10.2	34.8 ± 9.5	33.5 ± 8.8	31.8 ± 7.6	29.2 ± 6.2	27.2 ± 6.3	<.001
≤25	886 (18.3)	55 (12.3)	66 (11.5)	134 (12.7)	214 (15.7)	233 (24.6)	184 (39.9)	<.001
25 – 29.9	1437 (29.7)	86 (19.2)	118 (20.6)	293 (27.8)	431 (31.6)	345 (36.5)	164 (35.6)	
30 – 34.9	1188 (24.5)	110 (24.6)	152 (26.6)	271 (25.7)	362 (26.5)	221 (23.4)	72 (15.6)	
35 – 39.9	624 (12.9)	77 (17.2)	101 (17.7)	148 (14.0)	185 (13.6)	87 (9.2)	26 (5.6)	
≥40	711 (14.7)	119 (26.6)	135 (23.6)	209 (19.8)	173 (12.7)	60 (6.3)	15 (3.3)	
Pre-existing Comorbidities								
Congestive heart failure	515 (10.2)	16 (3.4)	23 (3.9)	90 (8.3)	161 (11.4)	138 (14.0)	87 (18.0)	<.001
Coronary artery disease	670 (13.3)	4 (0.8)	15 (2.5)	99 (9.1)	217 (15.4)	220 (22.3)	115 (23.8)	<.001
Chronic obstructive pulmonary disease	437 (8.7)	2 (0.4)	11 (1.9)	56 (5.1)	159 (11.3)	131 (13.3)	78 (16.2)	<.001
Hypertension	3085 (61.3)	103 (21.7)	232 (39.2)	622 (57.1)	985(69.7)	767(77.9)	376(77.9)	<.001
Active cancer	226 (4.5)	8 (1.7)	15 (2.5)	31 (2.8)	82 (5.8)	62 (6.3)	28 (5.8)	<.001
Chronic kidney disease	657 (13.0)	19 (4.0)	40 (6.8)	99 (9.1)	186 (13.2)	196 (19.9)	117 (24.2)	<.001
End-stage kidney disease	190 (3.8)	13 (2.7)	15 (2.5)	35 (3.2)	68 (4.8)	43 (4.4)	16 (3.3)	0.07
Acute physiologic factors in the ICU[a]								
≤3 days from symptom onset to ICU admission	1083 (21.6)	84 (17.8)	84 (14.3)	201 (18.5)	311 (22.1)	230 (23.6)	173 (36.0)	<.001
SOFA Renal score								
0	2393 (48.3)	311 (66.5)	363 (62.1)	559 (51.8)	606 (43.8)	385 (39.8)	169 (35.8)	<.001
1	1254 (25.3)	82 (17.5)	108 (18.5)	258 (23.9)	379 (27.4)	278 (28.7)	149 (31.6)	
2	646 (13.0)	29 (6.2)	46 (7.9)	126 (11.7)	192 (13.9)	163 (16.8)	90 (19.1)	
3	291 (5.9)	17 (3.6)	29 (5.0)	49 (4.5)	83 (6.0)	76 (7.9)	37 (7.8)	
4	371 (7.5)	29 (6.2)	39 (6.7)	87 (8.1)	123 (8.9)	66 (6.8)	27 (5.7)	
SOFA Liver score								
0	3942 (85.5)	380 (86.0)	470 (85.3)	852 (84.8)	1078 (84.2)	776 (85.9)	386 (89.6)	0.15
1	459 (10.0)	39 (8.8)	62 (11.3)	97 (9.7)	142 (11.1)	85 (9.4)	34 (7.9)	
2 – 4	212 (4.6)	23 (5.2)	19 (3.5)	56 (5.6)	61 (4.8)	42 (4.7)	11 (2.6)	
SOFA Coagulation score								
0	3796 (76.9)	386 (83.2)	492 (84.1)	845 (78.7)	1038 (75.3)	713 (74.1)	322 (68.4)	<.001
1	828 (16.8)	61 (13.2)	73 (12.5)	161 (15.0)	243 (17.6)	184 (19.1)	106 (22.5)	
2 – 4	311 (6.3)	17 (3.7)	20 (3.4)	68 (6.3)	98 (7.1)	65 (6.8)	43 (9.1)	
Invasive mechanical ventilation	3006 (59.7)	263 (55.5)	346 (58.5)	655 (60.1)	889 (62.9)	581 (59.0)	272 (56.3)	0.03
FiO2, (MV only)	0.79 ± 0.22	0.81 ± 0.23	0.82 ± 0.21	0.80 ± 0.22	0.79 ± 0.23	0.79 ± 0.22	0.76 ± 0.25	0.07

	Age, years							
	All patients N = 5037 60.9 ± 14.7	**18-39 N = 474 32.0 ± 5.3**	**40 – 49 N = 592 45.1 ± 2.9**	**50 – 59 N = 1090 54.9 ± 2.9**	**60 – 69 N = 1413 64.5 ± 2.9**	**70 – 79 N = 985 74.0 ± 2.8**	**≥80 N = 483 84.6 ± 3.8**	***P***
PEEP, cm H2O (MV only)	13.4 ± 4.2	15.1 ± 5.0	15.1 ± 4.6	14.0 ± 4.1	13.1 ± 3.7	12.5 ± 3.9	11.2 ± 3.9	<.001
PaO2 to FiO2 ratio (MV only)	120.8 ± 75.9	117.6 ± 81.6	108.2 ± 65.9	119.3 ± 79.0	119.7 ± 67.1	124.4 ± 70.7	140.1 ± 104.0	<.001
Shock	807 (16.0)	51 (10.8)	75 (12.7)	167 (15.3)	240 (17.0)	183 (18.6)	91 (18.8)	<0.001
Treatments for COVID-19 (ICU day 1 or 2)								
Remdesivir	347 (6.9)	50 (10.6)	57 (9.6)	79 (7.3)	85 (6.0)	58 (5.9)	18 (3.7)	<.001
Corticosteroids	1293 (25.7)	94 (19.8)	127 (21.5)	283 (26.0)	386 (27.3)	284 (28.8)	119 (24.6)	<.001
Tocilizumab	660 (13.1)	84 (17.7)	93 (15.7)	174 (16.0)	193 (13.7)	86 (8,7)	30 (6.2)	<.001
Number of ICU beds (pre-COVID-19)								<0.001
Small (<50 beds)	1647 (32.7)	118 (24.9)	163 (27.5)	356 (32.7)	500 (35.4)	365 (37.1)	145 (30.0)	
Medium (50-99 beds)	1390 (27.6)	138 (29.1)	169 (28.6)	302 (27.7)	376 (26.6)	241 (24.5)	164 (34.0)	
Large (≥100 beds)	2000 (39.7)	218 (46.0)	260 (43.9)	432 (39.6)	537 (38.0)	379 (38.5)	174 (36.0)	

Data are presented as count (percentage), mean ± standard deviation, or median (interquartile range)

[a]Represents worst value from ICU day 1 or day 2

Table Legend: abbreviations: cm H2O, centimeters of water; FiO2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; kg, kilograms; m^2, meters squared; mm Hg, millimeters of mercury; MV, mechanical ventilation; PaO2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment score

Missing data: N = 191 (3.8%) participants for body mass index, N = 27 (0.5%) participants for symptom onset ≤3 days to ICU day 1, N = 82 for SOFA Renal Score (1.6%), N = 424 (8.4%) for SOFA Liver Score, N = 102 (2.0%) for SOFA Coagulation Score, N = 118 (3.9%) for FiO2, N = 159 (5.3%) for PEEP, N = 204 (6.8%) for PaO2:FiO2 ratio, N = 546 (10.8%) for lymphocyte count

Supplemental Table 2. Association of Age Categories with 28-day and 90-day Mortality

Age groups	28-day Mortality					
	N	No. Events	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
< 65 years	2856	734	Reference	Reference	Reference	Reference
65 – 79 years	1698	751	2.29 (2.02 – 2.60)	2.10 (1.83 – 2.42)	2.08 (1.79 – 2.42)	2.06 (1.77 – 2.40)
≥ 80 years	483	301	4.78 (3.91 – 5.85)	4.70 (3.77 – 5.85)	5.09 (4.00 – 6.49)	5.09 (3.99 – 6.50)
	90-day Mortality					
Age groups	N	No. Events	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
< 65 years	2856	853	Reference	Reference	Reference	Reference
65 – 79 years	1698	846	2.33 (2.06 – 2.64)	2.12 (1.85 – 2.43)	2.11 (1.82 – 2.45)	2.10 (1.81 – 2.44)
≥ 80 years	483	318	4.53 (3.69 – 5.55)	4.37 (3.50 – 5.46)	4.78 (3.75 – 6.10)	4.86 (3.80 – 6.22)

Model 1 is unadjusted.
Model 2 is adjusted for sex, race, current smoking status, body mass index, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, and active malignancy.
Model 3 is adjusted for all Model 2 covariates along with symptom duration ≤3 days prior to ICU admission, number of ICU beds, shock, lymphocyte count <1000/uL, degree of hypoxemia and respiratory support, SOFA renal, SOFA liver, and SOFA coagulation scores.
Model 4 is adjusted for all Model 3 covariates along with remdesivir, tocilizumab, and corticosteroids

Supplemental Table 3. Risk Factors for 28-day Mortality

Factor	28 Day Mortality	
	Unadjusted OR (95% CI)*	**Adjusted** OR (95% CI)**
Male vs Female	**1.22 (1.08 – 1.38)**	**1.29 (1.21 – 1.38)**
Non-white vs White	1.03 (0.91– 1.16)	**1.08 (1.02 – 1.15)**
Body mass index, kg/m^2		
<25	[reference]	[reference]
25 – 30	0.96 (0.81 – 1.14)	1.08 (0.99 – 1.18)
30 – 35	0.78 (0.66 – 0.94)	1.02 (0.93 – 1.12)
35 – 40	0.79 (0.64 – 0.97)	1.15 (1.03 – 1.29)
≥40	0.85 (0.69 – 1.04)	1.43 (1.28 – 1.60)
Hypertension	**1.88 (1.66 – 2.13)**	1.03 (0.96 – 1.11)
Diabetes mellitus	**1.46 (1.30 – 1.64)**	**1.19 (1.12 – 1.27)**
Coronary artery disease	**1.87 (1.59 – 2.21)**	**1.17 (1.07 – 1.28)**
Congestive heart failure	**1.52 (1.27 – 1.83)**	0.95 (0.86 – 1.05)
Chronic obstructive pulmonary disease	**1.69 (1.38 – 2.06)**	**1.27 (1.14 – 1.41)**
Current smoker	1.06 (0.82 – 1.37)	**1.15 (1.01 – 1.31)**
Active cancer	**2.39 (1.83 – 3.13)**	**2.18 (1.90 – 2.51)**
Symptom onset ≤3 Days to ICU admission	**1.59 (1.39 – 1.82)**	**1.31 (1.22 – 1.41)**
Lymphocyte count < 1000/uL	**1.45 (1.26 – 1.67)**	**1.14 (1.06 – 1.22)**
Degree of hypoxemia and respiratory support		
No IMV	[reference]	[reference]
≥300	**2.63 (1.70 – 4.07)**	**1.91 (1.53 – 2.39)**
200 – 299	**1.58 (1.21 – 2.07)**	**1.15 (1.00 – 1.31)**
100 – 199	**1.80 (1.54 – 2.09)**	**1.66 (1.54 – 1.80)**
<100	**2.48 (2.15 – 2.86)**	**2.44 (2.27 – 2.63)**
Shock	**1.42 (1.26 – 1.61)**	**1.19 (1.11 – 1.27)**
SOFA coagulation score		
0	[reference]	[reference]
1	**1.50 (1.29 – 1.75)**	**1.29 (1.20 – 1.40)**
≥2	**2.25 (1.80 – 2.81)**	**1.76 (1.57 – 1.98)**
SOFA liver score		
0	[reference]	[reference]
1	**1.40 (1.16 – 1.69)**	**1.28 (1.16 – 1.41)**
≥2	**1.38 (1.11 – 1.70)**	**1.24 (1.11 – 1.39)**
SOFA renal score		
0	[reference]	[reference]
1	**1.89 (1.63 – 2.19)**	**1.35 (1.26 – 1.46)**
2	**3.73 (3.12 – 4.47)**	**2.19 (1.99 – 2.40)**
3	**4.16 (3.25 – 5.33)**	**2.54 (2.24 – 2.89)**
4	**3.27 (2.63 – 4.05)**	**2.41 (2.15 – 2.70)**
Number of ICU beds		
≥100	[reference]	[reference]
50 – 99	**1.67 (1.44 – 1.95)**	**1.67 (1.55 – 1.80)**
<50	**3.47 (3.02 – 4.00)**	**3.48 (3.24 – 3.74)**

*Univariate analyses, each variable is in its own model with 28-day mortality as the outcome
**Fully adjusted analyses, adjusted for age modeled as a spline, all other covariates listed in the table, and treatments for COVID-19: remdesivir, tocilizumab, and corticosteroids.

OR 95% CI in **bold** demonstrate statistical significance

Abbreviations: CI, confidence interval; FiO2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; kg, kilograms; m^2, meters squared; mm Hg, millimeters of mercury; IMV, invasive mechanical ventilation; OR, odds ratio; PaO2, arterial partial pressure of oxygen; SOFA, sequential organ failure assessment score

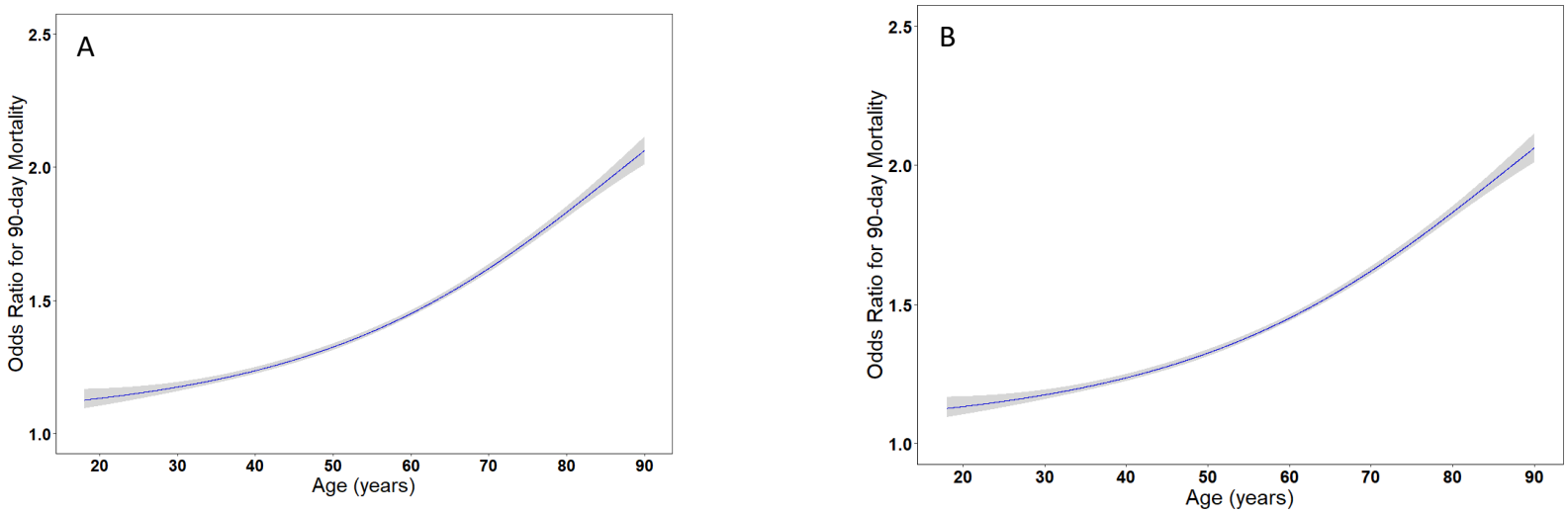
Supplemental Table 4. Risk factors associated with 28-day mortality

STOP-COVID variables significantly associated with 28-day mortality used to create risk factor score categories
Male Sex
Hypertension
Diabetes mellitus
Coronary artery disease
Congestive heart failure
Chronic obstructive pulmonary disease
Active Cancer
≤3 Days from Symptom Onset to ICU Admission
Lymphocyte Count < 1000/μL
Invasive Mechanical Ventilation
Shock
SOFA Coagulation Score > 0
SOFA Liver Score > 0
SOFA Renal Score > 0
No. ICU Beds < 100

Supplemental Table 5. Association of Age Categories with 28-day by Risk Factor Group

	Risk Factor Group		
Age groups	**0 – 4**	**5 – 6**	**7 – 13**
< 65 years	Reference	Reference	Reference
65 – 79 years	3.01 (2.27 – 3.98)	1.58 (1.27 – 1.95)	1.66 (1.31 – 2.10)
≥ 80 years	6.58 (4.18 – 10.37)	3.59 (2.54 – 5.07)	3.40 (2.34 – 4.94)

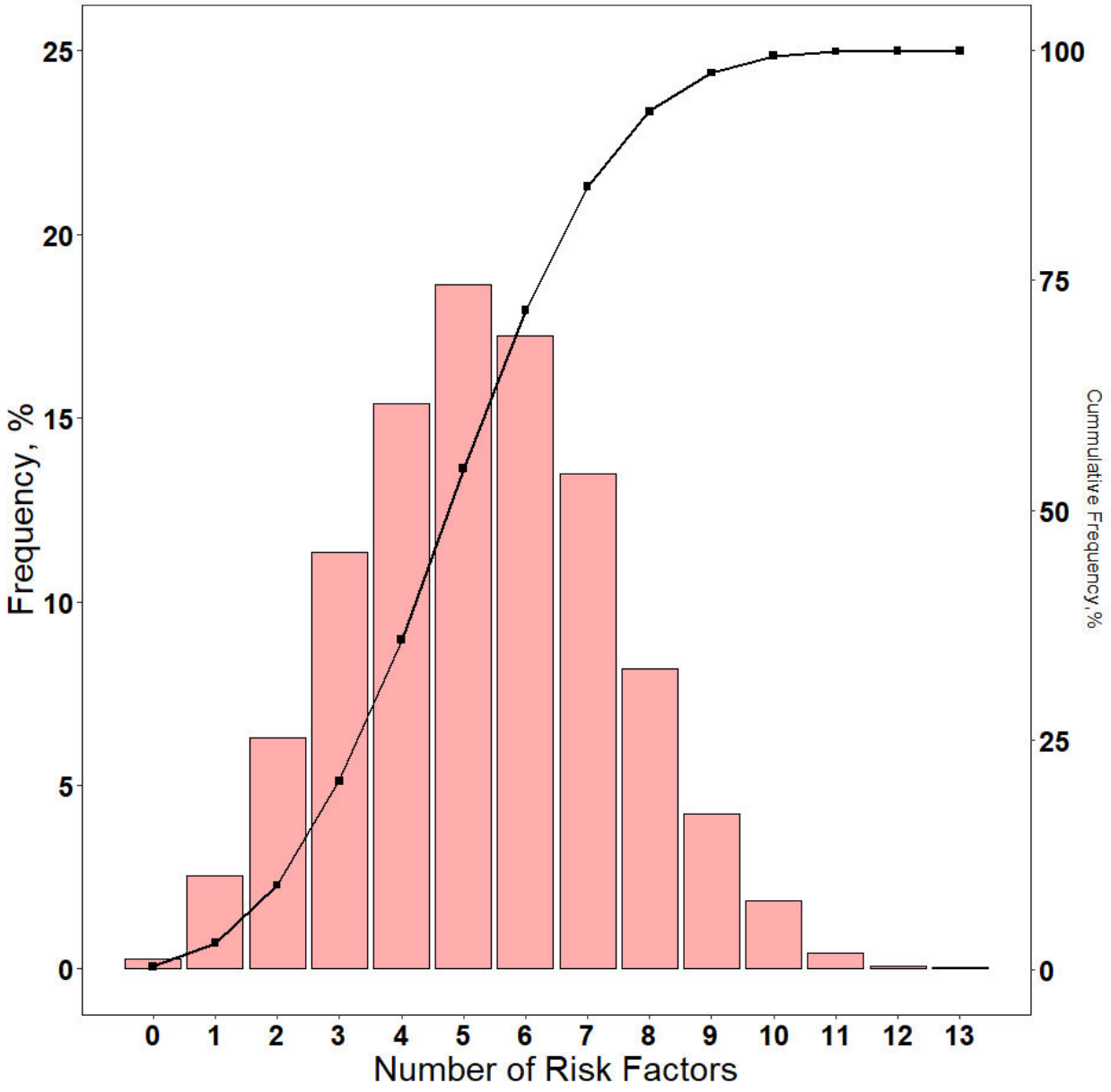
Adjusted for variables not included in the risk factor scores, including race (white vs non-white), body mass index, smoking status, and COVID-19 treatments: remdesivir, tocilizumab, corticosteroid use.



Supplemental Figure 1. Non-linear association between age and 90-day mortality

A) The model is unadjusted. Age-linear AIC: 31783 vs. Age-spline AIC: 31773, likelihood ratio test P-value for AIC difference: <0.001.

B) This model is fully adjusted for demographic characteristics (male sex, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and active cancer), acute physiology factors in the ICU (symptom onset ≤ 3 days prior to ICU admission, lymphocyte count <1000/uL, invasive mechanical ventilation, shock, SOFA coagulation > 0, SOFA liver > 0, and SOFA renal > 0), and ICU organizational factors (admission to a hospital with < 100 ICU beds) and COVID-19 treatments including remdesivir, tocilizumab, and corticosteroids). Age-linear AIC: 27543 vs. Age-spline AIC: 27444, likelihood ratio test P-value for AIC difference: < 0.01.



Supplemental Figure 2. Distribution of risk factors associated with 28-day mortality
Figure shows the frequency and cumulative frequency of risk factors present in STOP-COVID participants.

List of Participating Sites

Northeast
Beth Israel Deaconess Medical Center
Brigham and Women's Faulkner Hospital
Brigham and Women's Hospital
Cooper University Health Care
Hackensack Meridian Health Hackensack University Medical Center
Hackensack Mountainside Hospital
Johns Hopkins Hospital
Kings County Hospital Center
Lowell General Hospital
Massachusetts General Hospital
MedStar Georgetown University Hospital
Montefiore Medical Center
Mount Sinai
Newton Wellesley Hospital
New York-Presbyterian Queens Hospital
New York-Presbyterian/Weill Cornell Medical Center
New York University Langone Hospital
Rutgers/New Jersey Medical School
Rutgers/Robert Wood Johnson Medical School
Temple University Hospital
Thomas Jefferson University Hospital
Tufts Medical Center
United Health Services Hospitals
University of Pennsylvania Health System
University of Pittsburgh Medical Center
Westchester Medical Center
Yale University Medical Center
South
Baylor College of Medicine, Houston
Baylor University Medical Center/Baylor Scott White and Health
Duke University Medical Center
Mayo Clinic, Florida
Memphis VA Medical Center
Methodist University Hospital
Ochsner Medical Center
Tulane Medical Center
University of Alabama-Birmingham Hospital
University of Florida Health-Gainesville
University of Florida Health-Jacksonville
University of Miami Health System
University of North Carolina Hospitals
University of Texas Southwestern Medical Center
University of Virginia Health System
Midwest
Barnes-Jewish Hospital
Cook County Health
Mayo Clinic, Rochester
Froedtert Hospital
Indiana University Health Methodist Hospital
Northwestern Memorial Hospital
Promedica Health System
Rush University Medical Center
University Hospitals Cleveland Medical Center
University of Chicago Medical Center
University of Illinois Hospital and Health Sciences System
University of Kentucky Hospital
University of Michigan Hospital
University of Oklahoma Health Sciences Center
West
Loma Linda University Medical Center
Mayo Clinic, Arizona
Oregon Health and Science University Hospital
Renown Health
Stanford Healthcare
University of California-Davis Medical Center
University of California-Los Angeles Medical Center
University of California-San Diego Medical Center
University of California-San Francisco Medical Center
UCHealth University of Colorado
University Medical Center of Southern Nevada
University of Washington Medical Center