Title: Predictors at admission of mechanical ventilation and death in an observational cohort of adults hospitalized with COVID-19

Coauthors: Brendan R. Jackson*, MD1,2; Jeremy A. W. Gold, MD1,3; Pavithra Natarajan, BMBS1;

John Rossow, DVM1,2,3; Robyn Neblett Fanfair, MD1,2; Juliana da Silva, MD1; Karen K. Wong,

MD1,2; Sean D. Browning, MSc1,4; Sapna Bamrah Morris, MD1,2; Jessica Rogers-Brown, PhD1,4;

Alfonso C. Hernandez-Romieu, MD 1,2,3,5; Christine M. Szablewski, DVM1,2,3,6; Nadine

Oosmanally, MSPH6; Melissa Tobin-D'Angelo, MD6; Cherie Drenzek, DVM6; David J. Murphy, MD,

PhD5; Julie Hollberg, MD5; James M. Blum, MD5,7; Robert Jansen, MD8; David W. Wright, MD5,8;

William M. Sewell III, MD9; Jack D. Owens, MD9; Benjamin Lefkove, MD10; Frank W. Brown,

MD5,10; Deron C. Burton, MD1,2; Timothy M. Uyeki, MD1; Stephanie R. Bialek, MD1,2; Priti R. Patel,

MD1,2; Beau B. Bruce, MD, PhD1

Affiliations: ¹CDC COVID-19 Emergency Response; ²U.S. Public Health Service; ³Epidemic Intelligence Service, CDC; ⁴Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee; ⁵Emory University School of Medicine; ⁶Georgia Department of Public Health, Atlanta, Georgia; ⁷Georgia Clinical & Translational Science Alliance, Atlanta, Georgia; ⁸Grady Health System, Atlanta, Georgia; ⁹Phoebe Putney Memorial Hospital, Albany, Georgia; ¹⁰Emory Decatur Hospital, Decatur, Georgia.

***Corresponding author:** Brendan R. Jackson, 1600 Clifton Road NE, Mailstop: H24-9, Atlanta, GA, 30329, iyn0@cdc.gov, phone: 404-639-0536, fax: 404-471-8671

Summary: We conducted a retrospective observational cohort investigation of 297 hospitalized adult patients. In random forest models adjusting for numerous patient characteristics, older age was the strongest predictor of death, and pre-hospital angiotensin receptor blocker use was significantly associated with death.

Abstract:

Background: Coronavirus disease (COVID-19) can cause severe illness and death. Predictors of poor outcome collected on hospital admission may inform clinical and public health decisions.

Methods: We conducted a retrospective observational cohort investigation of 297 adults admitted to eight academic and community hospitals in Georgia, United States, during March 2020. Using standardized medical record abstraction, we collected data on predictors including admission demographics, underlying medical conditions, outpatient antihypertensive medications, recorded symptoms, vital signs, radiographic findings, and laboratory values. We used random forest models to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CI) for predictors of invasive mechanical ventilation (IMV) and death.

Results: Compared with age <45 years, ages 65–74 years and ≥75 years were predictors of IMV (aOR 3.12, Cl 1.47–6.60; aOR 2.79, Cl 1.23–6.33) and the strongest predictors for death (aOR 12.92, Cl 3.26–51.25; aOR 18.06, Cl 4.43–73.63). Comorbidities associated with death (aORs from 2.4 to 3.8, p <0.05) included end-stage renal disease, coronary artery disease, and neurologic disorders, but not pulmonary disease, immunocompromise, or hypertension. Pre-hospital use vs. non-use of angiotensin receptor blockers (aOR 2.02, Cl 1.03–3.96) and dihydropyridine calcium channel blockers (aOR 1.91, Cl 1.03–3.55) were associated with death.

Conclusions: After adjustment for patient and clinical characteristics, older age was the strongest predictor of death, exceeding comorbidities, abnormal vital signs, and laboratory test abnormalities. That coronary artery disease, but not chronic lung disease, was associated with death among hospitalized patients warrants further investigation, as do associations between certain antihypertensive medications and death.

Key words: COVID-19; SARS-CoV-2; hospitalization; mortality; angiotensin receptor antagonists

Background

Pandemic coronavirus disease 2019 (COVID-19) is causing severe illness and deaths across the United States and the world. Data from a variety of healthcare settings are needed on patient characteristics and clinical findings on admission to predict who is most likely to receive invasive mechanical ventilation (IMV) and die.

Analyses of medical records and administrative data have identified older age [1,2] and several common chronic conditions as possible risk factors for severe illness and death from COVID-19, including cardiovascular disease [2–5], hypertension [3,4,6–8], diabetes [2], chronic obstructive pulmonary disease (COPD) [9], obesity [10–13], and cigarette smoking [14]. However, some associations are inconsistent across studies and have differed by patient population and outcome measure (e.g., hospitalization, intensive care unit [ICU] admission, IMV, death). Several studies did not adjust for age and other confounders or had incomplete patient outcomes [1,8,15]. An association between COVID-19 outcomes and antihypertensive medications, particularly angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), is biologically plausible, given the role of the human ACE2 receptor in viral entry, but speculative [16]; recent studies have not identified associations between pre-hospital use of antihypertensive medication classes and diagnosed COVID-19 or composite adverse outcomes [17,18].

Several studies examined predictors of adverse outcomes in COVID-19 and proposed predictive criteria based on specialized laboratory testing [19], but some of these studies examined laboratory values obtained days into patients' hospital courses, making them less useful in predicting later outcomes than admission values [19–22]. Furthermore, predictors of IMV may be different from predictors of death, since many patients with IMV will recover and not all patients who die have received IMV. In this investigation, we gathered descriptive data available to most clinicians on patient hospital admission to examine predictors of IMV and death to inform clinical and public health practice.

3

Methods

The Centers for Disease Control and Prevention (CDC) and the Georgia Department of Public Health (DPH) partnered with three hospital networks to abstract medical records of patients hospitalized with COVID-19 in eight Georgia hospitals and assess the association between patient characteristics, underlying conditions, pre-hospital medications, and clinical findings on patient presentation with receipt of IMV or death. Seven hospitals were in metropolitan Atlanta, and one was in the southern region of Georgia; all provided tertiary care and included academic medical centers, a public teaching hospital, and community hospitals. CDC and Georgia DPH determined this investigation to be a non-research public health response activity.

Patient population

We collected data on patients hospitalized during March 2020 with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—the virus that causes COVID-19—confirmed by reverse transcription-polymerase chain reaction; observation stays and deaths in the emergency department were also eligible for inclusion. Patients transferred between participating hospitals or admitted multiple times to the same hospital during March were analyzed as having a single hospitalization. Hospitals provided lists of patients with SARS-CoV-2 infection admitted during March 1—March 30, 2020 (n=698). We abstracted data from medical records of 305 adult patients (≥18 years old) sequentially selected from these lists. For analysis, we included only patients with completed hospitalizations (i.e., discharge or death, n=297) as of May 8, 2020.

Data collection

During March 25–May 8, 2020, investigators abstracted medical records using a secure REDCap form [23] that included elements on patient demographics, underlying medical conditions, pre-hospital medications, whether reason for admission was COVID-19 related, presenting signs and symptoms, laboratory testing, radiographic imaging, and outcomes. Records reviewed included clinician notes and first recorded vital signs, laboratory values, and imaging. The database was continually reviewed to correct missing data and implausible values. History of stroke was included under cardiovascular and not neurologic conditions. Hypoxia on admission was defined as oxygen saturation ≤94% on room air or use of supplemental oxygen. Pre-hospital antihypertensive medications were classified as ACE inhibitors, ARBs, beta blockers, dihydropyridine calcium channel blockers (dCCBs), thiazide diuretics, non-thiazide diuretics (e.g., furosemide, spironolactone), other vasodilators (e.g., hydralazine), and other medications (e.g., clonidine, prazosin). Immunocompromise was defined as cancer with chemotherapy receipt within the previous year, history of solid organ or stem cell transplant, HIV infection, or current use of immunosuppressive medications. Outcomes were defined as IMV and death and were examined separately.

Analysis

To evaluate independent predictors of IMV and death at hospital admission, we used counterfactual random forest probability machines [24,25] to adjust for all other variables reported, including number of comorbidities and whether reason for admission was COVID-19–related. In brief, separate random forest models were developed using patients with each value of the covariate under consideration. Estimated probabilities of the outcome were generated for all patients, including those who experienced a different value of exposure (i.e., counterfactual). From the sum of the predicted probabilities, two-by-two tables were constructed and scaled to the data's exposure margins. Odds ratios and standard errors were subsequently calculated by standard methods. Continuous variables (age, body mass index [BMI], vital signs, and laboratory values) were entered into random forests as continuous, but we reported associations for individual variables using quantiles or standard categories (for age and BMI) that roughly aligned with quintiles. Categories with the lowest values were used as reference groups. We used quantiles rather than laboratory reference ranges to provide finer detail than reference ranges allowed, as use of reference ranges only might obscure clinically meaningful differences. R statistical software (version 3.6.3; The R Foundation) was used to conduct analyses. Random forests were generated using the randomForestSRC package (version 2.9.3) with default settings (1,000 trees per forest, square root of the number of variables randomly selected as node splitting candidates, 10 random splits considered for each continuous variable). Missing data, ranging from 0% (for 64% [55/86] of variables, e.g., age) to 29% for alkaline phosphatase, were imputed by a single random forest imputation (impute.rfsrc function).

To identify simple algorithms predictive of IMV and death independent of the random forest model, we developed machine-generated decision trees called fast-and-frugal trees (FFTs), which identify the variables and cut-points (for continuous variables) most predictive of outcome. Each decision point, or node, has two branches, one of which continues the tree, and the other is an exit. For the final node, both branches are exits. FFTs were generated using the ifan algorithm in the R FFTrees package (version 1.5.2) to best balance sensitivity and specificity. Final models rounded continuous variable cut-points to whole numbers to simplify use.

Results

As of May 8, 2020, 297 (97.4%) of 305 patients had completed hospitalizations: 51 (17.2%) died and 246 (82.8%) were discharged alive (**Supplemental figure**). Demographics and underlying medical conditions of this cohort have been previously described [26]. Of the 297, median age was 60 years (interquartile range [IQR] 45–69), 149 (50.2%) were female, 241 (81.1%) were non-Hispanic black, and 20 (6.7%) resided in a skilled nursing facility (SNF). Most (n=277, 93.3%) were hospitalized in metropolitan Atlanta. Over one-third (n=112, 37.7%) received ICU care, including 85 (28.6%) who received IMV. Of the 85 who received IMV, 38 (44.7%) died, whereas 13 (6.1%) died of the 212 who did not require/receive IMV. Median age of patients receiving IMV who died was older (70 years, IQR 63–76) than those who survived (61 years, IQR 48.5–67). Of the 13 who died without receiving IMV, median age was 81 years (IQR 73–91).

In random forest models, increasing age was the strongest predictor of death, with age ≥75 years having an adjusted odds ratio (aOR) of 18.06 (95% confidence interval [95%CI] 4.43–73.63) and age 65–74 years having an aOR of 12.92 (95%CI 3.26–51.25) vs. age <45 years (**Table 1**). For each older age stratum, aORs were 2–6 times higher for death compared with IMV. For IMV, elevated respiratory rate (aOR 5.46, 95%CI 2.41–12.34 for rates 20–22 vs. <19), end-stage renal disease (ESRD) on dialysis (aOR 4.05, 95%CI 1.43–11.44), and elevated aspartate aminotransferase (AST, aOR 3.5, 95%CI 1.58–7.76 for highest vs. lowest quintile) were stronger predictors than differences in age strata. Patients who resided in a SNF had higher odds of death (aOR 4.15, 95%CI 1.62–10.61) but not IMV (aOR 0.59, 95%CI 0.19–1.80) than those who resided elsewhere. Sex, insurance status, and non-Hispanic Black race were not significantly associated with IMV receipt or death.

Among the underlying conditions, independent predictors of death due to COVID-19 included preexisting end-stage renal disease (ESRD) on dialysis (aOR 3.84, 95%Cl 1.36–10.82), neurologic disorders (aOR 2.94, 95%Cl 1.39–6.23), and coronary artery disease (CAD, aOR 2.37, 95%Cl 1.08–5.23). Over half of patients with neurologic conditions had dementia or Parkinson's disease. History of stroke had a non-significantly elevated odds ratio (aOR 2.97, 95%Cl 0.93–9.47) for death. Diabetes mellitus was associated with greater odds of receiving IMV (aOR 1.90, 95%Cl 1.14– 3.16, p=0.01) and with death (aOR 1.77, 95%Cl 0.99–3.19, p=0.06). Hemoglobin A1c \geq 8% was associated with IMV (aOR 2.10, 95% 1.01–4.35) but not death. Elevated BMI, hypertension, heart failure, COPD, asthma, liver disease, chronic kidney disease (CKD) without dialysis, and immunocompromising conditions were not significantly associated with higher odds of IMV or death after controlling for other variables in the model. Number of comorbidities was not significantly associated with death independently of their individual contribution, although having \geq 3 comorbidities was associated with greater odds (aOR 2.29, 95%Cl 1.01–5.16) of IMV compared with having none. History of hypertension or number of antihypertensive medications before admission was not associated with IMV or death controlling for other variables in the models, including age and comorbidities. However, pre-hospital use of ARBs or dCCBs, specifically, were associated with twice the odds of death (aOR 2.02, 95%CI 1.03–3.96, and aOR 1.91, 95%CI 1.03–3.55, respectively) compared with patients not taking either. Pre-hospital ARB use was also significantly associated with IMV (aOR 1.84, 95%CI 1.02–3.32), but not dCCB use.

Among recorded admission signs and symptoms, altered mental status was significantly predictive of adverse outcomes, having 4.99 times the odds (95%Cl 2.07–12.01) of death compared with patients without this condition recorded (**Table 2**). Among presenting vital signs, hypoxia and elevated respiratory rate were significantly predictive of IMV. Admission systolic blood pressure <111 mmHg (first quintile) vs. 122–131 mmHg (third quintile) and diastolic blood pressures <65 (first quintile) vs. 78–85 mmHg (fourth quintile) were associated with significantly higher odds of IMV. For respiratory rate, the upper three quartiles of respiratory rate (≥19 breaths per minute) had elevated aORs for death compared with the referent lowest quartile, but respiratory rate was statistically significant only for the second quartile (aOR 3.87, 95%Cl 1.62–9.28).

Laboratory tests associated with increased odds of death included thrombocytopenia (lowest quintile, platelets <142 cells/mm³) compared with other quintiles and the highest quintile of AST (\geq 63 IU/L) compared with the lowest (**Table 3**). Compared to those with values in the lowest quintiles, the highest quintile of absolute lymphocyte count (\geq 1.47 cells/mm³) was protective for death, the highest blood urea nitrogen (BUN) quintile (\geq 27 mg/dL) had greater odds of IMV and death, and the highest creatinine quintile (\geq 1.65 mg/dL) was also associated with IMV and was nonsignificantly associated with death (p=0.15). Certain higher quintiles of alanine aminotransferase (ALT), AST, and total bilirubin were also associated with IMV compared with the lowest. Presence of a bilateral or multifocal infiltrate was significantly associated with death (aOR 1.98, 95%CI 1.05– 3.76); other abnormality or opacity on chest radiograph was not significantly associated with outcomes.

The selected FFT decision tree and selected cut-points for parsimoniously predicting IMV included respiratory rate (>20 breaths per minute), BUN (>21 mg/dL), hypoxia, and diastolic blood pressure (≤74 mmHg), with overall accuracy of 70%, sensitivity of 60%, and specificity of 74% (**Figure 1A**). The selected FFT for death included age (≥63 years), BUN (>16 mg/dL), and AST (>37 U/L), with overall accuracy of 75%, sensitivity of 78%, and specificity of 74% (**Figure 1B**).

Discussion

In this observational cohort of nearly 300 predominantly black adults hospitalized with COVID-19 early in the U.S. epidemic, age was by far the strongest predictor of death, with the odds of death increasing markedly among older patients (>12 times greater odds for age 65–74 years and >18 times greater odds for age \geq 75 vs. those <45 years). By comparison, death was less strongly associated with underlying conditions (i.e., ESRD, neurologic disorders, and CAD), SNF residence, and clinical findings (aORs \leq 4.2). The association between age and death persisted despite adjustment for a wide range of factors, including vital signs and laboratory results, which might be assumed to be more directly predictive of poor outcomes. Why older adults have a markedly higher risk of death merits further study but may relate to immune or vascular system changes that occur with aging.

Chronic lung disease [27], immunocompromise [27], tobacco use [28], and obesity [29] might be expected to be predictive of COVID-19-associated death based on data for influenza, another viral respiratory illness. However, in our analysis, these conditions were not associated with in-hospital death. Some earlier reports found associations between obesity and in-hospital death [13], in-ICU death [30], and severe illness [11] in COVID-19, although these studies also did not identify mortality associations for lung disease, immunocompromise, or smoking. However, various studies have linked all of these conditions to severe COVID-19 [31]. For example, a large U.K. study

9

found obesity and chronic lung disease to be associated with death from COVID-19 among the general population [2]. Although our investigation's relatively small sample size may have limited our power to detect associations, our results suggest that obesity without associated comorbidities was not a strong risk factor for in-hospital death. Further research is still needed to evaluate the associations between underlying conditions and risk of death in hospitalized COVID-19 patients.

That pre-hospital use of ARBs was associated with receiving IMV and in-hospital death, despite extensive adjustment for other factors, including black race, CAD, hypertension, and diabetes, is notable given that a link is biologically plausible and ARB use has been associated with renal dysfunction in COVID-19 [16,32]. However, other studies found no association between ARB use and mortality [33] or a composite adverse outcome [18] in COVID-19 patients. Why dCCB use was also associated with death in our investigation is unclear, and relationships between antihypertensives and COVID-19 outcomes warrant further examination in larger well-controlled studies. Given other studies have not linked pre-hospital antihypertensive use to death in COVID-19 and the limitations of our investigation, outpatients should continue on their prescribed antihypertensive regimens per existing guidance [34].

The simple FFT decision trees predicted outcomes with reasonable accuracy (70–75%), which was lower than a recently proposed 'rule-of-6' algorithm (~90%). However, this algorithm involved specialized laboratory testing (i.e., lactate dehydrogenase, C-reactive protein, ferritin) collected up to 48 hours after admission [35], whereas the FFT involve tests routinely ordered in the emergency department. Only three variables—age, AST, and BUN—were 75% predictive of death in the FFT model; elevated AST and BUN on admission may be markers of multisystem inflammation, which has been associated with severe disease. Several other clinical factors were also predictive of death in the random forest model: altered mental status, thrombocytopenia, and lower lymphocyte counts. Although previous studies have reported associations between elevated admission AST and death [3] and lower lymphocyte counts and severe COVID-19 [22], and others have identified

thrombocytopenia as a marker of poor outcomes [36], few studies have examined these factors on admission in a multivariable model. Notably, abnormal respiratory vital signs were less predictive of death, although they were strongly predictive of IMV in both the FFT and random forest models.

Our retrospective observational investigation has several notable limitations. Because data abstraction was limited to medical records, symptom data are less complete than those obtained by questionnaires. We were unable to evaluate certain specialized testing (e.g., C-reactive protein, lactate dehydrogenase, D-dimer) [20,22,37] because they were infrequently ordered on admission. Second, the outcome IMV is highly influenced by clinical practice, and some clinicians may have pursued early IMV to minimize non-invasive ventilation and avoid emergency endotracheal intubation, given potential risks of viral transmission. As such, using death as an outcome, rather than solely relying on IMV or a composite outcome, allows examination of predictors less dependent on individual medical practices. Third, we used quantiles rather than vital and laboratory reference ranges, and some quantiles included a mix of normal and abnormal values which could have biased those categories toward the null. Fourth, our analysis had limited power to detect weak associations, given the relatively small sample size and adjustment for many factors. However, random forest models allowed robust control for confounders, offering benefits over logistic regression, by allowing examination of more covariates, requiring fewer assumptions, and better accounting for interactions [24,25]. Fifth, we examined nearly 100 admission factors. Although our approach may tend toward a bias to the null with this number of factors [24], we did not incorporate adjustments for multiple testing, and some associations might still have occurred by chance. However, the FFT yielded similar findings to our more well-controlled analyses; FFT also offer benefits over logistic regression because they rarely overfit data and are easy to interpret and use [38,39]. Finally, although records were selected sequentially in the order in which hospitals identified cases, this cohort is ultimately a convenience sample, as it did not encompass all COVID-19 patients admitted to these hospitals during March 2020 [26]. While findings from this cohort, involving predominantly non-Hispanic black patients in a limited geographical area and time, may

not be generalizable to other populations, our investigation provides valuable data on black patients with COVID-19, who have been disproportionately impacted by COVID-19 [40].

In summary, we provide simple decision trees that found the most important predictors for IMV were hypoxia, elevated respiratory rate, elevated BUN, and low diastolic blood pressure; for death the most important predictors were older age (≥63 years), elevated BUN, and elevated AST. These predictors were confirmed and augmented by several additional predictors from our multivariable model. Furthermore, the significant association between pre-hospital use of ARBs and IMV and death and dCCBs and death warrants additional investigation.

Cepter

NOTES

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease control and Prevention.

Funding: This work was supported by the Centers for Disease Control and Prevention.

k certer

Conflict of interest disclosures: James M. Blum reports personal fees from Clew Medical, outside the submitted work. No other potential conflicts of interest were disclosed.

NS

References

- 1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet **2020**; 395:1054–1062.
- 2. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature **2020**; :1–11.
- 3. Chen R, Liang W, Jiang M, et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. CHEST **2020**; 0. Available at: https://journal.chestnet.org/article/S0012-3692(20)30710-8/abstract. Accessed 28 May 2020.
- 4. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect **2020**; Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177098/. Accessed 28 May 2020.
- 5. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis **2020**; 94:91–95.
- Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7098485/. Accessed 28 May 2020.
- 7. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. J Renin Angiotensin Aldosterone Syst **2020**; 21:1470320320926899.
- 8. Matsushita K, Ding N, Kou M, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. medRxiv **2020**; :2020.04.05.20054155.
- 9. Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). Respir Med **2020**; 167:105941.
- 10. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis Off Publ Infect Dis Soc Am **2020**; Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184372/. Accessed 28 May 2020.
- 11. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. medRxiv **2020**; :2020.04.08.20057794.
- 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 n/a. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/oby.22831. Accessed 28 May 2020.
- 13. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism **2020**; 108:154262.

- 14. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. Tob Induc Dis **2020**; 18. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7083240/. Accessed 28 May 2020.
- 15. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA **2020**; 323:2052–2059.
- 16. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin– Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med **2020**; 382:1653–1659.
- 17. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med **2020**; 0:null.
- 18. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. N Engl J Med **2020**; 0:null.
- 19. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. The BMJ **2020**; 369. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7222643/. Accessed 28 May 2020.
- 20. Yan L, Zhang H-T, Goncalves J, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell **2020**; 2:283–288.
- 21. Bhargava A, Fukushima EA, Levine M, et al. Predictors for Severe COVID-19 Infection. Clin Infect Dis Available at: https://academic.oup.com/cid/advancearticle/doi/10.1093/cid/ciaa674/5848851. Accessed 2 June 2020.
- 22. Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med **2020**; Available at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2766086. Accessed 3 June 2020.
- 23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–381.
- 24. Dasgupta A, Szymczak S, Moore JH, Bailey-Wilson JE, Malley JD. Risk estimation using probability machines. BioData Min **2014**; 7:2.
- 25. Malley JD, Kruppa J, Dasgupta A, Malley KG, Ziegler A. Probability Machines: Consistent Probability Estimation Using Nonparametric Learning Machines. Methods Inf Med **2012**; 51:74–81.
- 26. Gold JAW. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19

 Georgia, March 2020. MMWR Morb Mortal Wkly Rep 2020; 69. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6918e1.htm. Accessed 28 May 2020.
- 27. Pebody RG, McLean E, Zhao H, et al. Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Eurosurveillance **2010**; 15:19571.

- 28. Han L, Ran J, Mak Y-W, et al. Smoking and Influenza-associated Morbidity and Mortality: A Systematic Review and Meta-analysis. Epidemiology **2019**; 30:405–417.
- 29. Morgan OW, Bramley A, Fowlkes A, et al. Morbid Obesity as a Risk Factor for Hospitalization and Death Due to 2009 Pandemic Influenza A(H1N1) Disease. PLOS ONE **2010**; 5:e9694.
- Gupta S, Hayek SS, Wang W, et al. Factors Associated With Death in Critically III Patients With Coronavirus Disease 2019 in the US. JAMA Intern Med 2020; Available at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2768602. Accessed 17 July 2020.
- 31. CDC. People of Any Age with Underlying Medical Conditions. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medicalconditions.html. Accessed 17 July 2020.
- 32. Oussalah A, Gleye S, Clerc Urmes I, et al. Long-Term ACE Inhibitor/ARB Use Is Associated with Severe Renal Dysfunction and Acute Kidney Injury in Patients with severe COVID-19: Results from a Referral Center Cohort in the North East of France. Clin Infect Dis Available at: https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa677/5867535. Accessed 6 July 2020.
- Fosbøl EL, Butt JH, Østergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. JAMA 2020; Available at: https://jamanetwork.com/journals/jama/fullarticle/2767669. Accessed 22 June 2020.
- HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. Available at: http%3a%2f%2fwww.acc.org%2flatest-incardiology%2farticles%2f2020%2f03%2f17%2f08%2f59%2fhfsa-acc-aha-statement-addressesconcerns-re-using-raas-antagonists-in-covid-19. Accessed 28 May 2020.
- Simple 'Rule-of-6' predicts severe COVID-19 disease | Clinical Infectious Diseases | Oxford Academic. Available at: https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa938/5868031. Accessed 10 July 2020.
- Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta Int J Clin Chem 2020; 506:145–148.
- 37. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol **2020**; 127:104370.
- 38. Gigerenzer G, Brighton H. Homo heuristicus: why biased minds make better inferences. Top Cogn Sci **2009**; 1:107–143.
- Gigerenzer G, Czerlinski J, Martignon L. How Good are Fast and Frugal Heuristics? In: Shanteau J, Mellers BA, Schum DA, eds. Decision Science and Technology: Reflections on the Contributions of Ward Edwards. Boston, MA: Springer US, 1999: 81–103. Available at: https://doi.org/10.1007/978-1-4615-5089-1_6. Accessed 4 June 2020.

 Stokes EK. Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm. Accessed 19 June 2020.

Accepted Manuscript

Table 1: Demographic characteristics, underlying conditions, and pre-hospital antihypertensive

 medications as potential predictors in a random forest model of invasive mechanical ventilation

 (IMV) and death in a cohort of 297 patients with completed COVID-19 hospitalizations in the U.S.

 state of Georgia

~	_ °	I.	MV (n=85)		_	_		Death (n=51)		
Characteristic Domographic information	Expª	Unexp	aOR	95%CI [®]	Р	Exp	Unexp	aOR	95%CI	р
Age, years	85	212				51	246			
[23,45) ^c	12	62	ref	ė		1	73	ref	÷	
[45,55)	9	30	1.35	-	0.52	4	35	3.75	-	0.11
[55,65)	21	52	1.73	•	0.15	7	66	4.12		0.056
[65,75)	27	38	3.12	•	0.003	18	47	12.92	-	< 0.001
[75,95]	16	30	2.79	•	0.01	21	25	18.06	-	< 0.001
Female	38/85	111/212	0.76	•	0.28	22/51	127/246	0.89	•	0.70
Non-Hispanic Black	69/84	172/205	0.82	•	0.56	40/50	201/239	0.78	•	0.51
Resided in a skilled nursing facility before admission	5/84	15/210	0.59		0.35	11/51	9/243	4.15	•	0.003
Insurance status	84	210				50	244			
Uninsured	12	32	ref			3	41	ref		
Medicaid	8	24	0.66	-	0.43	3	29	0.71		0.67
Other	64	154	0.93	•	0.84	44	174	1.86	•	0.22
Substance use										
Current tobacco use	4/85	12/212	0.99	÷	0.98	1/51	15/246	0.23		0.20
Previous tobacco use	22/85	47/212	0.99	•	0.96	18/51	51/246	1.61	•	0.15
Illicit drug use	3/85	5/212	1.48	÷	0.60	1/51	7/246	0.65		0.69
Underlying conditions				_						
Hypertension	67/85	134/212	1.18	•	0.55	44/51	157/246	1.10	•	0.77
Body mass index, kg/m ²	81	204				46	239			
[15.1,25.0)	9	31	ref			7	33	ref		
[25.0,30.0), overweight	18	64	0.90	•	0.81	16	66	1.12	•	0.82
[30.0,35.0), class 1 obesity	25	49	1.68	•	0.23	9	65	1.09	•	0.87
[35.0,40.0), class 2 obesity	18	34	1.82	-	0.20	11	41	1.89	•	0.23
[40.0,68.5], class 3 obesity	11	26	1.54	-	0.39	3	34	0.68	-	0.56
Diabetes mellitus	47/85	70/212	1.90	•	0.01	28/51	89/246	1.77	•	0.056
Hemoglobin A1c $\ge 8\%^d$	13/33	16/43	2.10	•	0.046	6/17	23/59	1.10	٠	0.83
Cardiovascular disease	28/85	46/212	1.36		0.28	21/51	53/246	1.47	•	0.23
Coronary artery disease	11/85	22/212	1.27	•	0.54	10/51	23/246	2.37	•	0.03
Heart failure	9/85	23/212	0.94	+	0.87	5/51	27/246	0.63	•	0.40
Other cardiovascular disease	12/85	18/212	1.43	-	0.38	7/51	23/246	1.71	•	0.22
Cerebrovascular accident/stroke	6/85	7/212	2.16	-	0.18	5/51	8/246	2.97	-	0.07
Chronic lung disease	17/85	34/212	1.37	•	0.33	6/51	45/246	0.67	•	0.36
Asthma	10/85	22/212	1.53	•	0.28	3/51	29/246	0.62	-	0.40

	Outcome												
		I	MV (n=	85)				Death (n	=51)				
Characteristic	Exp ^a	Unexp	aOR	95%CI ^b	Р	Exp	Unexp	aOR	95%CI	р			
COPD	5/85	10/212	1.23		0.72	3/51	12/246	1.16		0.83			
Other lung disease ^e	3/85	5/212	1.47		0.61	1/51	7/246	0.66		0.70			
Obstructive sleep apnea	6/85	10/212	1.73	-	0.30	5/51	11/246	2.31	-	0.13			
Hypothyroidism	1/85	12/212	0.19		0.12	1/51	12/246	0.38		0.36			
Liver disease	3/85	4/212	1.79		0.45	2/51	5/246	1.88		0.46			
Chronic kidney disease													
Without Dialysis	9/85	22/212	0.98	•	0.96	6/51	25/246	0.82	+	0.70			
End stage, on dialysis	9/85	7/212	4.05	-	0.008	6/51	10/246	3.84	-	0.01			
Rheumatologic/autoimmune conditions ^f	3/85	5/212	1.52	<u> </u>	0.57	3/51	5/246	3.00	÷	0.14			
Neurologic disorder ^g	12/85	26/212	1.02	÷	0.96	16/51	22/246	2.94	•	0.005			
Immunocompromising conditions or therapies ^h	9/83	19/206	1.07	÷	0.87	3/50	25/239	0.75	- - -	0.61			
Psychiatric diagnosis ⁱ	11/85	14/212	1.85	•	0.15	5/51	20/246	1.01	÷	0.98			
Cancer	4/85	8/212	1.23	÷-	0.75	1/51	11/246	0.39	• <u>-</u> -	0.38			
Number of comorbidities ^j	85	212				51	246						
0	6	37	ref	•		2	41	ref	÷				
1	10	52	0.96	+	0.93	5	57	0.66		0.47			
2	18	44	1.51	-	0.38	14	48	1.60	-	0.36			
[3,8]	51	79	2.29		0.046	30	100	1.31	+	0.57			
Number of hypertension medications													
≥2 classes	44/85	82/212	1.20	•	0.47	30/51	96/246	1.62	•	0.11			
1 class	13/85	44/212	0.78	•	0.46	9/51	48/246	0.77	•	0.51			
Any hypertension medication													
Calcium channel blockers (dihydropyridine)	29/85	58/212	1.17	+	0.57	24/51	63/246	1.91	•	0.04			
ARBs	26/85	35/212	1.84	•	0.044	17/51	44/246	2.02	•	0.04			
ACE inhibitors	15/85	35/212	1.15	•	0.68	8/51	42/246	1.00	÷	0.99			
Thiazide diuretics	17/85	32/212	1.55	•	0.18	7/51	42/246	1.06	+	0.88			
Beta blockers	16/85	32/212	1.08	+	0.83	13/51	35/246	1.51	•	0.28			
Non-thiazide diuretics	8/85	18/212	1.14	+	0.77	7/51	19/246	1.60	+	0.33			
Vasodilators	8/85	10/212	1.78	•	0.24	6/51	12/246	2.41	-	0.09			
Other medication ^k	3/85	8/212	0.89	- -	0.87	1/51	10/246	0.44	<u>+</u>	0.45			

^aExp indicates number of patients with each factor among those who received IMV or died, and unexp indicates number of patients without each factor who received IMV or died. Crude odds ratios can be calculated by standard techniques using these numbers. ^b95% confidence intervals (CI) are displayed on a log-odds scale with the dashed line indicating an adjusted odds ratio (aOR) of 1. Dark blue indicates a CI

^b95% confidence intervals (CI) are displayed on a log-odds scale with the dashed line indicating an adjusted odds ratio (aOR) of 1. Dark blue indicates a CI entirely <1 (i.e., statistically significant), light blue indicates an aOR <1 with a CI crossing 1, light red indicates an aOR >1 with a CI crossing 1, and dark red indicates a CI entirely >1.

^cBrackets indicate the respective value is included in the interval, and parentheses indicate the value not included in the interval.

^dAmong patients with diabetes, 76 had an HbA1c test collected within three months of hospitalization, and patients without diabetes were assumed to have normal HbA1c.

^eIncludes chronic respiratory failure with home oxygen (n=4), interstitial lung disease (n=3), and pulmonary fibrosis (n=1).

^fIncludes systemic lupus (n=1), rheumatoid arthritis (n=2), inflammatory bowel disease (n=1).

^gIncludes dementia (n=18), Parkinson's disease (n=4), seizures (n=7), multiple sclerosis (n=3), and other neurologic conditions (n=16). Some patients had more than one neurologic condition.

^hIncludes solid organ transplant (n=8), human immunodeficiency virus infection (n=8), cancer with chemotherapy receipt within the previous year (n=3), stem cell transplant (n=3), and leukemia (n=2); 16 patients were taking immunosuppressive medications.

¹Includes anxiety (n=11), depression (n=8), psychotic disorders (n=6), and other psychiatric conditions (n=8).

^jIncludes hypertension, severe obesity (BMI \geq 40), diabetes, cardiovascular disease, chronic lung disease, obstructive sleep a pnea, hypothyroidism, liver disease, chronic kidney disease, immunocompromising conditions or therapies, neurologic disorders, or psychiatric disorders. ^kIncludes alpha blockers (n=5) and central agonists (n=7). **Table 2**: Admission symptoms and vital signs as potential predictors in a random forest model ofinvasive mechanical ventilation (IMV) and death in a cohort of 297 patients with completed COVID-19 hospitalizations in the U.S. state of Georgia

	Outcome									
~			IMV (n=85)		_		Death	(n=51)	
Characteristic Presenting symptoms	Expª	Unexp	aOR	95%CI*	р	Ехр	Unexp	aOR	95%CI	р
Reported fever	70/85	170/212	1.07	•	0.84	42/51	198/246	1.34	+	0.47
Cough	62/85	154/212	1.08	÷	0.80	32/51	184/246	0.75		0.39
Dry cough	30/85	84/212	1.14	÷	0.62	16/51	98/246	1.07	•	0.83
Productive cough	17/85	41/212	1.18	•	0.60	8/51	50/246	0.73		0.44
Dyspnea	51/85	137/212	0.83	ė	0.48	29/51	159/246	1.02		0.95
Chest Pain	10/85	32/212	1.56	•	0.20	3/51	39/246	0.75	•	0.55
Fatigue	40/85	88/212	1.19	÷	0.49	20/51	108/246	0.85	÷	0.59
Chills/sweats	25/84	59/212	1.23	•	0.46	12/51	72/245	0.94	÷	0.86
Myalgia/arthralgia	24/85	70/212	1.10	•	0.72	8/51	86/246	0.63	•	0.19
Diarrhea	25/85	54/212	1.27	•	0.40	12/51	67/246	0.99	•	0.99
Nausea	11/85	54/212	0.52	•	0.057	6/51	59/246	0.52	•	0.13
Loss of appetite	14/85	35/212	1.07	÷	0.85	9/51	40/246	1.16	•	0.70
Vomiting	6/85	31/212	0.55		0.17	2/51	35/246	0.33		0.09
Abdominal pain	3/85	21/212	0.46	-	0.17	2/51	22/246	0.70		0.57
Headache	8/85	40/212	0.76	•	0.46	3/51	45/246	0.50	-	0.17
Altered mental status	8/85	15/212	1.28	+	0.59	12/51	11/246	4.99	•	< 0.001
Rhinorrhea or nasal congestion	8/85	25/212	0.80	-	0.61	6/51	27/246	1.48	-	0.38
Sore throat	7/85	18/212	1.37	•	0.48	3/51	22/246	0.96	+	0.94
Dehydration	2/85	17/212	0.30		0.10	2/51	17/246	0.46	- • :-	0.34
Non-COVID admission diagnosis	6/85	11/212	1.16	÷-	0.78	3/51	14/246	0.74		0.67
Vital signs		011				40	245			
Temperature, °C	83	211				49	245		÷	
	14	51	rei		0.14	8	57	rer		0.00
[36.8,37.2]	20	39	1.81		0.14	12	47	1.66		0.30
[37.2,37.6)	16	39	1.31		0.51	6	49	1.10		0.85
	15	42	1.27		0.56	9	48	1.64		0.32
[38.1,40.1]	18	40	1.62		0.24	14	44	2.48		0.052
Heart rate, beats per minute	83	210				49	244		÷	
[40, 74)	22	39	rei	:		15	48	rer		
[74, 84)	16	52	0.62	-	0.22	15	53	1.18	•	0.70
[84, 91)	15	35	0.84	•	0.66	6	44	0.86	+	0.75
[91,102)	16	41	0.80	•	0.57	6	51	0.54	-	0.23
[102,141]	14	43	0.69	•	0.35	9	48	0.89	+	0.79
Systolic blood pressure, mmHg	83	210				49	244			
[89,111)	26	39	ref	•		12	53	ref	•	

	Outcome											
			IMV (I	n=85)				Death (n=51)				
Characteristic	Exp ^a	Unexp	aOR	95%CI ^b	р	Exp	Unexp	aOR	95%CI	р		
[111,122)	19	40	0.76	•	0.47	6	53	0.43	•	0.10		
[122,131)	9	42	0.44	•	0.048	11	40	1.35	•	0.49		
[131,144)	13	48	0.55	•	0.12	7	54	0.68	•	0.40		
[144,208]	16	41	0.69	•	0.32	13	44	1.19	٠	0.68		
Diastolic blood pressure, mmHg	83	210				49	244					
[46, 65)	27	37	ref	÷		14	50	ref	÷			
[65, 71)	21	36	0.87	•	0.70	13	44	1.27	•	0.59		
[71, 78)	14	43	0.55	•	0.12	8	49	1.06	<u>+</u>	0.90		
[78, 85)	9	55	0.29	•	0.003	5	59	0.47	•	0.14		
[85,127]	12	39	0.48	•	0.08	9	42	0.97	• •	0.95		
Respiratory rate, breaths per minute	83	211				49	244		X			
[13,19)	29	123	ref	•		18	134	ref	!			
[19,20)	19	53	1.62	•	0.14	14	58	1.95	•	0.07		
[20,23)	16	12	5.46	•	< 0.001	9	19	3.77	•	0.003		
[23,40]	19	22	3.36	•	0.001	8	33	1.63	•	0.29		
Hypoxia ^d	58/83	91/210	2.51	•	< 0.001	33/50	116/243	1.71	٠	0.08		

^aExp indicates number of patients with each factor among those who received IMV or died, and unexp indicates number of patients without each factor who received IMV or died. Crude odds ratios can be calculated by standard techniques using these numbers.
^b95% confidence intervals (CI) are displayed on a log-odds scale with the dashed line indicating an adjusted odds ratio (aOR) of 1. Dark blue indicates a CI entirely <1 (i.e., statistically significant), light blue indicates an aOR <1 with a CI crossing 1, light red indicates an aOR <1 with a CI crossing 1, light red indicates an aOR <1 with a CI crossing 1, and dark red indicates a CI entirely >1.

^cBrackets indicate the respective value is included in the interval, and parentheses indicate the value not included in the interval. Vital sign data were divided into quintiles for analysis except for respiratory rate, which was divided into quartiles given narrower distribution of values.

 $^{\rm d}O_2$ saturation <95% or on oxygen for measurement.

Received

Table 3: Radiographic findings and laboratory values as potential predictors in a random forestmodel of invasive mechanical ventilation (IMV) and death in a cohort of 297 patients with completedCOVID-19 hospitalizations in the U.S. state of Georgia

	Outcome									
		IMV (I	n=85)			Death (n=51)			
Characteristic Chest x-ray findings	Exp ^a	Unexp aOR	95%CI⁵	р	Exp	Unexp aOR	95%CI	р		
Any abnormality	59/71	132/180 1.26	٠	0.49	35/42	156/209 1.60	٠	0.26		
Any opacity	52/76	126/190 0.90	•	0.70	30/47	148/219 0.71	•	0.27		
Bilateral/multifocal infiltrate	43/71	96/180 1.31	٠	0.30	25/42	114/209 1.98	٠	0.04		
Unilateral infiltrate	5/71	17/180 0.74	•	0.55	2/42	20/209 0.35		0.21		
Pleural effusion	7/76	11/190 2.02	•	0.15	5/47	13/219 1.09	-	0.89		
Interstitial changes	3/71	5/180 1.47	-	0.60	1/42	7/209 0.64	÷	0.68		
Laboratory values										
Hemoglobin, g/dL	82	212			50	244				
[5.3,11.2) ^c	21	40 ref	•		11	50 ref	•			
[11.2,12.2)	14	50 0.67	•	0.30	13	51 1.17	•	0.72		
[12.2,13.0)	15	37 1.04	•	0.92	9	43 1.09	+	0.85		
[13.0,14.0)	19	44 0.98	<u> </u>	0.95	12	51 1.08	•	0.87		
[14.0,19.3]	13	41 0.67	•	0.33	5	49 0.55	•	0.26		
Platelets, cells per mm ³	83	211			50	244				
[33,142)	25	35 ref	•		20	40 ref	÷			
[142,175)	17	42 0.65	•	0.26	6	53 0.35	•	0.03		
[175,208)	17	41 0.71	•	0.37	12	46 0.69	•	0.38		
[208,269)	10	49 0.36	•	0.02	5	54 0.24	•	0.006		
[269,494]	14	44 0.51	•	0.09	7	51 0.45	•	0.07		
White blood cell, cells per mm ³	83	212			50	245				
[1.3, 4.2)	16	50 ref	÷		12	54 ref				
[4.2, 5.4]	15	42 1.11	•	0.79	9	48 1.04	+	0.93		
[5.4, 6.5]	13	43 0.90	+	0.79	6	50 0.66	•	0.41		
[6.5, 8.8)	18	39 1.40	•	0.38	6	51 0.60	•	0.31		
[8.8,22.1]	21	38 1.43	•	0.36	17	42 1.75	•	0.19		
Absolute lymphocyte count, cells per mm ²	75	182	•		45	212	•			
[0.06, 0.77)	21	39 ref	÷		16	44 ref	÷			
[0.77, 0.99)	21	40 1.10	•	0.80	13	48 0.90	+	0.81		
[0.99, 1.20)	10	33 0.82	•	0.61	7	36 0.92	+	0.84		
[1.20, 1.42)	11	23 0.79	•	0.56	5	29 0.56	•	0.23		
[1.42,10.10]	12	47 0.54	•	0.14	4	55 0.29	•	0.03		
Blood urea nitrogen, mg/dL	82	212	-		49	245	-			
[3, 10)	10	50 ref	÷		5	55 ref	÷			
[10, 14)	13	63 0.79	•	0.54	5	71 0.66	•	0.42		
[14, 18)	16	29 1.53	٠	0.31	8	37 1.32	٠	0.59		
[18, 27)	16	38 1.11	٠	0.80	11	43 1.37	•	0.52		

	Outcome								
Charactoristic	F vn ^a	IMV (r Unovn aOP	n=85)	n	Fyn	Death (n=51) $U_{\text{Deave}} = 05\%$ CL = 7			
[27 157]	Елр 27	32 2 19	, , , , , , , , , , , , , , , , , , ,	Р 0.041	Ехр 20	39 2 44	, , , , , , , , , , , , , , , , , , ,	р 0.048	
Creatinine, mg/dL	82	212	:	0.011	49	245	:	0.010	
[0.33, 0.81)	17	49 ref	ė		9	57 ref	ė		
[0.81, 0.95)	8	47 0.51	•	0.13	4	51 0.47		0.18	
[0.95, 1.20)	16	43 0.96	•	0.91	8	51 1.12	•	0.81	
[1.20, 1.65)	18	43 0.89	•	0.75	12	49 1.16	+	0.74	
[1.65,23.57]	23	30 2.23	•	0.03	16	37 1.89	-	0.15	
Sodium, mEq/L	82	212	•		50	245	•		
[121,135)	29	49 ref	÷		12	66 ref	÷	X	
[135,136)	16	43 0.72	•	0.37	6	53 0.74	÷	0.55	
[136,139)	14	46 0.92	•	0.82	6	54 1.10	+	0.83	
[139,141)	8	40 0.41	•	0.041	8	40 1.22		0.68	
[141,155]	15	34 0.76	•	0.49	17	32 2.09	-	0.09	
Potassium, mEq/L	82	212	•		49	245			
[2.8,3.6)	21	42 ref	ė		16	47 ref	÷		
[3.6,3.9)	17	56 0.80	٠	0.54	10	63 0.64	•	0.30	
[3.9,4.2)	12	46 0.78	•	0.53	9	49 0.92	•	0.85	
[4.2,4.5)	10	38 0.67	•	0.36	5	43 0.42	•	0.11	
[4.5,6.1]	22	30 1.40	•	0.39	9	43 0.58	•	0.26	
Alanine aminotransferase, U/L	73	194			42	225	_		
[3, 16)	16	53 ref			13	56 ref			
[16, 21)	8	42 0.79	<u>_</u>	0.61	4	46 0.53	•	0.24	
[21, 30)	21	38 1.61	٠	0.22	11	48 0.93	•	0.87	
[30, 45)	8	31 1.08	•	0.85	4	35 0.77	-	0.57	
[45,1802]	20	30 2.78	•	0.008	10	40 1.56	•	0.29	
Aspartate aminotransferase, U/L	73	194			42	225			
[10.0, 22.0)	10	56 ref	•		6	60 ref	•		
[22.0, 30.0)	12	52 1.12	•	0.79	6	58 1.00	÷	0.99	
[30.0, 42.0)	21	31 2.68	•	0.02	10	42 1.91	-	0.21	
[42.0, 64.7)	12	28 1.48	•	0.37	10	30 2.06	-	0.15	
[64.7,4581.0]	18	27 3.50	•	0.002	10	35 3.35	-	0.01	
Alkaline phosphatase, IU/L	55	156			33	178			
[6.0, 49.0)	20	44 ref			10	54 ref			
[49.0, 60.1)	13	34 1.14	•	0.73	7	40 1.20	•	0.71	
[60.1, 64.1)	1	9 1.18	٠	0.66	2	8 1.47	•	0.40	
[64.1, 74.0)	9	27 0.64	•	0.26	4	32 0.96	•	0.93	
[74.0,217.0]	12	42 0.63	•	0.26	10	44 1.35	•	0.53	
Total bilirubin, mg/dL	73	193	-		42	224			
[0.200,0.500)	23	73 ref			14	82 ref	÷		
0.500	12	40 0.88	٠	0.76	10	42 1.42	•	0.42	
[0.532,0.607)	6	29 1.10	٠	0.80	3	32 1.11	+	0.81	
[0.607,0.800)	13	12 2.27	٠	0.04	4	21 1.35	•	0.52	

Characteristic	Outcome										
		IMV (r	n=85)		Death (n=51)						
	Exp ^a U	nexp aOR	95%CI ^b	р	Exp	Unexp aOR	95%CI	р			
[0.800,3.000]	19	39 1.54	•	0.23	11	47 1.10	•	0.83			

^aExp indicates number of patients with each factor among those who received IMV or died, and unexp indicates number of patients without each factor who received IMV or died. Crude odds ratios can be calculated by standard techniques using these numbers. ^b95% confidence intervals (CI) are displayed on a log-odds scale with the dashed line indicating an adjusted odds ratio (aOR) of 1. Dark

blue indicates a CI entirely <1 (i.e., statistically significant), light blue indicates an aOR <1 with a CI crossing 1, light red indicates an aOR >1 with a CI crossing 1, and dark red indicates a CI entirely >1.
 ^cBrackets indicate the respective value is included in the interval, and parentheses indicate the value not included in the interval. Laboratory

values were divided into quintiles for analysis.

Alls

Figure: Predictive models of invasive mechanical ventilation (IMV, panel A) death (panel B) in a cohort of 297 patients with completed COVID-19 hospitalizations in the U.S. state of Georgia using machine-derived fast-frugal-trees (FFTs) and cut-points. Green areas describe how well the decision point predicted survival and red areas indicate how well it predicted death. The IMV FFT had overall accuracy of 70%, sensitivity of 60%, and specificity of 74%, and the death FFT had overall accuracy of 78%, and specificity of 74%.

ceeteonicschir



