Characteristics and Outcomes of Mechanically Ventilated COVID-19 Patients—An Observational Cohort Study

Martin Krause, MD¹, David J. Douin, MD¹, Kevin K. Kim, MD¹, Ana Fernandez-Bustamante, MD, PhD¹, and Karsten Bartels, MD, PhD¹,2

Abstract
Background: The United States currently has more confirmed cases of COVID-19 than any other country in the world. Given the variability in COVID-19 testing and prevention capability, identifying factors associated with mortality in patients requiring mechanical ventilation is critical. This study aimed to identify which demographics, comorbidities, markers of disease progression, and interventions are associated with 30-day mortality in COVID-19 patients requiring mechanical ventilation. Methods: Adult patients with a confirmed diagnosis of COVID-19 admitted to one of the health system’s intensive care units and requiring mechanical ventilation between March 9, 2020 and April 1, 2020, were included in this observational cohort study. We used Chi-Square and Mann-Whitney U tests to compare patient characteristics between deceased and living patients and multiple logistic regression to assess the association between independent variables and the likelihood of 30-day mortality. Results: We included 85 patients, of which 20 died (23.5%) within 30 days of the first hospital admission. In the univariate analysis, deceased patients were more likely ≥60 years of age (p < 0.001), non-Hispanic (p = 0.026), and diagnosed with a solid malignant tumor (p = 0.003). Insurance status also differed between survivors and non-survivors (p = 0.019). Age ≥60 and malignancy had a 9.5-fold (95% confidence interval 1.4-62.3, p = 0.020) and 5.8-fold higher odds ratio (95% confidence interval 1.2-28.4, p = 0.032) for 30-day mortality after adjusted analysis using multivariable logistic regression, while other independent variables were no longer significant. Conclusions: In our observational cohort study of 85 mechanically ventilated COVID-19 patients, age, and a diagnosis of a solid malignant tumor were associated with 30-day mortality. Our findings validate concerns for the survival of elderly and cancer patients in the face of the COVID-19 pandemic in the United States, where testing capabilities and preventative measures have been inconsistent. Preventative efforts geared to patients at risk for intensive care unit mortality from COVID-19 should be explored.

Keywords
COVID-19, SARS-CoV-2, acute respiratory distress syndrome, mechanical ventilation

Background
The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide.¹ Patients with COVID-19 have high rates of hospitalization and intensive care unit (ICU) admission.² As of July 11th, 2020, there have been nearly 13 million confirmed cases and more than 500,000 deaths worldwide.³ Notably, the United States has more than 3 million confirmed cases, which is more than any other country and currently exceeds the second-ranked country Brazil by more than 1 million.³

Similar to other coronavirus infections, patients infected with SARS-CoV-2 have a variable clinical course.⁴,⁵ While many patients do not require hospitalization, nearly 8 in 10 hospitalized patients require supplemental oxygen and as many as one-third of these patients require some form of mechanical ventilation.⁵-⁷ Virtually all COVID-19 patients who require mechanical ventilation meet the criteria for acute respiratory distress syndrome (ARDS).⁸,⁹ ARDS is a progressive, life-threatening inflammatory pulmonary process characterized by diffuse alveolar damage and rapid clinical deterioration.⁸,¹⁰ However, clinicians worldwide have noted that COVID-19...
patients have a different disease trajectory than most other ARDS patients.\textsuperscript{2,4,11} Many patient characteristics are known to be associated with an increased risk of a severe disease course. These include hypertension,\textsuperscript{2,5,12} diabetes mellitus,\textsuperscript{12,13} and obesity.\textsuperscript{14,15} Given the variable ability to prevent, test for, and treat COVID-19 in the United States,\textsuperscript{16} understanding of factors associated with mortality in patients requiring scarce critical care and mechanical ventilation resources is highly relevant. We sought to validate findings from other countries by analyzing a COVID-19 patient cohort from a large United States healthcare system. Using an observational cohort study approach, we describe demographics, comorbidities, data on disease progression, interventions, and mortality of patients with a laboratory-confirmed COVID-19 diagnosis that required admission to the ICU and mechanical ventilation. Our hypothesis was that certain demographics, patient characteristics, and differences in disease progression and management would be associated with 30-day mortality.

**Methods**

Institutional Review Board approval (Colorado Multiple Institutional Review Board #20-0677) was obtained, and the requirement for informed consent was waived. Data were collected retrospectively for any events prior to this date and prospectively going forward. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.\textsuperscript{17}

**Aim, Design, and Setting**

The aim of this study was to provide early information on demographics, chronic comorbid conditions, disease progression, and treatment interventions associated with 30-day mortality in a cohort of COVID-19 patients requiring mechanical ventilation in a large United States health care system comprised of 12 hospitals. This study was designed as an observational cohort study using data collected from the electronic health record (EHR) and manual chart review as needed.

**Participants, Covariates, and Outcomes**

All adult patients diagnosed with COVID-19 and admitted to one of the health system’s ICUs, who required mechanical ventilation between March 9, 2020 and April 1, 2020, were eligible for inclusion. Patients were excluded if they were <18 years old and if they or their proxies indicated that they objected to observational data collection for research (Figure 1). Applicable patient demographics were obtained from the medical record. Demographics included: age in years, self-reported gender, body mass index (BMI) in kg/m\textsuperscript{2}, race, ethnicity, and insurance status. Chronic comorbidities were selected based on previously reported findings using pre-existing International Classification of Diseases codes (ICD-9 or ICD-10). These included: cardiac disease, pulmonary disease, hypertension, diabetes mellitus, renal disease, liver disease, and a history of a solid malignant tumor. Important information about disease progression and interventions were collected by manual chart review: time from symptom onset to initial admission, time from initial admission to intubation, the most recent mode of respiratory treatment prior to intubation (nasal cannula, face mask, heated high flow nasal cannula, or non-invasive ventilation), as well as cannulation for veno-venous extracorporeal membrane oxygenation (VV-ECMO), proning, and total days with a positive end-expiratory pressure (PEEP) \(\geq 15\text{ mmHg}\) within the first 30 days of the initial admission for COVID-19. Thirty-day mortality following the first admission for COVID-19 was assessed based on the date of death as recorded in the EHR.

**Statistical Analysis**

We summarized data by means of descriptive statistics. Continuous data were evaluated for normality of distribution using the Kolmogorov-Smirnov test. Univariate comparisons were made using Pearson’s Chi-Square and Mann-Whitney U tests. Next, we checked for an association between patient demographics, comorbidities, information on disease progression, or interventions, and the likelihood of 30-day mortality by fitting a multiple logistic regression model. Based on published findings and the significant results from our univariate results,\textsuperscript{12,14,15,19-21} we included age, BMI, ethnicity, hypertension, diabetes mellitus, insurance status, and a history of a solid malignant tumor as covariates in our model. The software program SPSS, Version 26 (IBM Corporation, Armonk, NY) was used for statistical analysis.

**Results**

We included 85 patients on mechanical ventilation, who had tested positive for COVID-19 in this study. Of these patients, 20 died within 30 days of their index admission (23.5\%). Baseline demographics, patient comorbidities, data about disease progression, and treatment interventions are summarized in Table 1. Deceased patients were more likely \(\geq 60\) years of age vs. younger (40.9\% vs. 4.9\% of these had died, \(p < 0.001\)), diagnosed with a solid malignant tumor vs. not (63.6\% vs. 17.6\% of these had died, \(p = 0.003\)), and non-Hispanic vs. Hispanic (31.0\% vs. 7.4\% of these had died \(p = 0.026\)). Insurance status also differed between survivors and non-survivors: 30-day mortality was 12.5\% for Managed Care, 40.6\% for Medicare, and 14.3\% for Medicaid and others (\(p = 0.019\)). There were no other significant differences in demographics, comorbidities, disease progression, and treatment interventions.

Adjusted results from a multivariable regression model are summarized in Table 2. After adjusting for age, hypertension, insurance status, ethnicity, BMI, diabetes mellitus, and any history of solid malignant tumor, age \(\geq 60\) had 9.5-fold higher odds ratio (95\% confidence interval 1.4-62.3, \(p = 0.020\)) and malignancy had 5.8-fold higher odds ratio (95\% confidence interval 1.2-28.4, \(p = 0.032\)) for 30-day mortality.
Age, malignancy, insurance status, and ethnicity were associated with increased 30-day mortality in mechanically ventilated COVID-19 patients upon univariate analysis. After fitting a multiple logistic regression model, age ≥60 years and malignancy remained associated with 30-day mortality in this United States-based patient cohort. Given that to date, the United States has more confirmed COVID-19 cases than any other country in the world,³ and that the capability to prevent and treat COVID-19 has been variable,¹⁶ our results contribute to the emerging knowledge about the critical care implications of the COVID-19 pandemic. Furthermore, these data confirm our hypothesis that certain patient characteristics would also be associated with increased mortality in our patient sample obtained from a large United States health system.

Similar to our results, initial reports from China and Italy recognized age as a risk factor for increased mortality.²,⁵ Improved protective measures in elderly patients may decrease overall-mortality of COVID-19-infected patients.²² However, which specific protective measures should be recommended for at-risk populations such as the elderly, and the determination and degree to which such interventions lead to reductions of COVID-19 related mortality requires additional research.²³

In addition to older age, patients diagnosed with solid malignant tumors displayed increased mortality. In line with this finding, a retrospective study from Wuhan, China, concluded
Table 1. Patient Demographics, Comorbidities, Data on Progression of Disease, and Interventions.

| Characteristic                                      | All   | Alive | 30-day mortality | p-value |
|-----------------------------------------------------|-------|-------|------------------|---------|
| Total—no.                                           | 85    | 65    | 20               | <0.001  |
| Age—no. (%)                                         |       |       |                  |         |
| ≥ 60 years                                          | 44    | 26    | 18               | 0.809   |
| <60 years                                           | 41    | 39    | 2                |         |
| Gender—no. (%)                                       |       |       |                  | 0.276   |
| Men                                                 | 57    | 46    | 11               |         |
| Women                                               | 28    | 19    | 9                |         |
| Body mass index—no. (%)                             |       |       |                  | 0.019   |
| <30 kg/m²                                           | 30    | 22    | 8                |         |
| ≥30 to <35 kg/m²                                     | 24    | 18    | 6                |         |
| ≥35 kg/m²                                           | 31    | 25    | 6                |         |
| Race—no. (%)                                         |       |       |                  | 0.896   |
| Caucasian or White                                   | 42    | 32    | 10               |         |
| African American or Black                           | 22    | 16    | 6                |         |
| Multiple races or other                              | 21    | 17    | 4                |         |
| Ethnicity—no. (%)                                    |       |       |                  | 0.026   |
| Hispanic                                            | 27    | 25    | 2                |         |
| Not Hispanic                                        | 58    | 40    | 18               |         |
| Insurance status—no. (%)                            |       |       |                  | 0.180   |
| Managed care                                        | 32    | 28    | 4                |         |
| Medicare                                            | 32    | 19    | 13               |         |
| Medicaid, self pay, indigent, or other              | 21    | 18    | 3                |         |
| Chronic cardiac disease—no. (%)                     |       |       |                  |         |
| Yes                                                 | 30    | 20    | 10               | 0.003   |
| No                                                   | 55    | 45    | 10               |         |
| Hypertension—no. (%)                                 |       |       |                  | 0.988   |
| Yes                                                 | 58    | 42    | 16               |         |
| No                                                   | 27    | 23    | 4                |         |
| Chronic pulmonary disease—no. (%)                   |       |       |                  | 0.003   |
| Yes                                                 | 30    | 20    | 10               |         |
| No                                                   | 55    | 45    | 10               |         |
| Diabetes mellitus—no. (%)                            |       |       |                  | 0.003   |
| Yes                                                 | 33    | 25    | 8                |         |
| No                                                   | 52    | 40    | 12               |         |
| Preexisting renal disease—no. (%)                   |       |       |                  | 0.003   |
| Yes                                                 | 24    | 18    | 6                |         |
| No                                                   | 61    | 47    | 14               |         |
| Chronic liver disease—no. (%)                        |       |       |                  | 0.988   |
| Yes                                                 | 15    | 10    | 5                |         |
| No                                                   | 70    | 55    | 15               |         |
| History of solid malignant tumor—no. (%)            |       |       |                  | 0.003   |
| Yes                                                 | 11    | 4     | 7                |         |
| No                                                   | 74    | 61    | 13               |         |
| Days from symptom onset to admission – median (25th percentile; 75th percentile) | 6 (4; 10) | 7 (5; 10) | 5 (2; 9) | 0.154 |
| Hours from admission to intubation – median (25th percentile; 75th percentile) | 33 (5; 76) | 33 (5; 75) | 29 (9; 99) | 0.988 |
| Respiratory therapy prior to intubation—no. (%)     |       |       |                  | 0.731   |
| Nasal cannula                                        | 14    | 12    | 2                |         |
| Face mask                                            | 51    | 38    | 13               |         |
| Heated high flow nasal cannula                       | 16    | 12    | 4                |         |
| Non-invasive ventilation                             | 2     | 1     | 1                |         |
| Unknown                                              | 2     | 2     | 0                |         |
| Days on PEEP ≥ 15 mmHg within 30 days of admission – median (25th percentile; 75th percentile) | 1 (0; 4) | 0 (0; 4) | 2 (0; 6) | 0.154 |
| VV-ECMO within 30 days of admission—no. (%)          |       |       |                  | 0.579   |
| Yes                                                 | 3     | 3     | 0                |         |
| No                                                   | 82    | 62    | 20               |         |
| Proned within 30 days of admission—no. (%)           |       |       |                  | 0.795   |
| Yes                                                 | 51    | 40    | 11               |         |
| No                                                   | 34    | 25    | 9                |         |

The p-values signify exact 2-sided Chi-Square test results for binary outcomes and Mann-Whitney U test results for continuous outcomes. PEEP—positive end-expiratory pressure, VV-ECMO—veno-venous extracorporeal membrane oxygenation.
overall-mortality of COVID-19, but further randomized controlled trials are warranted to confirm this association.

Authors’ Note
MK drafted the manuscript, helped collect the data, and interpret the results. DJD helped interpret the data, and helped draft the manuscript. KKK helped collect the data. AFB helped interpret the data. KB helped draft the manuscript, helped collect the data, performed the analysis, and helped interpret the results. MK, DJD, KKK, AFB, and KB critically reviewed the manuscript and agreed with the final version and findings. All authors read and approved the final manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The Colorado Multiple Institutional Review Board, Aurora, Colorado, U.S.A., approved this study on April 3rd, 2020 (#20-0677), and the requirement for informed consent was waived.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health (NIH), Award Number K23DA040923 to Karsten Bartels. The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The NIH had no involvement in study design, collection, analysis, interpretation of data, writing of the report, or the decision to submit the article for publication.

ORCID iD
Karsten Bartels, MD, PhD @ https://orcid.org/0000-0003-2028-4664

References
1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.
2. Grasselli G, Zaninotto A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020;323(16):1574-1581.
3. The Center for Systems Science and Engineering at Johns Hopkins University. Coronavirus COVID-19 global cases. 2020. Accessed July 11, 2020. https://coronavirus.jhu.edu/map.html
4. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care. 2020;24(1):154.
5. 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):1-11. doi:10.1001/jamainternmed.2020.0994
6. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):1-8. doi:10.1001/jamacardio.2020.1017

Table 2. Multiple Logistic Regression Analysis: Odds Ratio and 95% Confidence Interval for 30-Day Mortality.

| Characteristic                          | Odds ratio | 95% confidence interval | p-value |
|----------------------------------------|------------|-------------------------|---------|
| Age                                    |            |                         |         |
| ≥ 60 years vs <60 years                | 9.451      | 1.433-62.316            | 0.020   |
| Ethnicity                              |            |                         |         |
| Hispanic vs non-Hispanic               | 0.281      | 0.044-1.802             | 0.181   |
| Insurance status                       |            |                         |         |
| Managed Care                           |            | 0.745                   |         |
| Medicare                               | 1.098      | 0.218-5.529             | 0.910   |
| Medicaid                               | 2.064      | 0.294-14.481            | 0.466   |
| Body mass index                        |            |                         |         |
| <30 kg/m²                              |            | 0.855                   |         |
| ≥ 30-35 kg/m²                          | 1.124      | 0.229-5.519             | 0.886   |
| ≥35 kg/m²                              | 1.541      | 0.332-7.155             | 0.581   |
| Hypertension                           | 1.979      | 0.450-8.703             | 0.366   |
| Diabetes mellitus                      | 0.745      | 0.195-2.867             | 0.671   |
| History of solid malignant tumor       | 5.756      | 1.165-28.447            | 0.032   |

For insurance status the reference group is “managed care”.

that cancer patients demonstrate poorer outcomes after COVID-19 infections. Prevention and control measures for patients with cancer are, therefore, warranted.

Our 30-day mortality in a tertiary care center in ventilated patients (23.5%) is lower than previously reported mortality in ventilated patients in Wuhan, China (65.7%), and critically ill patients in Washington State (67%). We speculate that this finding could, in part, reflect a positive correlation between mortality and a heavier healthcare burden in proximity to epicenters of this pandemic, but could also be due to factors such as different follow-up times and modes of data collection.

Limitations
This study has several limitations. We performed an observational study, and unaccounted confounders may be present. However, our study included patients admitted from 12 different hospitals in our health system, which hopefully ensured the diversity of the population studied. Furthermore, results from our Colorado-based study may not be representative of other regions in the United States. Inferences should, therefore, be made with caution. Finally, our study assessed 30-day mortality in only 85 ventilated patients. A larger number of subjects could potentially identify other characteristics or laboratory findings associated with mortality.

Conclusion
In this observational cohort study of 85 COVID-19 positive patients, who required mechanical ventilation, we report an association between age ≥60 years and a history of solid malignancy with 30-day mortality. Improved protective measures in patients of older age and a history of cancer may decrease
7. 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. *Lancet*. 2020;395(10229):1054-1062.
8. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526-2533.
9. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623. doi:10.1016/j.tmaid.2020.101623:101623
10. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2019;7(7):CD004477.
11. Wilson JG, Calfee CS. ARDS subphenotypes: understanding a heterogeneous syndrome. *Crit Care*. 2020;24(1):102.
12. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
13. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020;323(16):1612-1614. doi:10.1001/jama.2020.4326
14. Simonnet A, Chetboun M, Poissy J, et al. Obesity study g. 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.
15. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis*. 2020;71(15):896-897.
16. Shear MD, Goodnough A, Kaplan S, Fink S, Thomas K, Weiland N. The lost month: how a failure to test blinded the U.S. to Covid-19. *New York Times*. March 28, 2020. Accessed April 15, 2020. http://www.nytimes.com/2020/03/28/us/testing-coronavirus-pandemic.html
17. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499.
18. Walkey AJ, Del Sorbo L, Hodgson CL, et al. Higher PEEP versus Lower PEEP strategies for patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(suppl 4):S297-S303.
19. Yancy CW. COVID-19 and African Americans. *JAMA*. 2020;323(19):1891-1892.
20. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31(7):894-901.
21. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med*. 2020;382(26):2534-2543.
22. Pan A, Liu L, Wang C, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. *JAMA*. 2020;323(19):1-9. doi:10.1001/jama.2020.6130
23. Koo JR, Cook AR, Park M, et al. Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study. *Lancet Infect Dis*. 2020;20(6):678-688.
24. Tan J, Yang C. Prevention and control strategies for the diagnosis and treatment of cancer patients during the COVID-19 pandemic. *Br J Cancer*. 2020;123(1):5-6.
25. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. *Lancet Glob Health*. 2020;8(4):e480.
26. Sedgwick P. Bias in observational study designs: case-control studies. *BMJ*. 2015;350:h560.