Abstract word count: 327
Text word count: 2900

Obesity, Circulating Inflammatory and Thrombotic Markers, and Major Clinical Outcomes in Critically Ill Patients with COVID-19 in the US

Allon N. Friedman, MD,[1] John Guirguis, MD[1], MD, Raj Kapoor, MD,[2] Shruti Gupta, MD, MPH,[3] PhD, David E. Leaf,[3†] MD, Lava R. Timsina, MPH, PhD[4†]; for the STOP-COVID Investigators*

[†]DEL and LRT contributed equally
*A full list of the STOP-COVID investigators is provided in the eAppendix

[1]Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN
[2]Division of Pulmonary and Critical Care Medicine, Indiana University School of Medicine, Indianapolis, IN
[3]Division of Renal Medicine, Brigham and Women's Hospital, Boston MA
[4]Department of Surgery, Indiana University School of Medicine, IN

Author Contributions:
ANF, RK, SG, JG, and DEL generated the data. ANF conceived of the project and was the primary author of the manuscript. LRT performed the statistical analyses. All authors critically revised the final manuscript.

Running headline: Obesity and clinical outcomes in critically ill COVID

Corresponding Author:
Allon N. Friedman, MD
550 University Blvd, Suite 6100
Indianapolis, IN 46202
allfried@iu.edu

Conflict of Interest:
None for all the authors

Funding Sources:
None

This is the author's manuscript of the article published in final edited form as:

Friedman, A. N., Guirguis, J., Kapoor, R., Gupta, S., Leaf, D. E., Timsina, L. R., & STOP-COVID Investigators. (2021). Obesity, inflammatory and thrombotic markers, and major clinical outcomes in critically ill patients with COVID-19 in the US. Obesity (Silver Spring, Md.), 29(10), 1719–1730. https://doi.org/10.1002/oby.23245

ABBREVIATIONS

AKI-RRT- acute kidney injury requiring renal replacement therapy
ARDS- acute respiratory distress syndrome
BMI- body mass index
COVID-19- coronavirus disease 2019
ICU- intensive care unit

ABSTRACT

Background: Major gaps exist in our understanding of the relationship between obesity and clinical outcomes in patients with severe COVID-19.

Research Question: Is obesity independently associated with major adverse clinical outcomes in critically ill patients with COVID-19?

Study Design and Methods: We used data from a multicenter cohort study of 4925 critically ill patients with COVID-19 admitted to ICUs at 68 hospitals across the US between XXX and XXX. The primary exposure was body mass index (BMI). The primary outcome was in-hospital mortality. Secondary outcomes included acute respiratory distress syndrome (ARDS), acute kidney injury requiring renal replacement therapy (AKI-RRT), thrombotic events, and seven circulating markers of inflammation and thrombosis (interleukin-6, C-reactive protein, albumin, ferritin, procalcitonin, fibrinogen, d-dimer). Unadjusted and multivariable-adjusted models were used.

Results: Among the 4908 patients included in the analysis, the mean (SD) age was 60.9 (14.7) years, 3095 (62.8%) were male, 1930 (39.2%) were white, 1496 (30.4%) were black, and 2552 (52.0%) were obese. A total of 1933 patients (39.4%) died during hospitalization. BMI was not independently associated with mortality. In contrast, higher BMI beginning at 25 kg/m^2 was associated with a greater risk of ARDS and AKI-RRT. BMI was also not associated with risk of thrombotic events. Of the seven markers of inflammation and thrombosis examined, only serum albumin was associated with BMI albeit in a clinically marginal manner.

Interpretation: In a large population of critically ill patients with COVID-19, higher BMI was not associated with a higher risk of death. BMI throughout the range of overweight and obese was, however, linked to greater risk of ARDS and AKI-RRT. The absence of any clinically

significant association between BMI and circulating biomarkers of inflammation and thrombosis challenges their hypothesized links with obesity and adverse outcomes in COVID-19.

INTRODUCTION

Over the course of the coronavirus disease 2019 (COVID-19) pandemic, obesity has emerged as an issue of great interest due to its prognostic significance. Several observational studies have identified obesity, particularly in its more severe forms, as an independent risk factor for hospitalization, critical illness, mechanical ventilation, and death.[1-6] The importance of obesity as a predictor of outcomes cannot be understated given its wide prevalence in the US and worldwide and its modifiable nature.[7] Nevertheless, major gaps exist in our understanding of the interplay between obesity and COVID-19.

One such gap involves the relationship between obesity and outcomes in the sickest cohort of patients—those admitted to intensive care units (ICUs). With few exceptions,[6,8] most analyses of this topic have been single center, limited by small sample size, or lacking in detailed descriptive data.[9-12] Moreover, most studies focused solely on the relationship between obesity and death without examining other major clinical outcomes. It is therefore not well understood if obesity is an independent risk factor for mortality and other major clinical outcomes like acute kidney injury requiring renal replacement therapy (AKI-RRT), acute respiratory distress syndrome (ARDS), and thrombotic events in critically ill patients with COVID-19.

The mechanisms underlying obesity's potential link with adverse outcomes in patients with COVID-19 are also poorly understood. Several postulated mechanisms include excess fat as a source of upregulated inflammation, a reservoir for viral replication, and/or a trigger for hypercoagulability.[13-17] However, there is a dearth of biochemical evidence in humans directly linking obesity to increased systemic inflammation or thrombosis.

To address these knowledge gaps, we used data from a multicenter cohort study of 4877 well-characterized critically ill adults admitted to ICUs at hospitals across the US. We examined the relationship between obesity and major clinical outcomes (mortality, ARDS, AKI-RRT, and thrombotic events). We also studied the relationship between body mass index (BMI) and circulating inflammatory and thrombotic markers to better understand how obesity may exert its detrimental effects.

METHODS

Study Design, Oversight, and Patient Population

The Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) is a multicenter cohort study that enrolled consecutive adults (≥18 years old) with laboratory-confirmed COVID-19 who were admitted to ICUs at 68 hospitals across the United States between March 4 and June 30, 2020. Patients were followed until the first of hospital discharge, death, or August 1, 2020, the date on which the database for the current analysis was locked. STOP-COVID only included ICU patients in an effort to focus on patients at highest risk of acute organ injury or death. For the current analysis, we excluded patients with missing data for BMI (n=228). For the AKI-RRT analysis, we also excluded patients with end-stage renal disease (ESRD) ESRD (eFigure 1). The study was approved with a waiver of informed consent by the Institutional Review Board at each participating site. Further information on STOP-COVID and its primary findings are reported elsewhere.[6]

Data Collection

Study personnel at each site collected data by detailed chart review and used a standardized case report form to enter data into a secure online database (REDCap). Patient-level data included: demographics and comorbidities; longitudinal laboratory values and physiologic parameters collected during the first 14 days of ICU admission; medications, treatments, organ support (including RRT) following ICU admission; and clinical outcomes, including acute organ injury and death. We also collected hospital-level data, including hospital size (assessed by the number of pre-COVID ICU beds, not including surge capacity beds). A complete list of variables is provided in the Case Report Form available elsewhere.[6]

Exposure and Outcomes

The primary exposure was body mass index (BMI), assessed at time of ICU admission and categorized in the following manner: <18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, ≥40 kg/m^2. BMI of 18.5-24.9 was used as a reference category. The primary outcome was in-hospital death. Secondary outcomes included clinical outcomes and biomarker analyses. Clinical outcomes included the development of ARDS, AKI-RRT, or thrombotic events during the first 14 days of ICU admission. The presence of ARDS was defined using the following modified Berlin criteria:[18] partial pressure of arterial oxygen:fractional inspired oxygen (PaO_2:FiO_2)<300 mmHg, the need for invasive mechanical ventilation, and a diagnosis of ARDS per chart review. AKI-RRT was defined as receiving any form of RRT, including intermittent hemodialysis, continuous renal replacement therapy, or peritoneal dialysis. Thrombotic events were defined as any of the following: deep vein thrombosis, pulmonary embolus, stroke, or other thrombotic event per chart review.

Secondary outcome biomarker analyses included the relationships between BMI and seven circulating markers of inflammation and thrombosis: interleukin (IL)-6, C-reactive protein (CRP), albumin, ferritin, procalcitonin, fibrinogen, and D-dimer,[19-24] measured during the first 14 days of ICU admission. Only the first value in any one day was used for this analysis.

Statistical Analyses

The population was described using univariable analysis with continuous variables expressed as mean (standard deviation) and median (interquartile ranges), and categorical variables as count

and percentage. We used unadjusted and multivariable-adjusted models to examine the association between BMI and the primary and secondary outcomes. The covariates selected for the multivariable models were tailored on the basis of prior knowledge and biological plausibility (further details are shown in the eMethods).[6,25]

For the primary outcome of mortality, we used time-to-event analysis involving Cox Proportional-Hazards modeling that included time-varying covariates to account for the non-proportionality of the hazards.[26] The other three clinical outcomes (ARDS, AKI-RRT, and thrombotic events) were assessed only during the first 14 days following ICU admission, and mortality was assumed to be a competing outcome. Individuals who had no outcomes or were discharged from the hospital were censored using a competing risk model based on the Fine and Gray method.[27-29] To account for the correlation of patients in the same hospital we used clustered robust standard error using health facility as the clustering variable.[30] For each BMI category, we presented unadjusted and multivariable-adjusted hazard ratios for mortality and competing risk subhazard ratios for predicting other clinical outcomes. In all outcome models, missing or unknown data were coded as a separate missing/unknown category.

When analyzing the relationship between BMI and circulating biomarkers during the first 14 days following ICU admission, we developed unadjusted and multivariable adjusted models using a generalized estimating equation (GEE) with an assumption of an exchangeable correlation structure whereby daily observations for the markers within a subject are assumed to be equally correlated. A repeated measure design helped to account for variability between subject measurements and allowed us to focus primarily on the effect due to the difference in

BMI.[31] All multivariable models included the same variables listed in the eMethods. The GEE allowed us to account for incomplete data for each biomarker.[32]

The following sensitivity analyses were performed that limited the analysis to: (1) biomarkers assessed during the first 3 days following ICU admission to limit additional influencing factors that could arise later during the ICU stay; (2) patients without diabetes to exclude the additional influence of the pro-inflammatory diabetic milieu;[33] and (3) patients admitted to the ICU within 72 hours of hospitalization to avoid major changes in BMI prior to ICU admission. Additional details on definitions, the GEE model, and biomarker analyses are found in the eMethods. Hypotheses were tested at 0.05 level of significance and the analyses were performed using Stata/MP 16.1.[34]

RESULTS

Baseline Characteristics

Baseline characteristics of the 4925 patients included (eFigure 1) stratified by categories of BMI categories are shown in Table 1 (abbreviated) and eTable 1 (complete). Mean (SD) age was 60.9 (14.7) years, 3095 (62.8%) were male, 1930 (39.2%) were white, and 1496 (30.4%) were black. The most common comorbidities were hypertension (61.6%) and diabetes (42.2%). A total of 2552 patients (52.0%) were obese, defined as a BMI>30 kg/m^2 (eFigure 2). Univariate relationships between obesity and patient characteristics and clinical factors are shown in Table 1. A total of 1933 of 4908 patients (39.4%) died during hospitalization (eFigure 1), and the median time to death was 10 days (IQR, 5-18) after ICU admission.

BMI and Major Adverse Clinical Outcomes

In the unadjusted model, a BMI of 30-34.9, 35-39.9, and 40 or higher kg/m^2 were each associated with a lower risk of death, while a BMI of <18.5 kg/m^2 was associated with a higher risk of death. However, in the multivariable adjusted model there was no association between BMI and mortality (Figure 1, eTables 2-3).

ARDS was observed in 3545 of 4907 patients (72.2%) (eFigure 1). Results from the unadjusted competing risk analysis were very similar to that of the multivariable analysis, which showed an independent increase in risk of ARDS for BMI starting at 25 kg/m^2 (25-29.9 kg/m^2: 1.21 (1.11, 1.33); 30-34.9 kg/m^2: 1.40 (1.24, 1.58); 35-39.9 kg/m^2: 1.36 (1.24, 1.48); ≥40 kg/m^2: 1.34 (1.15, 1.56)) (Figure 2; eTables 4,5).

AKI-RRT developed in 900 of 4739 patients (19.0%) (eFigure 1). Unadjusted and multivariable competing risk models were similar in that risk for AKI-RRT progressively rose beginning at a BMI of 25 (multivariable model, 25-29.9 kg/m^2, 1.46 (1.10, 1.94); 30-34.9 kg/m^2, 1.83 (1.37, 2.43); 35-39.9 kg/m^2, 2.01 (1.44, 2.79); ≥40 kg/m^2, 2.27 (1.56, 3.31)) (Figure 2; eTables 6, 7).

Thrombotic events occurred in 552 of 4907 (11.2%) (eFigure 1). In both unadjusted and multivariable analyses BMI was not associated with a higher risk of thrombosis (Figure 2; eTables 8, 9).

BMI and Circulating Biomarkers of Inflammation and Thrombosis

The number of patients with missing biomarker data ranged from 2.9% (platelets) to 62.3% (IL-6) (Table 1). The multivariable-adjusted relationship between BMI and each circulating biomarker during ICU admission appears in Figure 3. With the exception of serum albumin, which had a statistically significant and positive association with BMI, no association with BMI was observed using the other six biomarkers. Results did not change regardless of whether BMI was examined as a continuous or categorical variable. Of note, the relationship between BMI and albumin was clinically marginal (for every 10 kg/m^2 increase in BMI, serum albumin rose by 0.1 g/dL). Sensitivity analyses that only included data from the first 72 hours of ICU admission (n=4925) (eFigure 3), in the subgroup of patients without diabetes during the first 72 hours of ICU admission (n=2845) (eFigure 4), or only including patients admitted to the ICU within 72 hours of hospital admission (n=3978) (eFigure 5) did not have qualitatively different results.

DISCUSSION

Our study examined whether the previously identified association between obesity and mortality also applied to the sickest population of patients with COVID-19 and extended beyond just mortality to include other major adverse COVID-associated complications like ARDS, AKI-RRT, and thrombotic events. We also evaluated possible underlying mechanisms of the obesity-COVID-19 link by assessing the relationship between BMI and commonly used blood biomarkers of inflammation and thrombotic risk. Our results provide new insights into the obesity-COVID connection.

The pathophysiological link between excess adiposity and adverse COVID-19 outcomes is incompletely understood though several mechanisms have been hypothesized. Visceral adipose tissue promotes low grade inflammation through infiltration of macrophages and secretion of pro-inflammatory mediators including interleukin-6 (IL-6).[13] By expressing relatively high levels of angiotensin converting enzyme-2 (ACE2), adipocytes can become reservoirs for COVID-19, thereby leading to amplification of the infection and possibly the inflammatory cascade.[14,15] Obesity can also promote a hypercoagulable state through several mechanisms including upregulation of pro-coagulant factors (e.g., plasminogen activator inhibitor-1, tissue factor), enhanced platelet activation, and inhibition of fibrinolysis and thus potentiate the pro-thrombotic effects of COVID-19.[16,17]

In our analyses the only independent association between obesity and adverse events were seen with ARDS and AKI-RRT. ARDS is a relatively common and deadly complication of COVID-19.[35] Risk of ARDS increased beginning at a BMI of 25 kg/m^2 independent of other factors.

Similar findings have been reported in other studies of patients with COVID-19[36,37] and are contrary to the "obesity-ARDS paradox" observation that describes a lower incidence of ARDS in individuals with obesity.[38] Some proposed reasons why obesity is an independent risk factor for ARDS include increased inflammation, immune system dysfunction, decreased wound healing, accumulation of lipofibroblasts that differentiate into fibrosis-promoting myofibroblasts, and associated restrictive lung disease.[39,40]

We previously reported that AKI-RRT is relatively frequent in critically ill patients with COVID-19 and carries a poor prognosis.[25] In this study BMI was strongly and progressively associated with increased risk of AKI-RRT starting at a BMI of 25 kg/m^2. Obesity is a known predictor for AKI in critically individuals without COVID-19.[41] Possible mechanisms making individuals with obesity particularly susceptible to COVID-19 related injury include underlying glomerular hyperfiltration and shear-related stress, podocyte damage with segmental sclerosis, fatty kidney, pulmonary hypertension, and secretory products like leptin that may have nephrotoxic effects.[42-45]

We found that obesity was not independently associated with a higher risk for mortality. Our result is slightly different than our previous report, which found that obesity was linked to higher mortality but only in the highest BMI range ($\geq$ 40 kg/m^2).[6] We suspect the minor difference between the two results is due to this study's much larger sample size and its accounting for interventions that have, subsequent to the earlier publication, been proven to influence outcomes.[46,47]

Critically ill patients with COVID-19 have a very high incidence of thrombotic events.[48-50] Despite the documented association between obesity, hypercoagulability, and thrombotic risk in the general and ICU populations[16,51-53] we found no independent association between obesity and an increased risk of thrombotic events in our ICU patients. Perhaps any prothrombotic contribution of obesity was subsumed by a much larger risk associated with COVID-19.

To better understand the underlying pathophysiology between the putative relationship between excess adipose tissue and upregulation of pro-inflammatory and pro-thrombotic pathways in the COVID population,[13-17] we examined the relationship between BMI and seven circulating inflammatory and thrombotic markers. To our surprise we found no clinically significant relationship between the two, despite that fact that several of the biomarkers are known to be secreted by adipocytes (i.e. IL-6, C-reactive protein, fibrinogen).[13,54-56] Our analysis also accounted for extraneous factors that could have influenced inflammation or BMI such as diabetes or long pre-ICU hospital stays. While serum albumin was positively associated with BMI, the relationship was marginal in terms of clinical significance. Though often considered a good indicator of nutritional status, reductions in serum albumin are far more reflective of inflammation or illness, including in patients with severe COVID-19.[20,57] An obvious explanation for the albumin-BMI relationship we observed is not available but could be explained by the fact that production of serum albumin by adipocytes can be independent of the inflammatory process.[58] Our preliminary findings raise into question the paradigm that obesity contributes to poor outcomes in critically ill patients with COVID-19 by upregulating systemic inflammatory and prothrombotic pathways. However, further research in this area is clearly

required. Of note, our study could not exclude upregulation of these pathways in ways that could not be directed measured by blood sampling (i.e. intra-organ signaling).

Our study has several strengths. It was the performed in the largest and best characterized cohort of critically ill patients with COVID-19 to date. It is the first to examine the relationship between BMI and several of the most common and serious clinical outcomes in that population, including death. It is also the first to evaluate the link between BMI and markers of inflammation and thrombosis to try and better understand the mechanistic underpinnings between adiposity and COVID-19 that until this point has lacked direct correlation in humans. We chose to examine these questions in the critically ill population because we thought the relationship between obesity and biomarkers would be more easily discernible. However, this strategy also limited the generalizability of our findings and could have obscured pathophysiological mechanisms that would have been more apparent earlier in the course of the illness. Other limitations include missing data, lack of serial biomarker measurements, lack of a single study laboratory, and the insensitivity of BMI in differentiating visceral from subcutaneous fat.

In summary, in a large population of critically ill patients with COVID-19, obesity was not associated with mortality or thrombotic events but was consistently linked to a higher risk of developing ARDS and AKI-RRT throughout the range of elevated BMI. The absence of an association between BMI and circulating biomarkers of inflammation and thrombosis challenges their hypothesized links with obesity and adverse outcomes in COVID-19.

ACKNOWLEDGMENTS
ANF is responsible for the content of the manuscript, including data and analysis. ANF, RK, SG, JG, and DEL generated the data. ANF conceived of the project and was the primary author of the manuscript. LRT performed the statistical analyses. DEL and LRT contributed equally. All authors critically revised the final manuscript. A full list of the STOP-COVID investigators is provided in the Supplemental Appendix.

REFERENCES

1. Fresan U, Guevara M, Elia F, et al. Independent role of morbid obesity as a risk factor for COVID-19 hospitalization: a Spanish population-based cohort study. *Obesity (Silver Spring).* 2020.
2. Fried MW, Crawford JM, Mospan AR, et al. Patient Characteristics and Outcomes of 11,721 Patients with COVID19 Hospitalized Across the United States. *Clin Infect Dis.* 2020.
3. Hamer M, Gale CR, Kivimaki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: A community-based cohort study of adults in the United Kingdom. *Proc Natl Acad Sci U S A.* 2020;117(35):21011-21013.
4. Simonnet A, Chetboun M, Poissy J, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring).* 2020;28(7):1195-1199.
5. Tartof SY, Qian L, Hong V, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. *Ann Intern Med.* 2020.
6. Gupta S, Hayek SS, Wang W, et al. Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US. *JAMA Intern Med.* 2020.
7. Organization WH. Obesity and overweight fact sheet. 2020; https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed April 2, 2020.
8. Network C-IGobotR, the C-ICUI. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med.* 2020.
9. Barrasa H, Rello J, Tejada S, et al. SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria. *Anaesth Crit Care Pain Med.* 2020.
10. Chand S, Kapoor S, Orsi D, et al. COVID-19-Associated Critical Illness-Report of the First 300 Patients Admitted to Intensive Care Units at a New York City Medical Center. *J Intensive Care Med.* 2020;35(10):963-970.
11. Capone S, Abramyan S, Ross B, et al. Characterization of Critically Ill COVID-19 Patients at a Brooklyn Safety-Net Hospital. *Cureus.* 2020;12(8):e9809.
12. Halvatsiotis P, Kotanidou A, Tzannis K, et al. Demographic and clinical features of critically ill patients with COVID-19 in Greece: The burden of diabetes and obesity. *Diabetes Res Clin Pract.* 2020;166:108331.
13. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112(12):1796-1808.
14. Yang XH, Deng W, Tong Z, et al. Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. *Comp Med.* 2007;57(5):450-459.
15. Wang Y, Wang Y, Luo W, et al. A comprehensive investigation of the mRNA and protein level of ACE2, the putative receptor of SARS-CoV-2, in human tissues and blood cells. *Int J Med Sci.* 2020;17(11):1522-1531.
16. Faber DR, de Groot PG, Visseren FL. Role of adipose tissue in haemostasis, coagulation and fibrinolysis. *Obes Rev.* 2009;10(5):554-563.
17. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-128.
18. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526-2533.
19. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med.* 1998;128(2):127-137.
20. Friedman AN, Fadem SZ. Reassessment of albumin as a nutritional marker in kidney disease. *J Am Soc Nephrol.* 2010;21(2):223-230.

21. Kappert K, Jahic A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. *Biomarkers.* 2020;25(8):616-625.
22. Whang KT, Steinwald PM, White JC, et al. Serum calcitonin precursors in sepsis and systemic inflammation. *J Clin Endocrinol Metab.* 1998;83(9):3296-3301.
23. Pabinger I, Ay C. Biomarkers and venous thromboembolism. *Arterioscler Thromb Vasc Biol.* 2009;29(3):332-336.
24. Kattula S, Byrnes JR, Wolberg AS. Fibrinogen and Fibrin in Hemostasis and Thrombosis. *Arterioscler Thromb Vasc Biol.* 2017;37(3):e13-e21.
25. Gupta S, Coca SG, Chan L, et al. AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19. *J Am Soc Nephrol.* 2020.
26. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med.* 2018;6(7):121.
27. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94:496–509.
28. Pintilie M. *Competing risks: A practical perspective.* Chichester, U.K.: John Wiley & Sons Ltd; 2006.
29. Grunkemeier GL, Jin R, Eijkemans MJ, Takkenberg JJ. Actual and actuarial probabilities of competing risks: apples and lemons. *Ann Thorac Surg.* 2007;83(5):1586-1592.
30. Dutca I, Stancioiu PT, Abrudan IV, Ioras F. Using clustered data to develop biomass allometric models: The consequences of ignoring the clustered data structure. *PLoS One.* 2018;13(8):e0200123.
31. Singh V, Rana RK, Singhal R. Analysis of repeated measurement data in the clinical trials. *J Ayurveda Integr Med.* 2013;4(2):77-81.
32. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. *J Clin Epidemiol.* 2002;55(4):329-337.
33. Donath MY. Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat Rev Drug Discov.* 2014;13(6):465-476.
34. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.
35. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020;180(7):934-943.
36. Lemyze M, Courageux N, Maladobry T, et al. Implications of Obesity for the Management of Severe Coronavirus Disease 2019 Pneumonia. *Crit Care Med.* 2020;48(9):e761-e767.
37. Chiumello D, Pozzi T, Storti E, Caccioppola A, Pontiroli AE, Coppola S. Body mass index and acute respiratory distress severity in patients with and without SARS-CoV-2 infection. *Br J Anaesth.* 2020;125(4):e376-e377.
38. Bustamante AF-, Repine J. Adipose-lung corsstalk in the obesity-ARDS paradox. *J Pulmon Resp Med.* 2013(3):144.
39. Kruglikov IL, Scherer PE. The Role of Adipocytes and Adipocyte-Like Cells in the Severity of COVID-19 Infections. *Obesity (Silver Spring).* 2020;28(7):1187-1190.
40. Kalil AC, Thomas PG. Influenza virus-related critical illness: pathophysiology and epidemiology. *Crit Care.* 2019;23(1):258.
41. Danziger J, Chen KP, Lee J, et al. Obesity, Acute Kidney Injury, and Mortality in Critical Illness. *Crit Care Med.* 2016;44(2):328-334.

42. Chagnac A, Zingerman B, Rozen-Zvi B, Herman-Edelstein M. Consequences of Glomerular Hyperfiltration: The Role of Physical Forces in the Pathogenesis of Chronic Kidney Disease in Diabetes and Obesity. *Nephron.* 2019:1-5.
43. Chen HM, Liu ZH, Zeng CH, Li SJ, Wang QW, Li LS. Podocyte lesions in patients with obesity-related glomerulopathy. *Am J Kidney Dis.* 2006;48(5):772-779.
44. Simonds SE, Pryor JT, Ravussin E, et al. Leptin mediates the increase in blood pressure associated with obesity. *Cell.* 2014;159(6):1404-1416.
45. de Vries AP, Ruggenenti P, Ruan XZ, et al. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. *The lancet. Diabetes & endocrinology.* 2014;2(5):417-426.
46. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
47. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med.* 2020;383(19):1813-1826.
48. Maatman TK, Jalali F, Feizpour C, et al. Routine Venous Thromboembolism Prophylaxis May Be Inadequate in the Hypercoagulable State of Severe Coronavirus Disease 2019. *Crit Care Med.* 2020;48(9):e783-e790.
49. Trigonis RA, Holt DB, Yuan R, et al. Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. *Crit Care Med.* 2020;48(9):e805-e808.
50. Motaganahalli RL, Kapoor R, Timsina LR, et al. Clinical and laboratory characteristics of patients with novel coronavirus disease-2019 infection and deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2020.
51. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. *Am J Med.* 2005;118(9):978-980.
52. Minet C, Potton L, Bonadona A, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care.* 2015;19:287.
53. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res.* 2020;191:148-150.
54. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA.* 1999;282(22):2131-2135.
55. Iwasaki T, Nakajima A, Yoneda M, et al. Serum ferritin is associated with visceral fat area and subcutaneous fat area. *Diabetes Care.* 2005;28(10):2486-2491.
56. Hunt BJ. Hemostasis at Extremes of Body Weight. *Semin Thromb Hemost.* 2018;44(7):632-639.
57. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. *Crit Care.* 2020;24(1):255.
58. Sirico ML, Guida B, Procino A, et al. Human mature adipocytes express albumin and this expression is not regulated by inflammation. *Mediators Inflamm.* 2012;2012:236796.

Table 1: Patient Characteristics[a] at Baseline Stratified by Categories of BMI (N= 4908)

Characteristic	Full Sample (N=4908)	<18.5 (n=55)	18.5-24.9 (n=848)	25-29.9 (n=1453)	30-34.9 (n=1198)	35-39.9 (n=631)	40+ (n=723)	P-value
Demographics								
Age (yr) – median (IQR)	60.91 (14.7)	68.84 (17.02)	66.51 (15.15)	63.44 (13.69)	59.99 (13.93)	57.19 (14.04)	53.42 (13.5)	<0.001
Male sex – no. (%)	3095 (62.8)	33 (60)	566 (66.4)	1038 (71.1)	778 (64.8)	353 (55.9)	327 (45)	<0.001
Race – no. (%)								<0.001
White	1930 (39.2)	24 (43.6)	326 (38.3)	590 (40.4)	469 (39.1)	260 (41.2)	261 (36)	
Black	1496 (30.4)	15 (27.3)	218 (25.6)	376 (25.8)	369 (30.7)	215 (34.1)	303 (41.7)	
Other	389 (7.9)	6 (10.9)	116 (13.6)	137 (9.4)	82 (6.8)	22 (3.5)	26 (3.6)	
Unknown	1110 (22.5)	10 (18.2)	192 (22.5)	357 (24.5)	281 (23.4)	134 (21.2)	136 (18.7)	
Hispanic – no. (%)	445 (20.1)	288 (20.1)	157 (20.0)					
Coexisting conditions – no. (%)[a]								
Diabetes	2080 (42.2)	18 (32.7)	304 (35.7)	590 (40.4)	540 (45)	273 (43.3)	355 (48.9)	<0.001
Hypertension	3032 (61.6)	35 (63.6)	492 (57.8)	873 (59.8)	759 (63.2)	388 (61.5)	485 (66.8)	0.004
Chronic lung disease								
COPD	433 (8.8)	10 (18.2)	87 (10.2)	121 (8.3)	81 (6.7)	54 (8.6)	80 (11)	0.002
Asthma	532 (10.8)	1 (1.8)	76 (8.9)	101 (6.9)	125 (10.4)	96 (15.2)	133 (18.3)	<0.001
Coronary artery disease	661 (13.4)	15 (27.3)	120 (14.1)	225 (15.4)	154 (12.8)	69 (10.9)	78 (10.7)	<0.001
Congestive heart failure	496 (10.1)	10 (18.2)	87 (10.2)	125 (8.6)	114 (9.5)	61 (9.7)	99 (13.6)	0.002
Chronic kidney disease	645 (13.1)	8 (14.6)	117 (13.7)	183 (12.5)	155 (12.9)	79 (12.5)	103 (14.2)	0.877
Chronic liver disease	165 (3.4)	2 (3.6)	48 (5.6)	41 (2.8)	36 (3)	17 (2.7)	21 (2.9)	0.01
End-stage renal disease	186 (3.8)	6 (10.9)	55 (6.5)	43 (3)	40 (3.3)	19 (3)	23 (3.2)	<0.001
Cancer	227 (4.6)	2 (3.6)	50 (5.9)	84 (5.8)	48 (4)	20 (3.2)	23 (3.2)	0.01
Immunodeficiency	278 (5.6)	4 (7.3)	67 (7.9)	89 (6.1)	69 (5.8)	24 (3.8)	25 (3.4)	0.001
Blood laboratory findings on day of ICU admission, Median IQR)								
White blood cell count, /µL[b]	8.4 (6, 11.8)	9.4 (6.6, 13.3)	8.7 (5.9, 12.4)	8.5 (5.9, 11.8)	8.4 (6.1, 11.8)	7.6 (8.5, 6.2)	5.3 (7.9, 5.9)	0.6802
Lymphocyte count, /µL[c]	822.5 (550.8, 1177.9)	738.9 (455.5, 960)	742.2 (483.8, 1132.2)	782.1 (525.6, 1140.9)	829 (531.2, 1179.1)	944.7 (885.6, 624.2)	672.5 (915.4, 635)	0.7071
Platelet count, 1000/mm3[d]	215 (164, 278)	221.5 (167, 343)	215 (158.5, 285)	217 (163, 279)	211.5 (165, 273)	92.2 (218, 165)	86.4 (215, 167)	0.0579
D-dimer level, ng/ml[e]	1300 (670, 3437.5)	1620 (860, 4390)	1601.5 (780, 4010)	1415 (714, 3700)	1117 (579, 2980)	1270 (690, 3030)	1110 (614.5, 2355)	0.3787
Fibrinogen level, mg/ml[f]	601 (475, 744)	593 (462.5, 660.5)	552 (424, 710)	624.5 (508.5, 769)	619 (491, 768)	597.5 (495, 751.5)	575 (459, 701)	0.3694
Interleukin-6 level, pg/ml[g]	56.6 (17.9, 160)	36.7 (30.6, 70.4)	60 (25.5, 130.3)	55.5 (17.9, 169)	76.1 (24.4, 171)	46.6 (15, 138)	48.6 (10, 137.4)	0.7738
C-reactive protein level, mg/L	149.1 (80.9, 230)	125 (69.3, 178.9)	141.9 (74, 229.4)	158.1 (84.7, 238)	151 (82.3, 232.9)	152 (88, 238.2)	138 (79.1, 200)	0.01
Albumin, g/dL[i]	3.2 (2.8, 3.6)	3.1 (2.5, 3.5)	3.1 (2.6, 3.5)	3.2 (2.8, 3.5)	3.2 (2.8, 3.6)	3.3 (2.9, 3.6)	3.3 (2.9, 3.7)	<0.001
Ferritin, ng/ml[j]	977 (485, 1935)	744.5 (424, 1581)	1067 (440.5, 2109)	1061.3 (585, 2000)	1045 (528, 1985)	839.7 (421.9, 1653.4)	663.8 (352.4, 1410)	0.0001
Procalcitonin, ng/ml[k]	0.4 (0.2, 1.3)	0.5 (0.3, 1.5)	0.5 (0.2, 2)	0.4 (0.2, 1.4)	0.4 (0.2, 1.3)	0.4 (0.2, 1.2)	0.3 (0.1, 0.9)	0.5382
Severity-of-illness on the day of ICU admission, no. (%)[a]								
Shock	488 (9.9)	10 (18.2)	92 (10.8)	129 (8.8)	124 (10.3)	69 (10.9)	64 (8.8)	0.117

Altered mental status	1130 (22.9)	24 (43.6)	270 (31.7)	352 (24.1)	254 (21.2)	105 (16.6)	125 (17.2)	<0.001
Mechanical Ventilation								<0.001
HFNC or nonrebreather mask	1211 (24.6)	14 (25.5)	213 (25)	376 (25.8)	264 (22)	165 (26.2)	179 (24.7)	
Invasive mechanical ventilation	2930 (59.5)	28 (50.9)	480 (56.3)	872 (59.8)	748 (62.3)	377 (59.8)	425 (58.5)	
Noninvasive mechanical ventilation (BiPAP/CPAP)	134 (2.7)	1 (1.8)	12 (1.4)	26 (1.8)	39 (3.3)	16 (2.5)	40 (5.5)	
Treatment interventions, no. (%)								
Vasopressors	1924 (39.1)	20 (36.4)	337 (39.6)	575 (39.4)	470 (39.1)	258 (40.9)	264 (36.4)	0.635
Renal replacement therapy	1056 (21.4)	10 (18.2)	134 (15.7)	279 (19.1)	284 (23.7)	152 (24.1)	197 (27.1)	<0.001
ECMO	184 (3.7)	1 (1.8)	13 (1.5)	47 (3.2)	48 (4)	41 (6.5)	34 (4.7)	<0.001
Corticosteroids	1864 (37.9)	25 (45.5)	299 (35.1)	585 (40.1)	423 (35.2)	240 (38)	292 (40.2)	0.029
Remdesivir	425 (8.6)	3 (5.5)	59 (6.9)	117 (8)	103 (8.6)	67 (10.6)	76 (10.5)	0.06
Prone	1946 (39.5)	7 (12.7)	261 (30.6)	584 (40)	489 (40.7)	292 (46.3)	313 (43.1)	<0.001
Convalescent plasma	275 (5.6)	4 (7.3)	49 (5.8)	85 (5.8)	63 (5.3)	30 (4.8)	44 (6.1)	0.826

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BiPAP, bilevel positive airway pressure; BMI, body mass index, in kg/m^2; COPD, chronic obstructive lung disease; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; NSAID, non-steroidal anti-inflammatory drug

[a]Definitions are described more completely in [6].
[b]Data for white blood cell count were missing in 317 patients (6.4%)
[c]Data for lymphocyte count were missing in 999 patients (20.3%)
[d]Data for platelet count were missing in 142 patients (2.9%)
[e]Data for D-dimer were missing in 787 patients (16%)
[f]Data for fibrinogen were missing in 2405 patients (48.8%)
[g]Data for interleukin-6 were missing in 3068 patients (62.3%)
[h]Data for C-reactive protein were missing in 620 patients (12.6%)
[i]Data for albumin were missing in 264 patients (5.4%)
[j]Data for ferritin were missing in 692 patients (14.1%)
[k]Data for procalcitonin were missing in 1803 patients (36.6%)

FIGURES

Figure 1: Association between BMI and Mortality. BMI, body mass index. N=4801 patients included in the analysis.

Figure 2: Association between BMI and ARDS, AKI-RRT, and Thrombotic Events. ARDS, adult respiratory distress syndrome; AKI-RRT, acute kidney injury treated with renal replacement therapy. N=3827 for ARDS, N=4693 for AKI-RRT, N=4799 for thrombotic events.

Figure 3: Relationship between BMI and circulating biomarkers of inflammation and thrombosis during the first 14 days of ICU admission after controlling for all other variables in the model. The error bars represent the 95% confidence interval around the marginal mean for each marker within each BMI category. Missing biomarker data (% of total cohort): Interleukin-6 3047 (62.5%), C-reactive protein 615 (12.6%), albumin 262 (5.4%), ferritin 687 (14.1%), procalcitonin 1798 (36.9%), fibrinogen (2378 (48.8%), D-dimer 780 (16%).

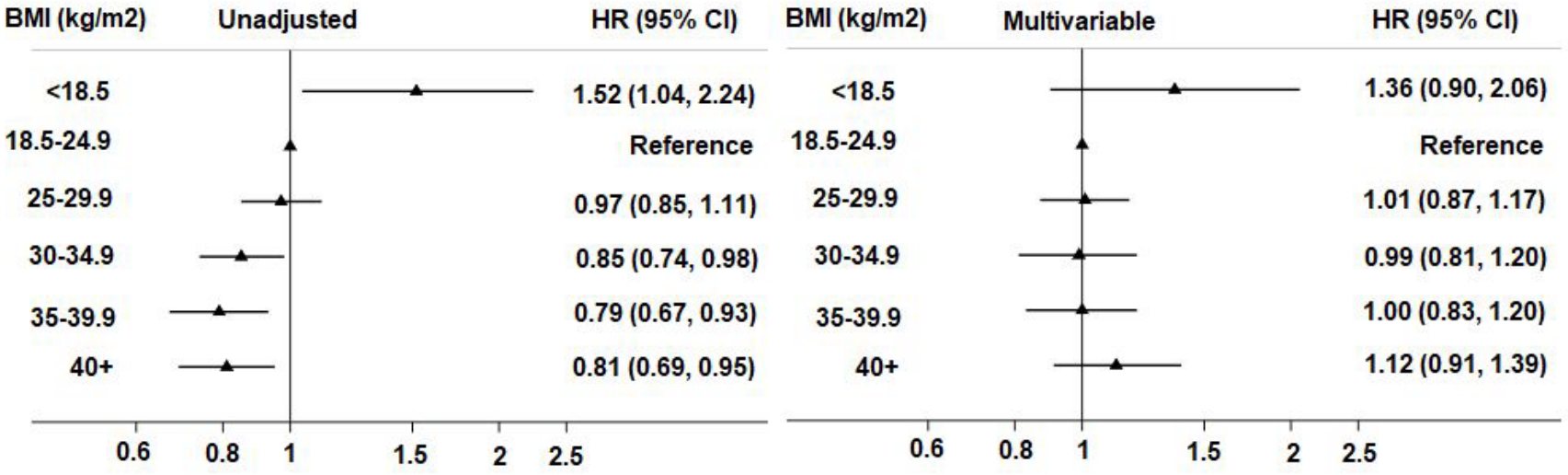

BMI (kg/m2)
Unadjusted
HR (95% CI)
<18.5
1.52 (1.04, 2.24)
18.5-24.9
Reference
25-29.9
0.97 (0.85, 1.11)
30-34.9
0.85 (0.74, 0.98)
35-39.9
0.79 (0.67, 0.93)
40+
0.81 (0.69, 0.95)
0.6
0.8
1
1.5
2
2.5
BMI (kg/m2)
Multivariable
HR (95% CI)
<18.5
1.36 (0.90, 2.06)
18.5-24.9
Reference
25-29.9
1.01 (0.87, 1.17)
30-34.9
0.99 (0.81, 1.20)
35-39.9
1.00 (0.83, 1.20)
40+
1.12 (0.91, 1.39)
0.6
0.8
1
1.5
2
2.5

Figure 1

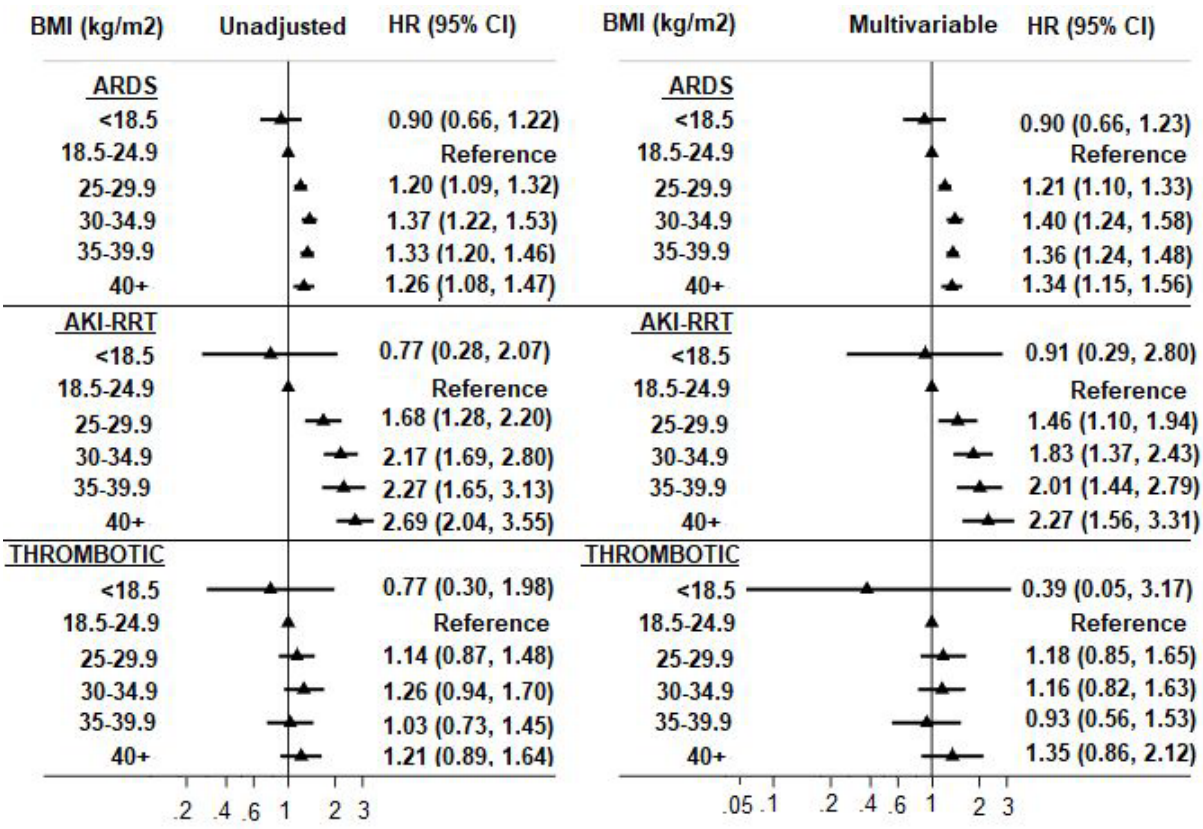

BMI (kg/m2)
Unadjusted
HR (95% CI)
ARDS
<18.5
0.90 (0.66, 1.22)
18.5-24.9
Reference
25-29.9
1.20 (1.09, 1.32)
30-34.9
1.37 (1.22, 1.53)
35-39.9
1.33 (1.20, 1.46)
40+
1.26 (1.08, 1.47)
AKI-RRT
<18.5
0.77 (0.28, 2.07)
18.5-24.9
Reference
25-29.9
1.68 (1.28, 2.20)
30-34.9
2.17 (1.69, 2.80)
35-39.9
2.27 (1.65, 3.13)
40+
2.69 (2.04, 3.55)
THROMBOTIC
<18.5
0.77 (0.30, 1.98)
18.5-24.9
Reference
25-29.9
1.14 (0.87, 1.48)
30-34.9
1.26 (0.94, 1.70)
35-39.9
1.03 (0.73, 1.45)
40+
1.21 (0.89, 1.64)
.2 .4 .6 1 2 3
BMI (kg/m2)
Multivariable
HR (95% CI)
ARDS
<18.5
0.90 (0.66, 1.23)
18.5-24.9
Reference
25-29.9
1.21 (1.10, 1.33)
30-34.9
1.40 (1.24, 1.58)
35-39.9
1.36 (1.24, 1.48)
40+
1.34 (1.15, 1.56)
AKI-RRT
<18.5
0.91 (0.29, 2.80)
18.5-24.9
Reference
25-29.9
1.46 (1.10, 1.94)
30-34.9
1.83 (1.37, 2.43)
35-39.9
2.01 (1.44, 2.79)
40+
2.27 (1.56, 3.31)
THROMBOTIC
<18.5
0.39 (0.05, 3.17)
18.5-24.9
Reference
25-29.9
1.18 (0.85, 1.65)
30-34.9
1.16 (0.82, 1.63)
35-39.9
0.93 (0.56, 1.53)
40+
1.35 (0.86, 2.12)
.05 .1 .2 .4 .6 1 2 3

Figure 2

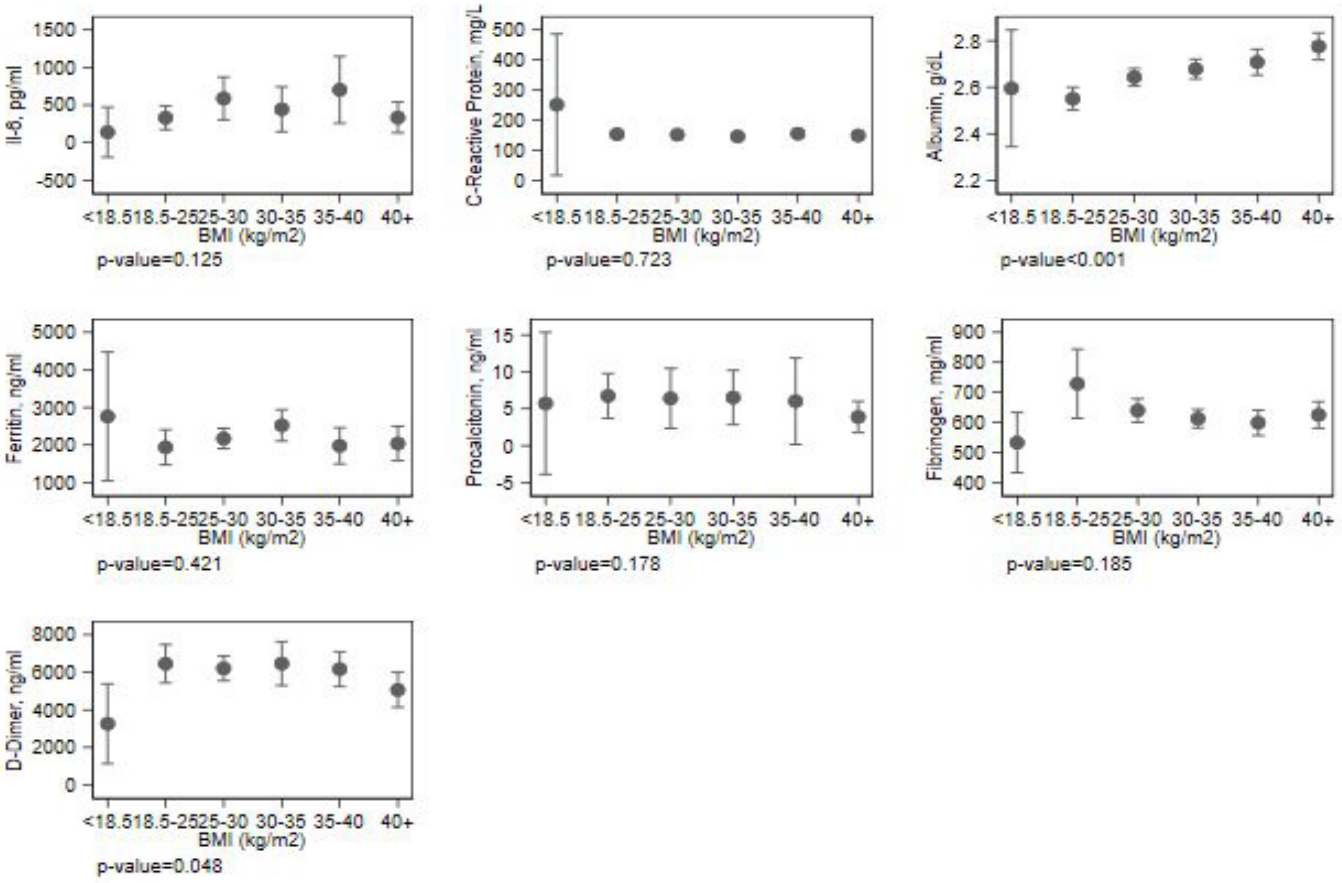

Il-6, pg/ml
1500
1000
500
0
-500
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value=0.125
C-Reactive Protein, mg/L
500
400
300
200
100
0
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value=0.723
Albumin, g/dL
2.8
2.6
2.4
2.2
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value<0.001
Ferritin, ng/ml
5000
4000
3000
2000
1000
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value=0.421
Procalcitonin, ng/ml
15
10
5
0
-5
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value=0.178
Fibrinogen, mg/ml
900
800
700
600
500
400
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value=0.185
D-Dimer, ng/ml
8000
6000
4000
2000
0
<18.5 18.5-25 25-30 30-35 35-40 40+
BMI (kg/m2)
p-value=0.048

Figure 3

SUPPLEMENTARY ONLINE CONTENT

eAppendix: Full list of STOP-COVID investigators
eMethods: Supplementary Methods
eFigure 1: Flow diagram describing exclusion criteria and number of patients available for analysis
eFigure 2: Distribution of patients by BMI
eFigure 3: Floating bar graph comparing BMI categories and levels of circulating biomarkers during the first 72 hours of ICU admission
eFigure 4: Floating bar graph comparing BMI categories and levels of circulating biomarkers in patients without diabetes during the first 72 hours of ICU admission
eFigure 5: Floating bar graph comparing BMI categories and levels of circulating biomarkers in patients admitted to the ICU within 72 hours of hospital admission
eTable 1: Complete table of patient characteristics stratified by BMI
eTable 2: Unadjusted and multivariable adjusted relationship between BMI and mortality
eTable 3: Complete multivariable model for mortality outcome
eTable 4: Unadjusted and multivariable adjusted relationship between BMI and ARDS
eTable 5: Complete multivariable model for ARDS outcome
eTable 6: Unadjusted and multivariable adjusted relationship between BMI and AKI-RRT
eTable 7: Complete multivariable model for AKI-RRT outcome
eTable 8: Unadjusted and multivariable relationship between BMI and thrombotic events
eTable 9: Complete multivariable model for thrombotic events outcome

STOP-COVID INVESTIGATORS

Baylor College of Medicine: Carl P. Walther*, Samaya J. Anumudu

Baylor University Medical Center: Justin Arunthamakun*, Kathleen F. Kopecky, Gregory P. Milligan, Peter A. McCullough, Thuy-Duyen Nguyen

Beth Israel Deaconess Medical Center: Shahzad Shaefi*, Megan L. Krajewski, Sidharth Shankar, Ameeka Pannu, Juan D. Valencia

Boston Medical Center: Sushrut S. Waikar*, Zoe A. Kibbelaar

Cook County Health: Ambarish M. Athavale*, Peter Hart, Shristi Upadhyay, Ishaan Vohra

Cooper University Health Care: Adam Green*, Jean-Sebastien Rachoin, Christa A. Schorr, Lisa Shea

Duke University Medical Center: Daniel L. Edmonston*, Christopher L. Mosher

Hackensack Meridian Health Mountainside Medical Center: Alexandre M. Shehata*, Zaza Cohen, Valerie Allusson, Gabriela Bambrick-Santoyo, Noor ul aain Bhatti, Bijal Mehta, Aquino Williams

Hackensack Meridian Health Hackensack University Medical Center: Samantha K. Brenner*, Patricia Walters, Ronaldo C. Go, Keith M. Rose

Harvard University: Rebecca Lisk, Amy M. Zhou, Ethan C. Kim

Icahn School of Medicine at Mount Sinai: Lili Chan*, Kusum S. Mathews*, Steven G. Coca, Deena R. Altman, Aparna Saha, Howard Soh, Huei Hsun Wen, Sonali Bose, Emily A. Leven, Jing G. Wang, Gohar Mosoyan, Girish N. Nadkarni, Pattharawin Pattharanitima, Emily J. Gallagher

Indiana University School of Medicine/Indiana University Health: Allon N. Friedman*, John Guirguis, Rajat Kapoor, Christopher Meshberger, Katherine J. Kelly

Johns Hopkins Hospital: Chirag R. Parikh*, Brian T. Garibaldi, Celia P. Corona-Villalobos, Yumeng Wen, Steven Menez, Rubab F. Malik, Elena Cervantes, Samir Gautam

Kings County Hospital Center: Mary C. Mallappallil*, Jie Ouyang, Sabu John, Ernie Yap, Yohannes Melaku, Ibrahim Mohamed, Siddartha Bajracharya, Isha Puri, Mariah Thaxton, Jyotsna Bhattacharya, John Wagner, Leon Boudourakis

Loma Linda University: H. Bryant Nguyen*, Afshin Ahoubim

Mayo Clinic, Arizona: Leslie F. Thomas*, Dheeraj Reddy Sirganagari

Mayo Clinic, Florida: Pramod K. Guru*

Medical College of Wisconsin: Yan Zhou,* Paul A. Bergl, Jesus Rodriguez, Jatan A. Shah, Mrigank S. Gupta

MedStar Georgetown University Hospital: Princy N. Kumar*, Deepa G. Lazarous, Seble G. Kassaye

Montefiore Medical Center/Albert Einstein College of Medicine: Michal L. Melamed*, Tanya S. Johns. Ryan Mocerino, Kalyan Prudhvi, Denzel Zhu, Rebecca V. Levy, Yorg Azzi, Molly Fisher, Milagros Yunes, Kaltrina Sedaliu, Ladan Golestaneh, Maureen Brogan, Neelja Kumar, Michael Chang, Jyotsna Thakkar

New York-Presbyterian Queens Hospital: Ritesh Raichoudhury*, Akshay Athreya, Mohamed Farag

New York-Presbyterian/Weill Cornell Medical Center: Edward J. Schenck*, Soo Jung Cho, Maria Plataki, Sergio L. Alvarez-Mulett, Luis G. Gomez-Escobar, Di Pan, Stefi Lee, Jamuna Krishnan, William Whalen

New York University Langone Hospital: David Charytan*, Ashley Macina, Sobaata Chaudhry, Benjamin Wu, Frank Modersitzki

Northeastern University: Amey Bhivshet

Northwestern Memorial Hospital: Northwestern University Feinberg School of Medicine - Anand Srivastava*, Alexander S. Leidner, Carlos Martinez, Jacqueline M. Kruser, Richard G. Wunderink, Alexander J. Hodakowski

Ochsner Medical Center: Juan Carlos Q. Velez*, Eboni G. Price-Haywood, Luis A. Matute-Trochez, Anna E. Hasty, Muner MB. Mohamed

Oregon Health and Science University Hospital: Rupali S. Avasare*, David Zonies*

Partners Healthcare: Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Massachusetts General Hospital, and Newton Wellesley Hospital - David E. Leaf*, Shruti Gupta*, Meghan E. Sise, Erik T. Newman, Samah Abu Omar, Kapil K. Pokharel, Shreyak Sharma, Harkarandeep Singh, Simon Correa, Tanveer Shaukat, Omer Kamal, Wei Wang, Heather Yang, Jeffery O. Boateng, Meghan Lee, Ian A. Strohbehn, Jiahua Li, Ariel L. Mueller

ProMedica Health System: Roberta Redfern,* Nicholas S. Cairl, Gabriel Naimy, Abeer Abu-Saif, Danyell Hall, Laura Bickley

Renown Health: Chris Rowan*, Farah Madhai-Lovely*

Rush University Medical Center: Vasil Peev*, Jochen Reiser, John J. Byun, Andrew Vissing, Esha M. Kapania, Zoe Post, Nilam P. Patel, Joy-Marie Hermes

Rutgers/New Jersey Medical School: Anne K. Sutherland*, Amee Patrawalla, Diana G. Finkel, Barbara A. Danek, Sowminya Arikapudi, Jeffrey M. Paer, Peter Cangialosi, Mark Liotta

Rutgers/Robert Wood Johnson Medical School: Jared Radbel*, Sonika Puri, Jag Sunderram, Matthew T. Scharf, Ayesha Ahmed, Ilya Berim, Jayanth S. Vatson

Stanford Healthcare: Stanford University School of Medicine – Shuchi Anand*, Joseph E. Levitt, Pablo Garcia

Temple University Hospital: Suzanne M. Boyle*, Rui Song, Ali Arif

Thomas Jefferson Health: Jingjing Zhang*, Sang Hoon Woo, Xiaoying Deng, Goni Katz-Greenberg, Katharine Senter

Tulane Medical Center: Moh'd A. Sharshir*, Vadym V. Rusnak

United Health Services Hospitals: Muhammad Imran Ali, Terri Peters, Kathy Hughes

University of Colorado Anschutz Medical Campus: Anip Bansal*, Amber S. Podoll, Michel Chonchol, Sunita Sharma, Ellen L. Burnham

University Hospitals Cleveland Medical Center: Arash Rashidi*, Rana Hejal

University of Alabama-Birmingham Hospital: Eric Judd*, Laura Latta, Ashita Tolwani

University of California-Davis Medical Center: Timothy E. Albertson*, Jason Y. Adams

University of California-Los Angeles Medical Center: Ronald Reagan-UCLA Medical Center - Steven Y. Chang*, Rebecca M. Beutler; Santa Monica-UCLA Medical Center – Carl E. Schulze

University of California-San Diego Medical Center: Etienne Macedo*, Harin Rhee

University of California-San Francisco Medical Center: Kathleen D. Liu*, Vasantha K. Jotwani

University of Chicago Medical Center: Jay L. Koyner*

University of Florida Health-Gainesville: Chintan V. Shah*

University of Florida-Health-Jacksonville: Vishal Jaikaransingh*

University of Illinois Hospital and Health Sciences System: Stephanie M. Toth-Manikowski*, Min J. Joo*, James P. Lash

University of Kentucky Medical Center: Javier A. Neyra*, Nourhan Chaaban

University Medical Center of Southern Nevada: Alfredo Iardino, Elizabeth H. Au, Jill H. Sharma

University of Miami Health System: Marie Anne Sosa*, Sabrina Taldone, Gabriel Contreras, David De La Zerda, Alessia Fornoni, Hayley B. Gershengorn

University of Michigan: Salim S. Hayek*, Pennelope Blakely, Hanna Berlin, Tariq U. Azam, Husam Shadid, Michael Pan, Patrick O' Hayer, Chelsea Meloche, Rafey Feroze, Kishan J. Padalia, Abbas Bitar, Jeff Leya, John P. Donnelly, Andrew J. Admon

University of North Carolina School of Medicine: Jennifer E. Flythe*, Matthew J. Tugman, Emily H. Chang

University of Oklahoma Health Sciences Center: Brent R. Brown*

University of Pennsylvania Health System: Amanda K. Leonberg-Yoo*, Ryan C. Spiardi, Todd A. Miano, Meaghan S. Roche, Charles R. Vasquez

University of Pittsburgh Medical Center: Amar D. Bansal*, Natalie C. Ernecoff, Sanjana Kapoor, Siddharth Verma, Huiwen Chen

University of Tennessee Health Science Center and Memphis VA Medical Center/Methodist University Hospital – Csaba P. Kovesdy*, Miklos Z. Molnar*, Ambreen Azhar

University of Texas Southwestern Medical Center and Parkland Health and Hospital System: S. Susan Hedayati*, Mridula V. Nadamuni, Shani Shastri, Duwayne L. Willett

University of Vermont Larner College of Medicine: Samuel A.P. Short

University of Virginia Health System: Amanda D. Renaghan*, Kyle B. Enfield

University of Washington Medical Center: Pavan K. Bhatraju*, A. Bilal Malik

Vanderbilt University Medical Center: Matthew W. Semler

Washington University in St. Louis/Barnes Jewish Hospital: Anitha Vijayan*, Christina Mariyam Joy, Tingting Li, Seth Goldberg, Patricia F. Kao

Wellforce Health System: Lowell General Hospital **-** Greg L. Schumaker*, Tufts Medical Center - Nitender Goyal*, Anthony J. Faugno, Greg L. Schumaker, Caroline M. Hsu, Asma Tariq, Leah Meyer, Ravi K. Kshirsagar, Daniel E. Weiner

Westchester Medical Center: Marta Christov*, Jennifer Griffiths, Sanjeev Gupta, Aromma Kapoor

Yale School of Medicine: Perry Wilson,* Tanima Arora, Ugochukwu Ugwuowo

*Site Principal Investigator

eMETHODS

Definitions

Renal, Liver, and Coagulation components of the Sequential Organ Failure Assessment (SOFA) score:

	Categories				
	0	**1**	**2**	**3**	**4**
SOFA Renal (Cr [mg/dl], UOP [ml/day], and acute RRT) Cr	Cr<1.2 and UOP≥500	Cr 1.2-1.9 and UOP≥500	Cr 2-3.4 and UOP≥500	Cr 3.5-4.9 and UOP≥500	Cr≥5 or UOP≤200 or acute RRT or ESRD
SOFA Liver (Bilirubin, mg/dl)	<1.2	1.2-1.9	≥2*	--	---
SOFA Coagulation (Platelets, K/mm^3)	≥150	100-149	≤99*	--	--

Abbreviations: Cr, creatinine (mg/dl); ESRD, end-stage kidney disease; RRT, renal replacement therapy; UOP, urine output. *The liver and coagulation components of the SOFA score were binned due to low frequency of events in categories "3" and "4".

Multivariable Models for Clinical Outcomes

MORTALITY

1. Age
2. Gender
3. Race
4. Ethnicity
5. Hypertension
6. Diabetes
7. Coronary artery disease
8. Congestive heart failure
9. Cancer
10. Immunodeficiency state
11. Current smoking
12. Absolute lymphocyte count
13. Presence of shock
14. Corticosteroid use
15. Remdesivir use
16. PaO2:FiO_2 ratio if mechanically ventilated
17. SOFA liver score
18. SOFA coagulation score
19. SOFA kidney score
20. Number of hospital ICU beds

ARDS

1. Age
2. Gender
3. Race

4. Ethnicity
5. Hypertension
6. Diabetes
7. Coronary artery disease
8. Congestive heart failure
9. Cancer
10. Immunodeficiency state
11. Chronic obstructive pulmonary disease (COPD)
12. Human immunodeficiency virus (HIV)
13. Home immunosuppressive or anticoagulant medications
14. Current smoking
15. Altered mentation
16. SOFA liver score
17. SOFA coagulation score
18. SOFA kidney score
19. Absolute lymphocyte count
20. Presence of shock
21. Corticosteroid use
22. Remdesivir use
23. Number of hospital ICU beds

AKI-RRT

1. Age
2. Gender
3. Race
4. Ethnicity
5. Hypertension
6. Diabetes
7. Coronary artery disease
8. Congestive heart failure
9. Cancer
10. Immunodeficiency state
11. Chronic kidney disease (CKD) stage
12. Current smoking
13. Absolute lymphocyte count
14. D-dimer
15. Presence of shock
16. PaO2:FiO2 ratio if mechanically ventilated
17. SOFA liver score
18. SOFA coagulation score
19. Corticosteroid use
20. Remdesivir use
21. Number of hospital ICU beds

THROMBOTIC EVENTS

1. Age

2. Gender
3. Race
4. Ethnicity
5. Hypertension
6. Diabetes
7. Coronary artery disease
8. Congestive heart failure
9. Cancer
10. Immunodeficiency state
11. COPD
12. Chronic liver disease
13. Immunodeficiency state
14. Alcoholism
15. Home immunosuppressive medications
16. Home anticoagulant medications
17. Current smoking
18. Absolute lymphocyte count
19. White blood cell (WBC)
20. Platelet
21. D-dimer
22. Fibrinogen levels
23. PaO2:FiO2 ratio if mechanically ventilated
24. SOFA liver score
25. SOFA kidney score
26. Presence of shock
27. Corticosteroid use
28. Remdesivir use

Multivariable Model for Inflammatory and Thrombotic Biomarkers

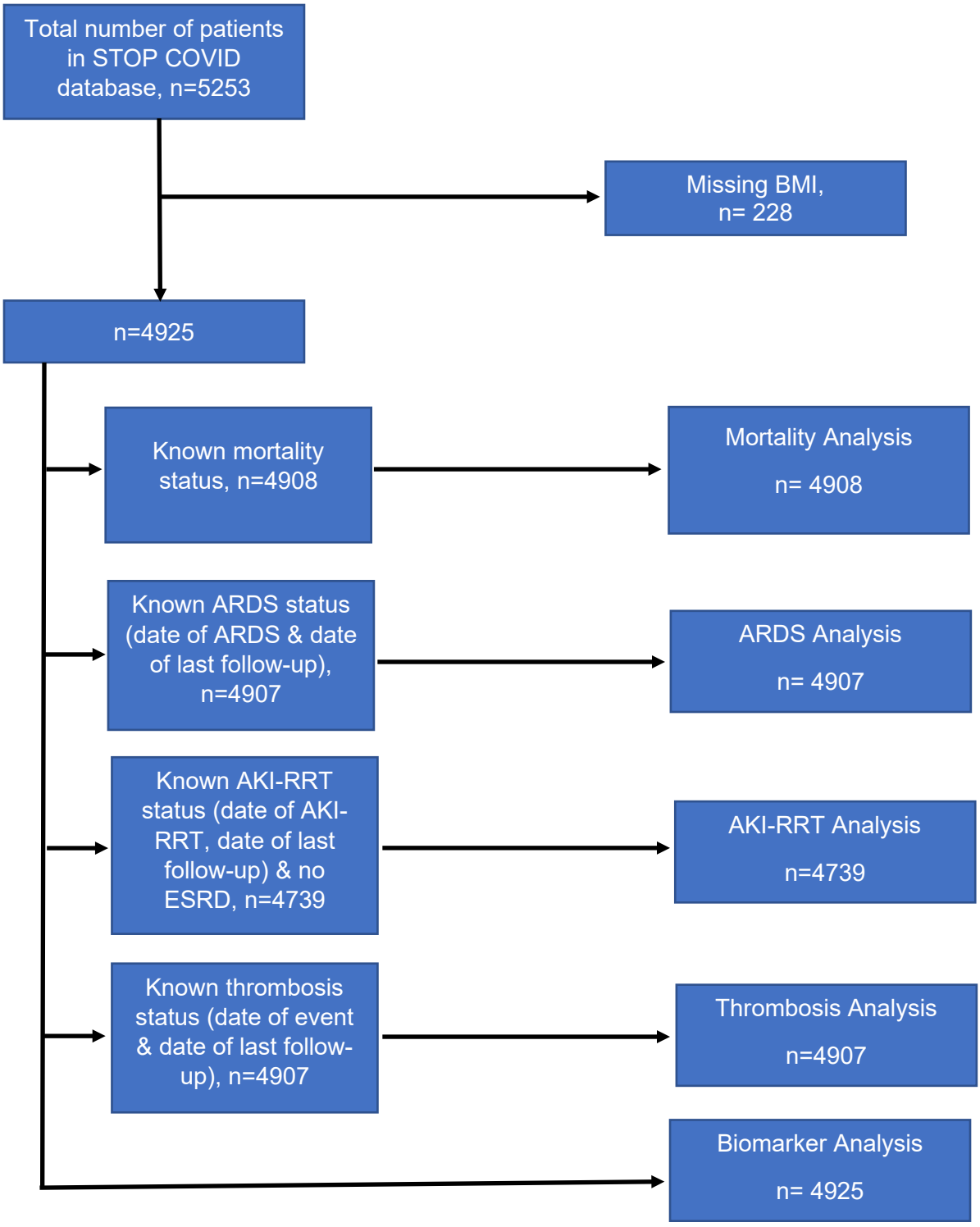
1. Age
2. Gender
3. Race
4. Ethnicity
5. Diabetes
6. Coronary artery disease
7. Chronic liver disease
8. Cancer
9. Current smoking
10. End-stage renal disease
11. Home medications (NSAID, aspirin, statin, any immunosuppression, chloroquine, hydroxychloroquine, azithromycin, corticosteroids)
12. WBC
13. Invasive mechanical ventilation
14. PaO_2/FiO_2 ratio
15. Vasopressor support

Modelling BMI and Inflammatory/Thrombotic Biomarkers

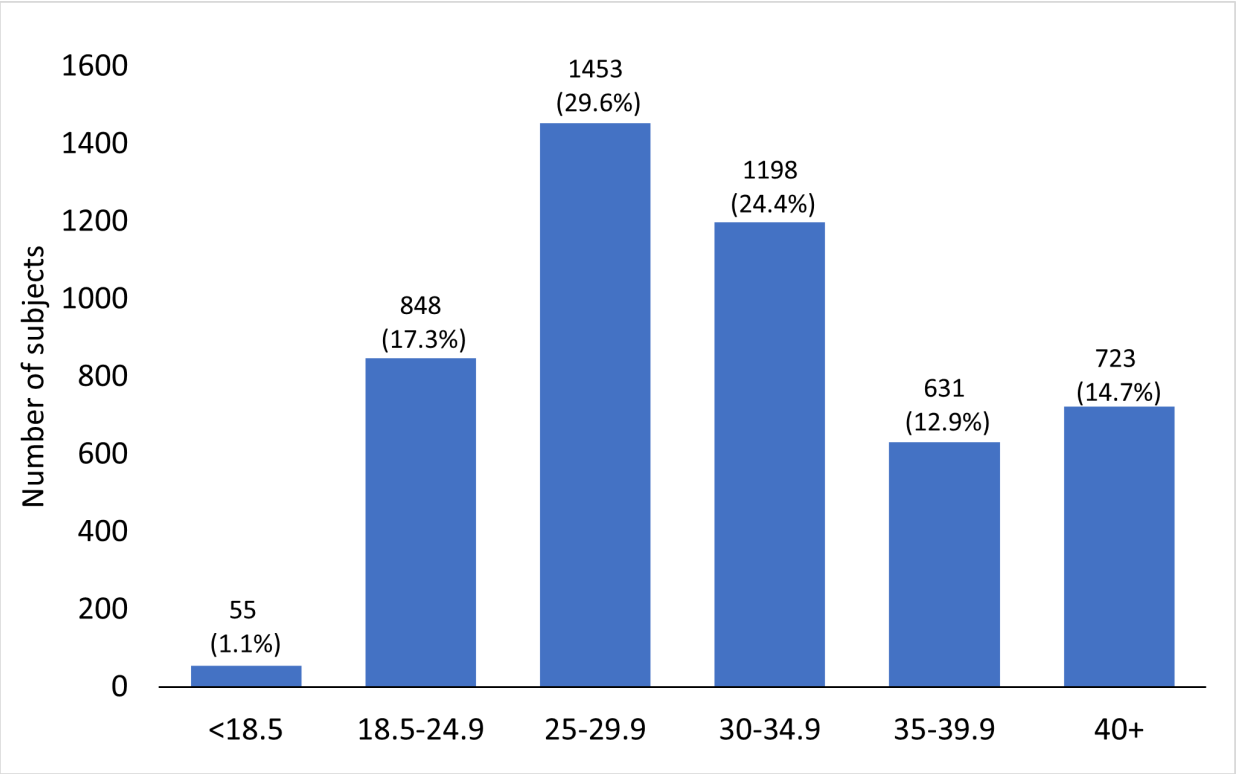
We used population-averaged panel data models involving generalized estimating equations (GEE) with an assumption of exchangeable correlation structure of exchangeable correlation structure in which daily observations for markers within a subject are assumed to be equally correlated. The choice of the exchangeable correlation structure was empirically driven using the following criteria: Rotnitzky–Jewell (RJ), Rule out, and Quasi-likelihood under the independence model criterion (QIC). RJ criteria[31] state that the working correlation structure should be close to the true structure with Huber-White (robust) Sandwich Estimation of the standard errors, which is considered robust to misspecification.[32, 33] Rule out criteria considers that, in practice, failure of convergence for a GEE would be used to rule out the correlation structure under consideration.[34] Using GEE also allowed us to account for incomplete biomarker data (e.g. when not available at each follow-up time point during the subject's ICU stay). If a particular subject was missing one or more out of 14 repeated measurements, the remaining available data was used in the analyses, instead of forcing the subject to drop out.

We performed several analyses of circulating biomarkers using BMI as a continuous or categorical variable. We also used Quasi-likelihood under the Independence model criterion (QIC) and Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to confirm the best fitting model when using BMI as a continuous or categorical variable. To interpret rate of change of the circulating biomarker for each unit increase in the BMI, we presented the findings for the continuous scaled BMI. For further sensitivity analyses we performed subgroup analyses limiting to those admitted to the ICU within 72 hours of hospitalization and/or those without diabetes.

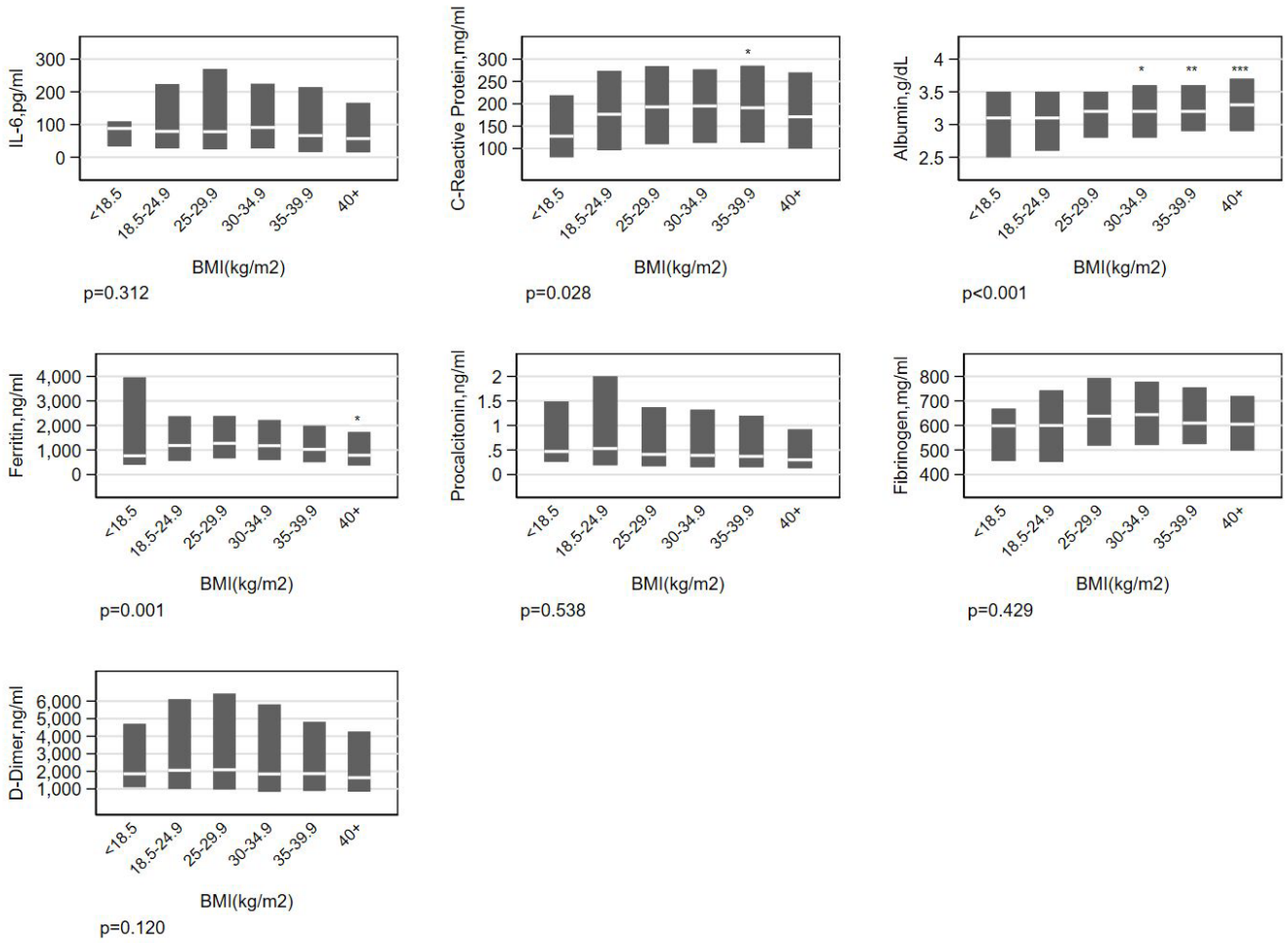
eFigure 1: Flow diagram describing exclusion criteria and number of patients available for analysis



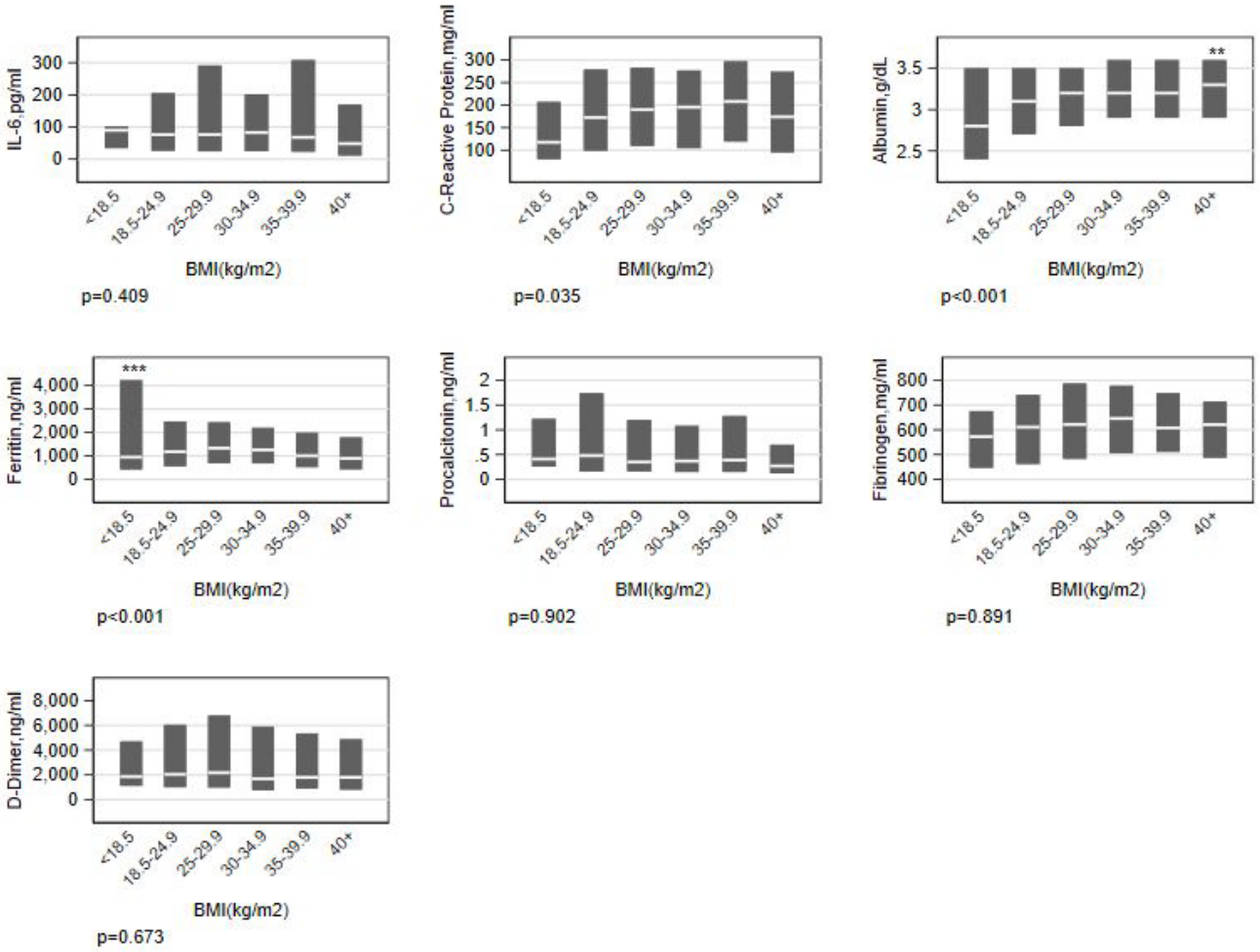
eFigure 2: Distribution of patients by BMI



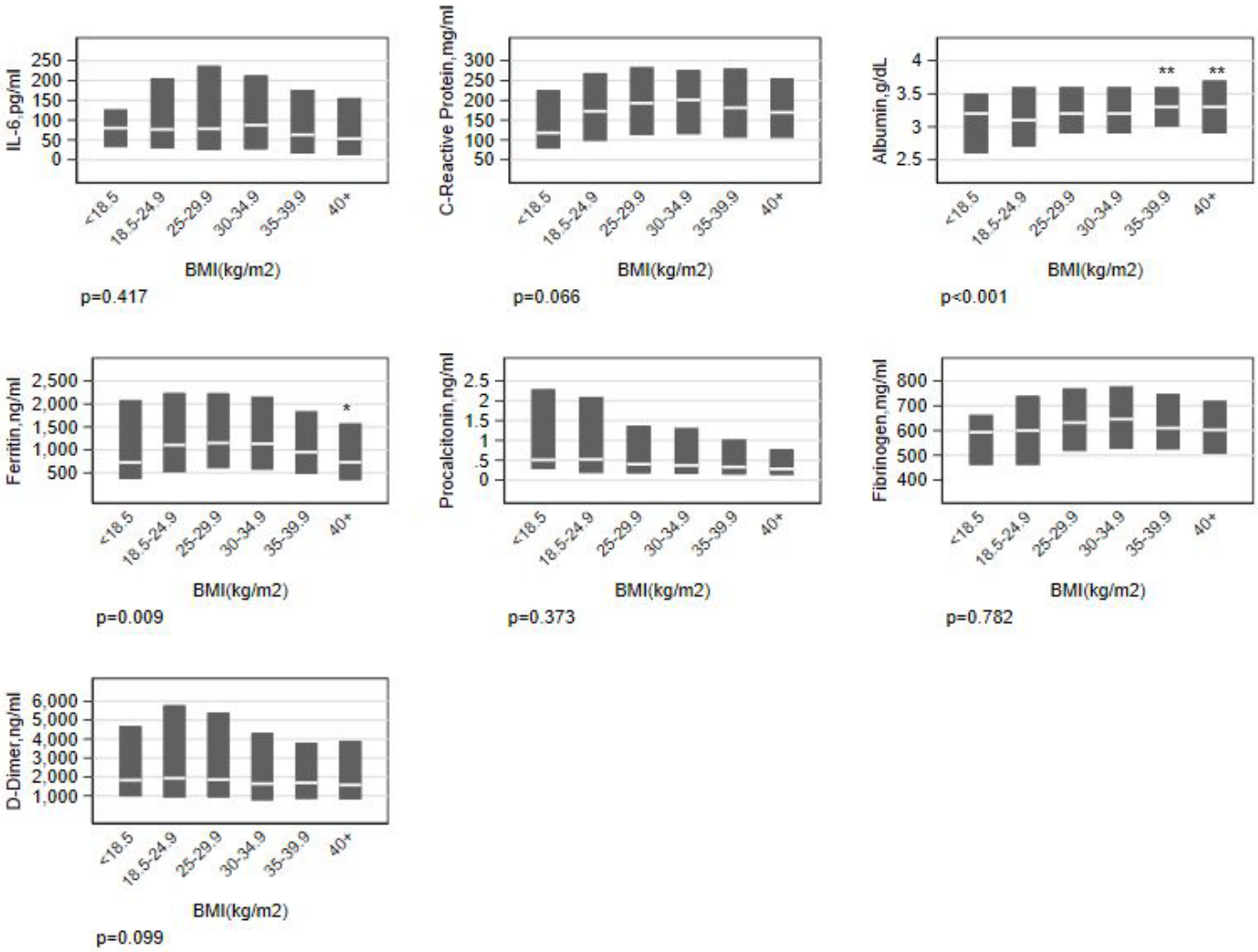
eFigure 3: Floating bar graph comparing BMI categories and levels of circulating biomarkers in the entire cohort but limited to the first 72 hours of ICU admission. The floating bar indicates the median (25-75th interquartile range). Only the highest daily values were used. P-values using Analysis of Variance (ANOVA). Tukey adjusted pairwise comparison with reference range (18.5-<25 kg/m^2) for overall significance. *p<0.05; **p<0.01; ***p<0.001.



eFigure 4: Floating bar graph comparing BMI categories and levels of circulating biomarkers in patients without diabetes during the first 72 hours of ICU admission. Only the highest daily values were used. P-values using Analysis of Variance (ANOVA). Tukey adjusted pairwise comparison with reference range (18.5-<25 kg/m^2) for overall significance. *p<0.05; **p<0.01; ***p<0.001.



eFigure 5: Floating bar graph comparing BMI categories and levels of circulating biomarkers in patients admitted to the ICU within 72 hours of hospitalization. Only the highest daily values were used. P-values using Analysis of Variance (ANOVA). Tukey adjusted pairwise comparison with reference range (18.5-<24.9 kg/m^2) for overall significance. *p<0.05; **p<0.01; ***p<0.001.



eTable 1: Complete Table of Patient Characteristics Stratified by Categories of Body Mass Index (N=4908)

Characteristic	Full Sample (N=4908)	<18.5 (n=55)	18.5-24.9 (n=848)	25-29.9 (n=1453)	30-34.9 (n=1198)	35-39.9 (n=631)	40+ (n=723)	P-value
Demographics								
Age (yr) – median (IQR)	60.91 (14.7)	68.84 (17.02)	66.51 (15.15)	63.44 (13.69)	59.99 (13.93)	57.19 (14.04)	53.42 (13.5)	<0.001
Male sex – no. (%)	3095 (62.8)	33 (60)	566 (66.4)	1038 (71.1)	778 (64.8)	353 (55.9)	327 (45)	<0.001
Race – no. (%)								<0.001
White	1930 (39.2)	24 (43.6)	326 (38.3)	590 (40.4)	469 (39.1)	260 (41.2)	261 (36)	
Black	1496 (30.4)	15 (27.3)	218 (25.6)	376 (25.8)	369 (30.7)	215 (34.1)	303 (41.7)	
Other	389 (7.9)	6 (10.9)	116 (13.6)	137 (9.4)	82 (6.8)	22 (3.5)	26 (3.6)	
Unknown	1110 (22.5)	10 (18.2)	192 (22.5)	357 (24.5)	281 (23.4)	134 (21.2)	136 (18.7)	
Hispanic – no. (%)	445 (20.1)	288 (20.1)	157 (20.0)					
Coexisting conditions – no. (%)[a]								
Diabetes	2080 (42.2)	18 (32.7)	304 (35.7)	590 (40.4)	540 (45)	273 (43.3)	355 (48.9)	<0.001
Hypertension	3032 (61.6)	35 (63.6)	492 (57.8)	873 (59.8)	759 (63.2)	388 (61.5)	485 (66.8)	0.004
Chronic lung disease								
COPD	433 (8.8)	10 (18.2)	87 (10.2)	121 (8.3)	81 (6.7)	54 (8.6)	80 (11)	0.002
Asthma	532 (10.8)	1 (1.8)	76 (8.9)	101 (6.9)	125 (10.4)	96 (15.2)	133 (18.3)	<0.001
Coronary artery disease	661 (13.4)	15 (27.3)	120 (14.1)	225 (15.4)	154 (12.8)	69 (10.9)	78 (10.7)	<0.001
Congestive heart failure	496 (10.1)	10 (18.2)	87 (10.2)	125 (8.6)	114 (9.5)	61 (9.7)	99 (13.6)	0.002
Chronic kidney disease	645 (13.1)	8 (14.6)	117 (13.7)	183 (12.5)	155 (12.9)	79 (12.5)	103 (14.2)	0.877
Chronic liver disease	165 (3.4)	2 (3.6)	48 (5.6)	41 (2.8)	36 (3)	17 (2.7)	21 (2.9)	0.01
End-stage renal disease	186 (3.8)	6 (10.9)	55 (6.5)	43 (3)	40 (3.3)	19 (3)	23 (3.2)	<0.001
Cancer	227 (4.6)	2 (3.6)	50 (5.9)	84 (5.8)	48 (4)	20 (3.2)	23 (3.2)	0.01
Immunodeficiency	278 (5.6)	4 (7.3)	67 (7.9)	89 (6.1)	69 (5.8)	24 (3.8)	25 (3.4)	0.001
Home medications, no. (%)								
Immunosuppressive	490 (10)	7 (12.7)	95 (11.2)	164 (11.2)	118 (9.8)	48 (7.6)	58 (8)	0.042
ACE-I	897 (18.2)	10 (18.2)	128 (15)	258 (17.7)	245 (20.4)	114 (18.1)	142 (19.6)	0.054
ARB	759 (15.4)	4 (7.3)	97 (11.4)	218 (14.9)	201 (16.7)	117 (18.5)	122 (16.8)	0.001
Statin	1890 (38.4)	24 (43.6)	305 (35.8)	595 (40.8)	478 (39.8)	230 (36.5)	258 (35.5)	0.051
NSAID	403 (8.2)	4 (7.3)	51 (6)	102 (7)	107 (8.9)	62 (9.8)	77 (10.6)	0.004
Aspirin	1124 (22.8)	19 (34.6)	192 (22.5)	347 (23.8)	281 (23.4)	141 (22.4)	144 (19.8)	0.107
Anticoagulation	505 (10.3)	5 (9.1)	85 (10)	158 (10.8)	110 (9.2)	61 (9.7)	86 (11.9)	0.485
Smoking history, no. (%)								<0.001
Non-smoker	2814 (57.1)	21 (38.2)	449 (52.7)	808 (55.3)	707 (58.9)	375 (59.4)	454 (62.5)	
Former smoker	1209 (24.6)	21 (38.2)	214 (25.1)	381 (26.1)	292 (24.3)	153 (24.3)	148 (20.4)	
Current smoker	257 (5.2)	3 (5.5)	67 (7.9)	62 (4.3)	55 (4.6)	29 (4.6)	41 (5.7)	
Unknown	645 (13.1)	10 (18.2)	122 (14.3)	209 (14.3)	147 (12.2)	74 (11.7)	83 (11.4)	
Alcoholism, no. (%)	269 (5.5)	4 (7.3)	65 (7.6)	59 (4)	59 (4.9)	42 (6.7)	40 (5.5)	0.005
Blood laboratory findings on day of ICU admission, Median IQR)								
White blood cell count, /μL[b]	8.4 (6, 11.8)	9.4 (6.6, 13.3)	8.7 (5.9, 12.4)	8.5 (5.9, 11.8)	8.4 (6.1, 11.8)	7.6 (8.5, 6.2)	5.3 (7.9, 5.9)	0.6802
Lymphocyte count, /μL[c]	822.5 (550.8, 1177.9)	738.9 (455.5, 960)	742.2 (483.8, 1132.2)	782.1 (525.6, 1140.9)	829 (531.2, 1179.1)	944.7 (885.6, 624.2)	672.5 (915.4, 635)	0.7071
Platelet count, 1000/mm3[d]	215 (164, 278)	221.5 (167, 343)	215 (158.5, 285)	217 (163, 279)	211.5 (165, 273)	92.2 (218, 165)	86.4 (215, 167)	0.0579
D-dimer level, ng/ml[e]	1300	1620	1601.5	1415	1117	1270	1110	0.3787

	(670, 3437.5)	(860, 4390)	(780, 4010)	(714, 3700)	(579, 2980)	(690, 3030)	(614.5, 2355)	
Fibrinogen level, mg/ml[f]	601 (475, 744)	593 (462.5, 660.5)	552 (424, 710)	624.5 (508.5, 769)	619 (491, 768)	597.5 (495, 751.5)	575 (459, 701)	0.3694
Interleukin-6 level, pg/ml[g]	56.6 (17.9, 160)	36.7 (30.6, 70.4)	60 (25.5, 130.3)	55.5 (17.9, 169)	76.1 (24.4, 171)	46.6 (15, 138)	48.6 (10, 137.4)	0.7738
C-reactive protein level, mg/L	149.1 (80.9, 230)	125 (69.3, 178.9)	141.9 (74, 229.4)	158.1 (84.7, 238)	151 (82.3, 232.9)	152 (88, 238.2)	138 (79.1, 200)	0.01
Albumin, g/dL[i]	3.2 (2.8, 3.6)	3.1 (2.5, 3.5)	3.1 (2.6, 3.5)	3.2 (2.8, 3.5)	3.2 (2.8, 3.6)	3.3 (2.9, 3.6)	3.3 (2.9, 3.7)	<0.001
Ferritin, ng/ml[j]	977 (485, 1935)	744.5 (424, 1581)	1067 (440.5, 2109)	1061.3 (585, 2000)	1045 (528, 1985)	839.7 (421.9, 1653.4)	663.8 (352.4, 1410)	0.0001
Procalcitonin, ng/ml[k]	0.4 (0.2, 1.3)	0.5 (0.3, 1.5)	0.5 (0.2, 2)	0.4 (0.2, 1.4)	0.4 (0.2, 1.3)	0.4 (0.2, 1.2)	0.3 (0.1, 0.9)	0.5382
Severity-of-illness on the day of ICU admission, no. (%)[a]								
Shock	488 (9.9)	10 (18.2)	92 (10.8)	129 (8.8)	124 (10.3)	69 (10.9)	64 (8.8)	0.117
Altered mental status	1130 (22.9)	24 (43.6)	270 (31.7)	352 (24.1)	254 (21.2)	105 (16.6)	125 (17.2)	<0.001
Mechanical Ventilation								<0.001
HFNC or nonrebreather mask	1211 (24.6)	14 (25.5)	213 (25)	376 (25.8)	264 (22)	165 (26.2)	179 (24.7)	
Invasive mechanical ventilation	2930 (59.5)	28 (50.9)	480 (56.3)	872 (59.8)	748 (62.3)	377 (59.8)	425 (58.5)	
Noninvasive mechanical ventilation (BiPAP/CPAP)	134 (2.7)	1 (1.8)	12 (1.4)	26 (1.8)	39 (3.3)	16 (2.5)	40 (5.5)	
Treatment interventions, no. (%)								
Vasopressors	1924 (39.1)	20 (36.4)	337 (39.6)	575 (39.4)	470 (39.1)	258 (40.9)	264 (36.4)	0.635
Renal replacement therapy	1056 (21.4)	10 (18.2)	134 (15.7)	279 (19.1)	284 (23.7)	152 (24.1)	197 (27.1)	<0.001
ECMO	184 (3.7)	1 (1.8)	13 (1.5)	47 (3.2)	48 (4)	41 (6.5)	34 (4.7)	<0.001
Corticosteroids	1864 (37.9)	25 (45.5)	299 (35.1)	585 (40.1)	423 (35.2)	240 (38)	292 (40.2)	0.029
Remdesivir	425 (8.6)	3 (5.5)	59 (6.9)	117 (8)	103 (8.6)	67 (10.6)	76 (10.5)	0.06
Prone	1946 (39.5)	7 (12.7)	261 (30.6)	584 (40)	489 (40.7)	292 (46.3)	313 (43.1)	<0.001
Convalescent plasma	275 (5.6)	4 (7.3)	49 (5.8)	85 (5.8)	63 (5.3)	30 (4.8)	44 (6.1)	0.826
Number of ICU beds, no. (%)								0.013
<50	1659 (33.7)	15 (27.3)	259 (30.4)	530 (36.3)	408 (34)	212 (33.6)	235 (32.4)	
50-199	2985 (60.6)	37 (67.3)	552 (64.8)	857 (58.7)	725 (60.4)	384 (60.9)	430 (59.2)	
≥200	281 (5.7)	3 (5.5)	41 (4.8)	73 (5)	68 (5.7)	35 (5.6)	61 (8.4)	
Mortality, no. (%)								0.001
Alive	2975 (60.62)	27 (49.09)	487 (57.43)	841 (57.88)	749 (62.52)	407 (64.5)	464 (64.18)	
Dead	1933 (39.38)	28 (50.91)	361 (42.57)	612 (42.12)	449 (37.48)	224 (35.5)	259 (35.82)	

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BiPAP, bilevel positive airway pressure; BMI, body mass index, in kg/m^2; COPD, chronic obstructive lung disease; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; NSAID, non-steroidal anti-inflammatory drug

[a]Definitions are described more completely in [6].
[b]Data for white blood cell count were missing in 317 patients (6.4%)
[c]Data for lymphocyte count were missing in 999 patients (20.3%)
[d]Data for platelet count were missing in 142 patients (2.9%)
[e]Data for D-dimer were missing in 787 patients (16%)
[f]Data for fibrinogen were missing in 2405 patients (48.8%)

[g]Data for interleukin-6 were missing in 3068 patients (62.3%)
[h]Data for C-reactive protein were missing in 620 patients (12.6%)
[i]Data for albumin were missing in 264 patients (5.4%)
[j]Data for ferritin were missing in 692 patients (14.1%)
[k]Data for procalcitonin were missing in 1803 patients (36.6%)

eTable 2: Unadjusted and Multivariable Adjusted Relationship between BMI and Mortality (N= 4908)

BMI Category	Unadjusted Analysis: Hazard Ratio (95% CI)	Multivariable Analysis*: Hazard Ratio (95% CI)
<18.5	1.52 (1.04, 2.24)	1.36 (0.90, 2.06)
18.5-24.9	1.00	1.00
25-29.9	0.97 (0.85, 1.11)	1.00 (0.87, 1.17)
30-34.9	0.85 (0.74, 0.98)	0.99 (0.81, 1.20)
35-39.9	0.79 (0.67, 0.93)	1.00 (0.83, 1.20)
40+	0.81 (0.69, 0.95)	1.12 (0.91, 1.39)

*model includes BMI§, age, sex, race, Hispanic ethnicity, comorbidities (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, cancer, immunodeficient state, smoking), absolute lymphocyte count on admission to ICU, sequential organ failure assessment (SOFA) kidney score§, SOFA liver score, SOFA coagulation score, presence of shock, PaO2/FiO2 ratio in invasively mechanically ventilated patients§, treatment interventions (corticosteroid or remdesivir)§, and number of ICU beds in hospital.

§Used as time-varying covariates

eTable 3: Multivariable Cox Model with Time-Varying Covariates for Mortality (n=4908)

Variable	Hazard Ratio (95% CI)
BMI (versus 18.5-24.9)	
<18.5	1.36 (0.90, 2.06)
25-29.9	1.00 (0.87, 1.17)
30-34.9	0.99 (0.81, 1.20)
35-39.9	1.00 (0.83, 1.20)
40+	1.12 (0.91, 1.39)
Age	1.03 (1.03, 1.04)
Female (versus male)	0.86 (0.75, 0.98)
Race (versus black)	
White	1.00 (0.86, 1.17)
Others	0.87 (0.67, 1.14)
Unknown	1.24 (1.02, 1.51)
Hispanic ethnicity	1.08 (0.93, 1.25)
Comorbidities	
Hypertension	1.08 (0.93, 1.25)
Diabetes mellitus	1.10 (0.99, 1.23)
CAD	1.19 (1.05, 1.35)
Congestive heart failure	0.99 (0.85, 1.17)
COPD	1.16 (0.97, 1.39)
Cancer	1.57 (1.31, 1.90)
Immunodeficiency	1.04 (0.82, 1.30)
Current smoker	1.05 (0.82, 1.34)
Absolute lymphocyte count	
≥ 1000	0.96 (0.85, 1.09)
Missing	0.94 (0.83, 1.08)
Mechanically ventilated (versus no ventilation)	
$PaO_2/FiO_2 \geq 200$	1.56 (1.22, 2.00)
PaO_2/FiO_2 100-199	1.34 (1.06, 1.70)
$PaO_2/FiO_2 < 100$	1.92 (1.54, 2.38)
Shock on Day 1 of ICU admission	1.09 (0.93, 1.29)
ICU beds in hospital	
50-199	0.52 (0.40, 0.67)
≥ 200	0.47 (0.37, 0.59)
SOFA kidney score	
1	1.53 (1.28, 1.82)
2	2.38 (1.78, 3.17)
3	2.64 (1.81, 3.85)
4	2.35 (1.88, 2.93)
Missing	1.33 (0.69, 2.54)
SOFA liver score	
1	1.17 (0.99, 1.38)
2	1.81 (1.46, 2.24)

Missing	1.16 (0.95, 1.42)
SOFA coagulation score	
1	1.15 (0.99, 1.34)
2	1.59 (1.33, 1.88)
Missing	1.13 (0.69, 1.84)
Treatment	
Corticosteroids	0.88 (0.72, 1.09)
Remdesivir	0.61 (0.39, 0.95)
Time Varying Covariates*	
Mechanically ventilated (versus no ventilation)	
$PaO_2/FiO_2 \geq 200$	0.98 (0.97, 0.99)
PaO_2/FiO_2 100-199	0.99 (0.98, 1.00)
$PaO_2/FiO_2 < 100$	0.98 (0.97, 0.99)
SOFA kidney score	
1	0.99 (0.98, 1.00)
2	0.97 (0.96, 0.99)
3	0.95 (0.92, 0.99)
4	0.98 (0.97, 0.99)
Missing	0.98 (0.94,1.01)
Treatment	
Corticosteroids	1.02 (1.01, 1.03)
Remdesivir	1.02 (1.01, 1.03)

* Only significant ($p<0.05$) time varying covariates were included in the model

eTable 4: Unadjusted and Multivariable Adjusted Relationship between BMI and ARDS in Patients (N= 4907)[†]

BMI Category	Unadjusted Analysis: Hazard Ratio (95% CI)	Multivariable Analysis[*]: Hazard Ratio (95% CI)
<18.5	0.90 (0.66, 1.22)	0.90 (0.66, 1.23)
18.5-24.9	1.00	1.00
25-29.9	1.20 (1.09, 1.32)	1.21 (1.11, 1.33)
30-34.9	1.37 (1.22, 1.53)	1.40 (1.24, 1.58)
35-39.9	1.33 (1.20, 1.46)	1.36 (1.24, 1.48)
40+	1.26 (1.08, 1.47)	1.34 (1.15, 1.56)

[*]model includes BMI, age, sex, race, Hispanic ethnicity, comorbidities (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, cancer, immunodeficient state, HIV), current smoker, home immunosuppressive and anticoagulation medications, absolute lymphocyte count on ICU admission, altered mentation, SOFA kidney score, SOFA liver score, SOFA coagulation score, presence of shock, interventions (corticosteroids, remdesivir), and number of ICU beds in hospital

[†]Death was treated as competing risk

eTable 5: Complete Multivariable Competing Risk Regression Model for ARDS that Includes all Patients

Variable	Hazard Ratio (95% CI)
BMI (versus 18.5-24.9)	
<18.5	0.90 (0.66, 1.22)
25-29.9	1.21 (1.11, 1.33)
30-34.9	1.40 (1.24, 1.58)
35-39.9	1.36 (1.24, 1.48)
40+	1.34 (1.15, 1.56)
Age	1.00 (1.00, 1.00)
Female (versus male)	0.93 (0.86, 0.99)
Race (versus black)	
White	1.07 (0.94, 1.22)
Others	1.21 (1.01, 1.45)
Unknown	1.11 (0.95, 1.30)
Hispanic ethnicity	1.10 (1.00, 1.22)
Comorbidities	
Hypertension	0.99 (0.92, 1.08)
Diabetes mellitus	1.04 (0.97, 1.12)
CAD	0.87 (0.79, 0.97)
Congestive heart failure	0.96 (0.86, 1.09)
COPD	0.99 (0.87, 1.13)
Cancer	0.89 (0.77, 1.03)
Immunodeficiency	0.99 (0.87, 1.13)
HIV	0.90 (0.69, 1.16)
Current smoker	1.00 (1.00, 1.00)
Home immunosuppressive medications	0.95 (0.83, 1.09)
Home anticoagulant medications	0.94 (0.85, 1.04)
Absolute lymphocyte count	
≥ 1000	0.94 (0.87, 1.01)
Missing	0.87 (0.77, 0.99)
Shock on Day 1 of ICU admission	1.34 (1.19, 1.50)
Altered mentation	
Yes	1.02 (0.92, 1.14)
Missing	1.20 (1.03, 1.39)
ICU beds in hospital	
50-199	1.05 (0.81, 1.34)
≥ 200	1.14 (0.70, 1.84)
SOFA kidney score	
1	1.14 (1.05, 1.25)
2	1.08 (0.94, 1.23)
3	0.85 (0.66, 1.08)
4	1.11 (0.99, 1.24)
Missing	1.16 (0.71, 1.89)

SOFA liver score	
1	0.93 (0.82, 1.04)
2	0.89 (0.76, 1.04)
Missing	0.68 (0.60, 0.77)
SOFA coagulation score	
1	1.06 (097, 1.15)
2	0.81 (0.71, 0.94)
Missing	1.09 (0.77, 1.55)
Treatment	
Corticosteroids	1.14 (0.99, 1.32)
Remdesivir	0.94 (0.78, 1.12)

eTable 6: Unadjusted and Multivariable Adjusted Relationship between BMI and AKI-RRT (N= 4739)[†]

BMI Category	Bivariate Analysis Hazard Ratio (95% CI)	Multivariable Analysis[*]: Hazard Ratio (95% CI)
<18.5	0.77 (0.28, 2.07)	0.91 (0.29, 2.80)
18.5-24.9	1.00	1.00
25-29.9	1.68 (1.28, 2.20)	1.46 (1.10, 1.94)
30-34.9	2.17 (1.69, 2.80)	1.83 (1.37, 2.43)
35-39.9	2.27 (1.65, 3.13)	2.01 (1.44, 2.79)
40+	2.69 (2.04, 3.55)	2.27 (1.56, 3.31)

[*]model includes BMI, age, sex, race, Hispanic ethnicity, comorbidities (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic kidney disease, cancer), current smoker, PaO2/FiO2 ratio in invasively mechanically ventilated patients, presence of shock, admission labs (lymphocyte count, d-dimer), SOFA liver score, SOFA coagulation score, number of ICU beds in hospital, interventions (corticosteroids, remdesivir)
[†]Death was treated as competing risk

eTable 7: Complete Multivariable Competing Risk Regression Model for AKI-RRT

Variable	Hazard Ratio (95% CI)
BMI (versus 18.5-24.9)	
<18.5	0.91 (0.29, 2.80)
25-29.9	1.46 (1.10, 1.94)
30-34.9	1.83 (1.37, 2.43)
35-39.9	2.01 (1.44, 2.79)
40+	2.27 (1.56, 3.31)
Age	0.99 (0.99, 1.00)
Female (versus male)	0.55 (0.47, 0.65)
Race (versus black)	
White	0.51 (0.40, 0.65)
Others	0.58 (0.41, 0.84)
Unknown	0.63 (0.50, 0.81)
Hispanic ethnicity	0.96 (0.71, 1.29)
Comorbidities	
Hypertension	1.46 (1.18, 1.81)
Diabetes mellitus	1.45 (1.19, 1.77)
CAD	0.90 (0.73, 1.11)
Congestive heart failure	1.05 (0.80, 1.37)
Cancer	0.94 (0.64, 1.37)
Current smoker	1.00 (1.00, 1.00)
Baseline CKD (versus no CKD)	
Stage 3	1.69 (1.28, 2.24)
Stage 4-5	4.23 (2.93, 6.11)
Missing	1.30 (1.06, 1.59)
Absolute lymphocyte count $\geq$ 1000 per mm^3	0.96 (0.82, 1.13)
PaO_2/FiO_2 ratio (versus not receiving mechanical ventilation)	
Mechanically ventilated, $PaO_2/FiO_2 \geq 200$	1.62 (1.30, 2.04)
Mechanically ventilated, PaO_2/FiO_2 100-199	2.10 (1.61, 2.75)
Mechanically ventilated, PaO_2/FiO_2 <100	2.73 (2.16, 3.45)
Shock on Day 1 of ICU admission	1.25 (0.95, 1.62)
D-dimer	
1000-2500	1.10 (0.92, 1.33)
>2500	1.60 (1.30, 1.97)
Missing	1.46 (1.15, 1.86)
ICU beds in hospital	
50-199	1.07 (0.79, 1.45)
$\geq$ 200	1.05 (0.76, 1.46)
SOFA liver score	
1	0.88 (0.62, 1.24)
2	1.16 (0.79, 1.70)
Missing	0.97 (0.67, 1.41)

SOFA coagulation score	
1	1.17 (0.93, 1.46)
2	1.24 (0.86, 1.79)
Missing	NE
Treatment	
Corticosteroids	1.21 (1.01, 1.45)
Remdesivir	0.73 (0.51, 1.03)

NE, not estimable due to small sample

eTable 8: Unadjusted and Multivariable Relationship between BMI and Thrombotic Events (N= 4907)[†]

BMI Category	Bivariate Analysis Hazard Ratio (95% CI)	Multivariable Analysis[*]: Hazard Ratio (95% CI)
<18.5	0.77 (0.30, 1.98)	0.39 (0.05, 3.17)
18.5-24.9	1.00	1.00
25-29.9	1.04 (0.87, 1.48)	1.18 (0.85, 1.65)
30-34.9	1.26 (0.94, 1.70)	1.16 (0.82, 1.63)
35-39.9	1.03 (0.73, 1.45)	0.93 (0.56, 1.53)
40+	1.21 (0.89, 1.64)	1.35 (0.86, 2.12)

[*]model includes BMI, age, sex, race, Hispanic ethnicity, comorbidities (hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic liver disease, alcoholism, cancer, immunodeficient state), current smoker, home medications (immunosuppressives, anticoagulants), ICU admission labs (lymphocyte count, WBC, platelets, d-dimer, fibrinogen), PaO2/FiO2 ratio in invasively mechanically ventilated patients, presence of shock, SOFA kidney score, SOFA liver score, treatment interventions (corticosteroids, remdesivir);
[†]Death was treated as competing risk in this model

eTable 9: Complete Multivariable Competing Risk Regression for Thrombotic Events

Variable	**Hazard Ratio (95% CI)**
BMI (versus 18.5-24.9)	
<18.5	0.39 (0.05, 3.17)
25-29.9	1.18 (0.85, 1.65)
30-34.9	1.16 (0.82, 1.63)
35-39.9	0.93 (0.56, 1.53)
40+	1.35 (0.86, 2.12)
Age	1.00 (0.99, 1.01)
Female (versus male)	0.66 (0.50, 0.87)
Race (versus black)	
White	0.65 (0.47, 0.88)
Others	0.45 (0.25, 0.82)
Unknown	0.48 (0.33, 0.69)
Hispanic ethnicity	1.38 (0.95, 2.01)
Comorbidities	
Hypertension	0.71 (0.53, 0.96)
Diabetes mellitus	0.91 (0.66, 1.27)
CAD	1.1 (0.73, 1.69)
Congestive heart failure	0.44 (0.25, 0.78)
COPD	0.99 (0.59, 1.69)
Chronic liver disease	0.92 (0.42, 2.02)
Alcoholism	0.84 (0.47, 1.49)
Cancer	1.50 (0.79, 2.84)
Immunodeficiency	0.56 (0.26, 1.18)
Current smoker	1.00 (1.00, 1.00)
Home immunosuppressive medications	0.99 (0.55, 1.79)
Home anticoagulant medications	0.91 (0.58, 1.42)
Absolute lymphocyte count ≥ 1000 per mm^3	1.22 (0.92, 1.63)
WBC	1.02 (1.00, 1.03)
Platelet count on Day 1 of ICU admission	1.00 (0.99, 1.00)
D-dimer	1.00 (1.00, 1.00)
Fibrinogen	1.00 (1.00, 1.00)
Mechanically ventilated (versus no ventilation)	
$PaO_2/FiO_2 \geq 200$	1.00 (0.66, 1.51)
PaO_2/FiO_2 100-199	1.01 (0.76, 1.34)
PaO_2/FiO_2 <100	0.82 (0.57, 1.17)
Shock on Day 1 of ICU admission	1.15 (0.78, 1.68)
SOFA kidney score	
1	1.11 (0.78, 1.58)
2	1.38 (0.86, 2.20)
3	1.60 (0.87, 2.93)
4	1.40 (0.89, 2.18)
SOFA liver score	

1	0.89 (0.66, 1.43)
2	1.43 (0.75, 2.73)
Missing	0.77 (0.35, 1.71)
Treatment	
Corticosteroids	0.92 (0.69, 1.23)
Remdesivir	1.27 (0.86, 1.90)

*NE=Not estimable due to zero thromboembolic event