Surge Effects and Survival to Hospital Discharge in Critical Care Patients with COVID-19 During the Early Pandemic: A Cohort Study

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Abstract

Background

The early months of the COVID-19 pandemic were fraught with much uncertainty and some resource constraint. We assessed the change in survival to hospital discharge over time for intensive care unit patients with COVID-19 during the first three months of the pandemic and the presence of any surge effects on patient outcomes.

Methods

Retrospective cohort study with electronic medical record data of all patients with laboratory-confirmed COVID-19 admitted to intensive care units from February 25, 2020 to May 15, 2020 admitted to intensive care units of 26 hospitals of an integrated delivery system in the Western United States. Patient demographic, comorbidity and severity of illness were measured along with exposure to pharmacologic and medical therapies and hospital outcomes over time. Multivariable logistic regression models were constructed to assess the change in survival to hospital discharge over time during the study period.

Results

Of 620 patients with COVID-19 admitted to the study ICUs (mean age 63.5 years (SD 15.7) and 69% male), 403 (65%) survived to hospital discharge and 217 (35%) died in hospital. Survival to hospital discharge increased over the study period from 60.0% in the first two weeks of patient admission to 67.6% in the last two weeks. In a multivariable logistic regression analysis, the risk-adjusted odds of survival to hospital discharge increased over time (bi-weekly change, adjusted odds ratio [aOR] 1.22, 95%CI 1.04-1.40, \( P = 0.02 \)). Additionally, an a priori-defined explanatory model showed that after adjusting for both hospital occupancy and COVID positive/PUI percent hospital capacity, and the same set of covariates, the temporal trend in risk-adjusted patient survival to hospital discharge remained the same (bi-weekly change, aOR 1.18, 95% CI 1.00 to 1.38, \( P = 0.04 \)) and a greater COVID positive/PUI percentage of hospital capacity remained significantly and inversely associated with survival to hospital discharge (aOR 0.95, 95% CI 0.92 to 0.98, \( P < 0.01 \)).

Conclusions

During the early COVID-19 pandemic, risk-adjusted survival to hospital discharge increased over time for critical care patients. This may have been partially explained by surge affects, as measured by a greater COVID positive/PUI percentage of hospital capacity.

Background

The coronavirus 2019 (COVID-19) global pandemic caused by SARS CoV-2 stressed Intensive Care Units (ICUs) across the world. Initial reports from China featured 83% survival in hospitalized patients, 61% in ICU patients and only 3% in patients receiving mechanical ventilation [1, 2] In the Western United States, where the first US case of COVID-19 was reported, investigators in the Seattle area initially reported approximately 50% survival in ICU patients [3, 4].

During the early months of the COVID-19 pandemic in the United States and Europe many organizations treated “surges” of patients during a time of incomplete understanding of the biology of critical illness related to SARS CoV-2 and a lack of clearly effective COVID-19 specific therapies. Reported data sets in initial publications were often incomplete with half or more of patients lacking hospital outcomes and there was significant uncertainty. [5–7] Social media and pre-print servers like MedRxIV became common and frequently shared sources of information on prognosis, treatments and outcomes. Drug therapy thought to be possibly-effective or touted as effective by political leaders on social medial evolved rapidly over the first several months of the pandemic with much fanfare and limited information. [8–10] There was significant interest in different therapies for hypoxemic respiratory failure, including the utility of delaying or minimizing intubation, using or not using non-invasive positive pressure ventilation and when to use high-flow oxygen. [11, 12] In addition to the ambiguous and evolving clinical situation, the surge nature of the COVID-19 pandemic itself led to resource constraints, rationing in some areas of the world and discussions of crisis standards of care in others and may have adversely affected patient outcomes. [13–15]

With critical care resources, including ventilators, nurses, respiratory therapists and ICU beds, at the center of crisis planning, we were interested changes outcomes of critical care patients with COVID-19 over the first several months of the pandemic. We hypothesized that survival to hospital discharge increased over the initial months of the COVID-19 pandemic in a cohort of COVID-19 positive patients admitted to ICUs of a large integrated delivery system in the Western United States. Additionally, we hypothesized that volume-related “surge effects” may have adversely impacted survival to hospital discharge in COVID-19 positive ICU patients during the initial months of the pandemic.

Methods

Study setting and data collection

We conducted an observational cohort study of all patients with positive SARS CoV-2 polymerase chain reaction assay (COVID-19 positive patients), admitted to an ICU for at least six hours, across twenty-six hospitals in a large healthcare system in the Western United States from February 25, 2020 to May 15, 2020. Data were collected through May 28, 2020 and patients still admitted at the end of the study period were excluded from the study, as were any subsequent readmissions of patients in the cohort. For simplicity of display, patient characteristics and outcomes were summarized in two-week cohorts by date of admission for bivariate analysis and the differences between and trend across the cohorts assessed. For our multivariable models, we modelled admissions by one-week interval for greater precision and report our results on a per-week basis, starting with the first week of the study.
Persons under investigation (PUIs) were defined as those patients in whom a COVID-19 PCR test had been sent, but not yet resulted. We modelled the surge effects of increased hospital volumes in two ways. First, hospital occupancy was defined as inpatient census on day of admission divided by total number of licensed hospital beds. Second, COVID-19 positive/PUI percent hospital capacity was similarly calculated by dividing the sum of COVID-19 positive and PUI censuses on the day of patient admission by number of licensed beds. The day of admission was chosen to summarize volume effects for clarity and reproducibility.

Patient data including socio-demographics, comorbidities, severity of illness, COVID-19 treatments, laboratory, and outcomes data were obtained from the electronic medical record (Epic Systems, Madison, WI). Median household income was imputed from patient's home ZIP code based on 2006–2010 data from the US Census. Treatments were assessed as binary variables depending upon having received one exposure to the treatment. The Sequential Organ Failure Assessment (SOFA) score was calculated based on the most severe values obtained in the first 24 hours of hospitalization. Exposures to drug and oxygen therapies were measured as binary variables based on any exposure to the therapy. Prone therapy included non-intubated proning based on medical record documentation.

**Statistical analysis**

We used descriptive statistics to assess the distribution of all variables of interest. Continuous variables are presented as means or median as appropriate, and categorical variables are presented as frequencies. Comparisons between groups were performed by ANOVA or Kruskal-Wallis rank sum tests for continuous variables, and Chi-squared or Fisher exact tests for categorical variables. If there was significant difference between groups, Jonckheere–Terpstra tests and Chi-squared tests for trend were used to evaluate for temporal trend (ordered differences) across sequential bi-weekly time period for continuous and categorical variables, respectively. To determine the temporal pattern and independent factors for survival to hospital discharge, we used multivariable logistic regression analyses, with admission date modelled on continuous basis. The odds ratios with corresponding 95% confidence intervals were presented.

Variables including time of admission, age, gender, BMI, race, income, smoking status, marital status, comorbidities and SOFA scores were evaluated and selected for adjusted regression based on the literature and a priori associations and informed by the bivariate associations. The linearity of the continuous variables in relation to the logit of the binary outcome (discharged alive, yes vs no), and final model diagnosis were assessed for linearity assumptions and the overall agreement between observed and fitted values.

Robustness of observed temporal trends from the final multivariable model was evaluated with a hierarchical random effects model to account of hospital-level cluster effects. In our a priori explanatory model on surge effects, the trend in the stress on the hospital system, estimated by percentage of hospital beds filled and filled with COVID-19 positive/person under investigation (PUI) patients, and the association of stress on the hospital system with survival to hospital discharge were evaluated. We also further evaluated whether the temporal trend in risk-adjusted patient survival to hospital discharge was explained by the trend in the hospital occupancy and the COVID/PUI percentage capacity, first individually in the multivariable model and then together, with the same set of covariates as in our main model for risk-adjusted survival to hospital discharge. This project was approved by the Swedish Health Services Institutional Review Board. Statistical analyses were performed in R, version 3.6.3 (R Core Team 2020).

**Results**

**Description of the study cohort**

**Patients**

During the study period, 650 patients with COVID-19 were admitted, 13 patients' subsequent readmissions were excluded and 17 (2.7%) patients were excluded as they remained hospitalized at the end of the data collection period. Among the 620 patients in our final analysis cohort, the mean age was 63.5 (SD 15.7) years and did not differ between two-week increments (P = 0.51). 430 (69.4%) were male and the median body mass index (BMI) was 28.2 (IQR 24.3–33.1) with significant difference in BMI among two-week cohorts (P < 0.01). 267 (43.1%) patients self-described their primary race/ethnicity as white and 181 (29.2%) as Hispanic or Latinx and the distribution differed by two-week cohorts (P = 0.01). The mean household median annual adjusted gross income in the patient's home ZIP code was $68,943 (SD $18,019) and differed across two-week cohort (P < 0.01). 31 (5.0%) patients described themselves as current smoked tobacco users and smoking status did not differ significantly across two-week cohort (p = 0.17). 303 (48.9%) patients described themselves as married and there was a significant difference across two-week cohorts in marital status (P = 0.01).

Hypertension by past medical history or problem list entry was present in 195 (31.5%) patients, 174 (28.1%) diabetes and 71 (11.5%) chronic kidney disease of any stage, 277 (44.7%) had no medical comorbidities and the distribution of medical comorbidities was not similar across two-week cohorts (P = 0.04). The mean initial 24-hour SOFA score was 4.0 (SD 3.0) and did not vary significantly across the two-week cohorts (P = 0.10). Additional patient details are summarized by two-week cohort on Table 1.

**Treatments**

321 (51.8%) received hydroxychloroquine but the percentage was not evenly distributed across the two-week cohorts (P < 0.01), with 127 (75.6%) of patients receiving hydroxychloroquine in the second two-week cohort in March 2020 and only 4 (11.8%) in the final cohort in May 2020. 109 (17.6%) patients received remdesivir with significant difference across the two-week cohorts (P = 0.03), with 4 (11.4%) receiving redesivir in the first two-week cohort and 6 (17.6%) in the final two-week cohort. 88 (14.2%) patients received tocilizumab and 28 (4.5%) dexamethasone, neither of which varied significantly across cohorts (P = 0.2 and P = 0.7, respectively).
507 (81.8%) patients were on room air at some point in their hospitalization and 529 (85.3%) patients received nasal cannula at some point and neither therapy differed significantly by two-week cohort \(P = 0.3\) for both. 371 (59.8%) patients underwent mechanical ventilation, with 23 (65.7%) patients during the first two-week cohort and significantly decreasing to 14 (41.2%) by the final two-week cohort \(P < 0.01\) for the trend). Additionally, overall 296 (47.7%) patients received high-flow nasal cannula. There was a significant increase in the use of high-flow oxygen from the first two-week cohort (10 patients, 28.6%) to the final cohort (18 patients, 52.9%; \(P < 0.01\)).

Outcomes

Overall, 403 (65.0%) patients were discharged alive, increased over the study period from 60.0% in the first two weeks of patient admission to 67.6% in the last two weeks (Fig. 1a). Of the 217 patients who died during their hospitalization, 176 (81.1% of deaths) occurred while the patient was in the ICU and 41 (18.9% of deaths) occurred after the patient left the ICU. Of those patients who underwent mechanical ventilation, the median (IQR) time on the ventilator was 9.1 (4.7–14.4) days and this decreased over time across the two-week cohorts \(P = 0.02\). Median duration of ICU stay was 6.2 (2.7–12.5) days and median duration of hospitalization was 12.7 (7.5–21.8) days and both of these varied significantly by two-week cohort \(P < 0.01\) and \(P = 0.01\), respectively). Additional outcomes are shown in Table 2.

Trend and predictors of survival to hospital discharge

Univariate analysis

As shown in Table 3, the odds of being discharged alive increased over time during the study period, not adjusting for other covariates (bi-weekly change, OR 1.14, 95% CI 1.00 to 1.28, \(P = 0.04\)). Year of age (OR 0.94, 95%CI 0.93–0.95, \(P < 0.01\)) and former smoker status (OR 0.51, 95%CI 0.35–0.74, \(P = 0.01\)) were both associated with decreased odds of survival to hospital discharge. Patient-designation of primary race/ethnicity both as Asian (OR 1.98, 95%CI 1.03–3.83, \(P = 0.04\)) and Hispanic/Latino (OR 1.63, 95%CI 1.09–2.43, \(P = 0.02\)) were also associated with greater odds of survival to hospital discharge than White/Caucasian. Household median income based on home ZIP code was associated with survival to hospital discharge ($1000 change, OR 1.02, 95% CI 1.01 to 1.03, \(P < 0.01\)). Hospital occupancy was inversely associated with survival to hospital discharge (OR 0.98, 95% CI 0.97 to 0.99, \(P < 0.01\)). COVID positive/PUI percent hospital capacity was also inversely associated with survival to hospital discharge (OR 0.94, 95% CI 0.92 to 0.97, \(P < 0.01\)).

Multivariable analysis

In the final multivariable logistic regression model, the odds of being discharged alive increased over time throughout the study period, after adjusting for age, gender, BMI, race, income, smoking status, marital status, hypertension, diabetes, chronic kidney disease, coronary artery disease, congestive heart failure, COPD, asthma, and SOFA scores (bi-weekly change, aOR 1.22, 95%CI 1.04–1.420, \(P = 0.02\), Table 3). On average, the risk-adjusted patient survival increased from 60.8% (first two weeks) to 69.5% (last two weeks) over the study period (Fig. 1B). This finding held true after accounting for hospital-level random effects (bi-weekly change, aOR 1.18, 95% CI 1.00 to 1.38, \(P = 0.049\)). Other significant predictors of survival to hospital discharge include greater household median income ($1,000 change, aOR 1.02, 95% CI 1.01 to 1.04, \(P < 0.01\)), age (yearly change, aOR 0.92, 95% CI 0.90 to 0.94, \(P < 0.01\)) and BMI (one-unit change, aOR 0.93, 95% CI 0.90 to 0.96, \(P < 0.01\)).

In our a priori defined explanatory models, greater hospital occupancy and higher COVID positive/PUI percent hospital capacity were each inversely associated with survival to hospital discharge (aOR 0.98, 95% CI 0.97 to 1.00, \(P = 0.04\) and aOR 0.94, 95% CI 0.92 to 0.97, \(P < 0.01\), respectively). After adjusting for both hospital occupancy and COVID positive/PUI percent hospital capacity, and the same set of covariates as in the primary model, the temporal trend in risk-adjusted patient survival to hospital discharge remained the same (bi-weekly change, aOR 1.18, 95% CI 1.00 to 1.38, \(P = 0.04\)). In this model, hospital occupancy was not significantly independently associated with survival to hospital discharge \((P = 0.3)\), however COVID positive/PUI percent hospital capacity remained significantly inversely associated with survival to hospital discharge \((1\%\ \text{increase}, \ aOR\ 0.95,\ \text{95\% CI}\ 0.92\ to\ 0.98,\ \text{P} < 0.01)\).

Discussion

In a large cohort of patients with COVID-19 admitted to the ICU, survival to hospital discharge increased over time during the first three months of the COVID-19 pandemic in the United States. To our knowledge this is one of the most complete reporting of outcomes for COVID patients hospitalized in the ICU with only 17 (2.7%) patients remaining hospitalized at the end of data collection and the first to report outcomes over time. This cohort includes patients from ICUs across the Western United States and is similar in age and sex to those reported previously, includes more Hispanic people than other cohorts and lower burden of many comorbidities, including hypertension and coronary artery disease, which have been associated with COVID-19 survival and were included in our model.[5, 7, 16–20] Additionally, this study supports the previously reported inverse association of age and BMI with survival to hospital discharge.[7, 18, 21] The association between median household income and COVID-19 outcomes also has been reported and may reflect access to care or biases in care delivery.[22] Both BMI and median ZIP code household income were included in our multivariable models.

The exact mechanism by which each week was associated with increased survival to hospital discharge is not clear from our study. Changes in evidence-based therapies over time seem unlikely to have played a significant role. Despite early promising data and initial enthusiasm for hydroxychloroquine, later trials and metaanalysis have not conclusively demonstrated a benefit.[23–27] Our organization was a significant early contributor to remdesivir trial enrollment based on initial data and our experience with the first COVID-19 patient in North America.[4, 28–30] This may have accounted for the 17.6% of patients who received remdesivir in this cohort, which is higher than reported elsewhere.[6, 7] However, changes in remdesivir by-week are unlikely to have caused the improved survival to hospital discharge as later trials and metaanalysis have not definitively shown remdesivir to have an effect on survival to hospital discharge, especially in an ICU cohort.[27, 31, 32] An increase in the use of steroids over time could have contributed to increased survival, but our study period
Acute respiratory distress syndrome (ARDS) volume.

Over the course of the early months of the 2020 COVID-19 pandemic in patients admitted to the ICUs of a large integrated delivery system in the Western

Conclusions

On day of admission and did not attempt to model it in more complex ways. Additional qualitative investigation is needed to address the mechanistic reasons

behaviors of patients, families, providers and care teams over time and imprecision in modelling the surge and we summarized volume simply by the volume

in our explanatory models, our ability to fully explain the change in survival to hospital discharge over time is limited by the lack of more detailed data on

causes of critical illness or respiratory failure. As learning about the biology and clinical course of COVID-19 associated respiratory compromise became more-

earlier transitions to comfort-focused care than we would routinely recommend for other patients with acute respiratory distress syndrome (ARDS) or other

survivability, especially in elderly intubated patients.\[1\] Anecdotally, in some of our critical care teams, this led to discussions with patients and surrogates on

earlier transitions to comfort-focused care than we would routinely recommend for other patients with acute respiratory distress syndrome (ARDS) or other

causes of critical illness or respiratory failure. As learning about the biology and clinical course of COVID-19 associated respiratory compromise became more-
clear, providers may have reverted to anchoring on survivability estimates based on other patients with ARDS in discussions with patients and surrogates and
this change may have been associated with increased survival to hospital discharge. Further work is needed move beyond these hypotheses and to separate
early-pandemic effects from surge effects and their respective independent contributions to survival to hospital discharge.

Limitations

Our study has several important limitations. First, our cohort is from ICUs in the Western United States and may not represent changes in survival to hospital

discharge observed in other regions or countries, as the Western United States had the first cases in America, but less of an intense peak than seen in New

York City or Italy. Thus, the generalizability of our learnings may be limited. Second, we focused on the initial months of the outbreak and extrapolation of our

findings to other points in time are limited. Third, our study looked at patients admitted to the ICU. We focused on the ICU as it is a critical resource constraint

in the pandemic and of great interest to the critical care community. However, it is possible that changes in the severity of illness of patients admitted to the

ICU varied over time. That the SOFA score did not vary over time speaks against this, though there could have been other unmeasured confounders. Fourth, we

were limited by variables we can extract from the electronic medical record and were not able to explore daily patient counts or drug exposures with more

subtlety and it's very possible that more refined variable collection could add additional information. Fifth, we chose to model surge effects in a linear manner,
and it's quite possible that there are threshold effects or that a non-linear relationship both between overall hospital volume or COVID-19/PUI volume may well
exist. Finally, though we tested for independent associations between hospital occupancy percentage and COVID positive/PUI percentage of hospital capacity
in our explanatory models, our ability to fully explain the change in survival to hospital discharge over time is limited by the lack of more detailed data on
behaviors of patients, families, providers and care teams over time and imprecision in modelling the surge and we summarized volume simply by the volume
on day of admission and did not attempt to model it in more complex ways. Additional qualitative investigation is needed to address the mechanic reasons for
the observed changes, especially differentiating early pandemic effects from surge effects.

Conclusions

Over the course of the early months of the 2020 COVID-19 pandemic in patients admitted to the ICUs of a large integrated delivery system in the Western
United States, survival to hospital discharge increased over time. This appears to have been partially explained by the surge effects of increased COVID-19/PUI
volume.

List Of Abbreviations

Acute respiratory distress syndrome (ARDS)
Body mass index (BMI)

Intensive Care Unit (ICU)

Person under investigation (PUI)

Sequential Organ Failure Assessment (SOFA)

**Declarations**

**Ethics approval and consent to participate:**

Waived by IRB approval based on minimal risk.

**Consent for publication:**

N/A

**Availability of data and materials:**

The dataset used during the current study is available from the corresponding author on reasonable request.

**Competing interests:**

No financial or non-financial competing interests exist. All study authors are employees of Providence family of health care delivery organizations.

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**Authors’ contributions:**

CD: Designed the study, participated in the analysis, prepared the manuscript and read and approves the final version.

RS: Designed the study, participated in the analysis, helped prepare the manuscript and read and approves the final version.

SC: Designed the study, participated in the analysis, did the statistical analysis, prepared the manuscript and read and approves the final version.

AR: Designed the study, helped with the analysis and read and approves the final version.

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**References**

1. Wang Y, Lu X, Chen H, Chen T, Su N, Huang F, et al. Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19. Am J Resp Crit Care. 2020;0.

2. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care. 2020;24:188.

3. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. Jama. 2020;323.

4. Holshue ML, DeBolt C, Lindquist S, Lozy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. New Engl J Med. 2020;382:929–36.

5. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. New Engl J Med. 2020;382:929–36.

6. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395:1763–70.
7. Auld SC, Caridi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, et al. ICU and Ventilator Mortality Among Critically Ill Adults With Coronavirus Disease 2019. Crit Care Med. 2020;Published Ahead of Print.

8. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

9. Trump DJ. Donald J. Trump on Twitter: "HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents)...." [Internet]. 2020 [cited 2020 Sep 5]. Available from: https://twitter.com/realdonaldtrump/status/1241367239900778501?

10. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Ag. 2020;56:105949.

11. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. Jama. 2020;323:2329–30.

12. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Ann Intensive Care. 2020;10:78.

13. Carenzo L, Costantini E, Greco M, Barra FL, Rendiniello V, Mainetti M, et al. Hospital surge capacity in a tertiary emergency referral centre during the COVID-19 outbreak in Italy. Anaesthesia. 2020;75:928–34.

14. Aziz S, Arabi YM, Alhazzani W, Evans L, Citerio G, Fischhoff K, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intens Care Med. 2020;46:1303–25.

15. Network NHR. Sars Resource Management and Crisis Standards of Care Overview and Materials [Internet]. 2020 [cited 2020 Sep 5]. Available from: https://nwhrn.org/wp-content/uploads/2020/03/Sars-Resource-Management-and-Crisis-Standards-of-Care-Overview-and-Materials-2020-3-16.pdf

16. Garg S, Kim L, Whitaker M, O’Halloran A, Cummings C, Holstein R, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory Confirmed Coronavirus Disease 2019 COVID-19, 14 States, March 1-30, 2020. Mmwr Morbidity Mortal Wkly Rep. 2020;69:458–64.

17. Piva S, Filippini M, Turia F, Catteneo S, Margola A, Fulvisi SD, et al. Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy. J Cite Care. 2020;58:29–33.

18. Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduz A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020;5:e444–51.

19. Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. Critical Care Lond Engl. 2020;24:219.

20. Borobia AM, Carcas AJ, Amalich F, Alvarez-Sala R, Montserrat J, Quintana M, et al. A cohort of patients with COVID-19 in a major teaching hospital in Europe. Medrxiv. 2020;2020.04.29.20080853.

21. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19 related death using OpenSAFELY. Nature. 2020;584:430–6.

22. Azar KMJ, Shen Z, Romanelli RJ, Lockhart SH, Smits K, Robinson S, et al. Disparities In Outcomes Among COVID-19 Patients In A Large Health Care System In California. Health Affair. 2020;39:1253–62.

23. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14:72–3.

24. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Medrxiv. 2020;2020.03.22.20040758.

25. Magagnoli J, Narendra S, Pereira F, Cummings T, Hardin JW, Sutton SS, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Medrxiv. 2020;2020.04.16.20065920.

26. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-hospital Mortality in Patients With COVID-19 in New York State. Jama. 2020;323:2493–502.

27. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Pardo-Hernandez H, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. Bmj. 2020;370:m2980.

28. Goldman JD, Lye DCS, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. New Engl J Med. 2020;

29. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569–78.

30. Spinner CD, Gottlieb RL, Criner GJ, López JRA, Cattelan AM, Viladomiu AS, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. Jama. 2020;323:2493–502.

31. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569–78.

32. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kallix AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. New Engl J Med. 2020;383:1813–26.

33. Coppo A, Bellani G, Winterton D, Pierro MD, Soria A, Faverio P, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Medicine. 2020;8:765–74.
34. Sartini C, Tresoldi M, Scarpellini P, Tettamanti A, Carcò F, Landoni G, et al. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. Jama. 2020;323:2338–40.

35. Elharrar X, Trigui Y, Dols A-M, Touchon F, Martinez S, Prud'homme E, et al. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. Jama. 2020;323:2336–8.

36. Schünemann HJ, Khabsa J, Solo K, Khamis AM, Brignardello-Petersen R, El-Harakeh A, et al. Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19: A Living Systematic Review of Multiple Streams of Evidence. Ann Intern Med. 2020;173:204–16.

37. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region — Case Series. New England Journal of Medicine [Internet]. 2020;NEJMoa2004500-11. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2004500?articleTools=true

38. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet. 2020;395:1225–8.

39. Vergano M, Bertolini G, Giannini A, Gristina GR, Livigni S, Mistaletti G, et al. Clinical ethics recommendations for the allocation of intensive care treatments in exceptional, resource-limited circumstances: the Italian perspective during the COVID-19 epidemic. Crit Care. 2020;24:165.

Tables
Table 1
Demographic and clinical characteristics of patients.

| Date Range                  | Overall (n = 620) | First Period (n = 35) | Second Period (n = 168) | Third Period (n = 164) | Fourth Period (n = 125) | Fifth Period (n = 94) | Sixth Period (n = 34) | p-value |
|-----------------------------|-------------------|-----------------------|-------------------------|------------------------|------------------------|----------------------|----------------------|---------|
| **Hospital occupancy** (%)<sup>a</sup>, median (IQR) | 54.5 (45.0–63.4)  | 70.7 (63.8–85.8)      | 55.35 (44.1–61.9)       | 48.1 (41.7–55.0)       | 53.7 (43.0–61.1)       | 59.4 (52.8–65.6)       | 61.7 (51.1–72.4)       | <0.001  |
| **COVID-19 positive/ PUI census (%)<sup>b</sup>, median (IQR)** | 9.8 (6.6–14.8)    | 4.7 (1.2–7.7)         | 10.5 (8.0–14.9)         | 12.0 (8.2–15.7)        | 9.2 (5.6–16.7)         | 8.1 (3.9–14.3)         | 7.2 (4.1–9.6)          | <0.001  |
| **COVID-19 positive census (%)<sup>c</sup>, median (IQR)** | 4.6 (1.7–7.7)     | 0.4 (0.0–2.1)         | 2.1 (0.8–4.5)           | 5.6 (3.3–8.2)          | 6.3 (3.4–10.7)         | 5.8 (2.7–10.7)         | 4.9 (1.6–6.8)          | <0.001  |
| **Age (years), mean (SD)** | 63.5 (15.7)       | 63.7 (15.7)           | 63.1 (14.6)             | 63.4 (15.5)            | 65.8 (14.7)            | 61.9 (17.2)            | 61.7 (19.6)            | 0.514   |
| **Male Sex, n (%)**        | 430 (69.4)        | 21 (60.0)             | 119 (70.8)              | 124 (75.6)             | 83 (66.4)              | 58 (61.7)             | 25 (73.5)             | 0.155   |
| **BMI, median (IQR)**      | 28.2 (24.3–33.1)  | 28.3 (23.5–32.5)      | 30.0 (25.8–34.1)        | 27.2 (23.6–31.2)       | 28.1 (24.4–33.9)       | 27.2 (22.9–32.5)       | 28.7 (24.3–35.3)       | 0.002   |
| **Race/ Ethnicity, n (%)** | 267 (43.1)        | 22 (62.9)             | 88 (52.4)               | 54 (32.9)              | 53 (42.4)              | 36 (38.3)             | 14 (41.2)             | 0.012   |
| **Smoking Status, n (%)**  | 368 (59.4)        | 21 (60.0)             | 96 (57.1)               | 102 (62.2)             | 71 (56.8)              | 56 (59.6)             | 22 (64.7)             | 0.170   |
| **Marital Status, n (%)**  | 279 (45.0)        | 13 (37.1)             | 67 (39.9)               | 62 (37.8)              | 65 (52.0)              | 52 (55.3)             | 20 (58.8)             | 0.005   |
| **Hypertension, n (%)**    | 195 (31.5)        | 12 (34.3)             | 50 (29.8)               | 45 (27.4)              | 41 (32.8)              | 36 (38.3)             | 11 (32.4)             | 0.588   |
| **Diabetes, n (%)**        | 174 (28.1)        | 9 (25.7)              | 41 (24.4)               | 51 (31.1)              | 31 (24.8)              | 33 (35.1)             | 9 (26.5)              | 0.420   |
| **Chronic Kidney Disease, n (%)** | 71 (11.5) | 4 (11.4) | 13 (7.7) | 14 (8.5) | 23 (18.4) | 7 (7.4) | 10 (29.4) | 0.001 |
| **Coronary Artery Disease, n (%)** | 53 (8.5) | 5 (14.3) | 13 (7.7) | 12 (7.3) | 11 (8.8) | 7 (7.4) | 5 (14.7) | 0.588 |
| **Congestive Heart Failure, n (%)** | 48 (7.7) | 5 (14.3) | 13 (7.7) | 6 (3.7) | 11 (8.8) | 11 (17.7) | 2 (5.9) | 0.138 |
| **COPD, n (%)**            | 43 (6.9)          | 3 (8.6)               | 11 (6.5)                | 6 (3.7)                | 13 (10.4)              | 8 (8.5)               | 2 (5.9)               | 0.341   |
| **Asthma, n (%)**          | 32 (5.2)          | 4 (11.4)              | 11 (6.5)                | 4 (2.4)                | 9 (7.2)                | 4 (4.3)               | 0 (0.0)               | 0.108   |
| **Cirrhosis, n (%)**       | 9 (1.5)           | 1 (2.9)               | 1 (0.6)                 | 3 (1.8)                | 2 (1.6)                | 2 (2.1)               | 0 (0.0)               | 0.802   |
| **ESRD, n (%)**            | 17 (2.7)          | 0 (0.0)               | 2 (1.2)                 | 4 (2.4)                | 6 (4.8)                | 3 (3.2)               | 2 (5.9)               | 0.319   |
| **Total Comorbidities, n (%)** | 0 | 277 (44.7) | 10 (28.6) | 74 (44.0) | 74 (45.1) | 63 (50.4) | 40 (42.6) | 16 (47.1) | 0.026   |
| **Initial SOFA Score, mean (SD)** | 3.97 (2.99) | 3.34 (2.63) | 3.61 (3.04) | 4.33 (3.02) | 4.16 (2.79) | 3.72 (2.95) | 4.62 (3.48) | 0.104   |
|                   | Overall (n = 620) | First Period (n = 35) | Second Period (n = 168) | Third Period (n = 164) | Fourth Period (n = 125) | Fifth Period (n = 94) | Sixth Period (n = 34) | p-value |
|-------------------|------------------|----------------------|-------------------------|------------------------|-------------------------|----------------------|-----------------------|---------|
| WHO at admission (%) |                  |                      |                         |                        |                         |                      |                       | 0.001   |
| 2                 | 14 (2.3)         | 0 (0.0)              | 3 (1.8)                 | 2 (1.2)                | 4 (3.2)                 | 5 (5.3)              | 0 (0.0)               |         |
| 3                 | 133 (21.5)       | 10 (28.6)            | 38 (22.6)               | 30 (18.3)              | 23 (18.4)               | 26 (27.7)            | 6 (17.6)              |         |
| 4                 | 293 (47.3)       | 18 (51.4)            | 85 (50.6)               | 80 (48.8)              | 56 (44.8)               | 35 (37.2)            | 19 (55.9)             |         |
| 5                 | 62 (10.0)        | 3 (8.6)              | 6 (3.6)                 | 10 (6.1)               | 24 (19.2)               | 17 (18.1)            | 2 (5.9)               |         |
| 6                 | 33 (5.3)         | 3 (8.6)              | 10 (6.0)                | 10 (6.1)               | 5 (4.0)                 | 3 (3.2)              | 2 (5.9)               |         |
| 7                 | 82 (13.2)        | 1 (2.9)              | 26 (15.5)               | 31 (18.9)              | 13 (10.4)               | 6 (6.4)              | 5 (14.7)              |         |
| 8                 | 3 (0.5)          | 0 (0.0)              | 0 (0.0)                 | 1 (0.6)                | 0 (0.0)                 | 2 (2.1)              | 0 (0.0)               |         |

a Inpatient census on day of admission / total number of licensed hospital beds x 100

b Sum of COVID-19 positive and PUI censuses on the day of patient admission / total number of licensed hospital beds x 100

c Sum of COVID-19 positive censuses on the day of patient admission / total number of licensed hospital beds x 100

Table 2
Treatments and (ICU) LOS by two-week cohorts.

| Date Range       | Overall (n = 620) | First Period (n = 35) | Second Period (n = 168) | Third Period (n = 164) | Fourth Period (n = 125) | Fifth Period (n = 94) | Sixth Period (n = 34) | p-value |
|------------------|------------------|----------------------|-------------------------|------------------------|-------------------------|----------------------|-----------------------|---------|
| Hydroxychloroquine, n (%) | 321 (51.8)       | 15 (42.9)            | 127 (75.6)              | 99 (60.4)              | 59 (47.2)               | 17 (18.1)            | 4 (11.8)              | <0.001  |
| Remdesivir, n (%)  | 109 (17.6)       | 4 (11.4)             | 31 (18.5)               | 33 (20.1)              | 11 (8.8)                | 24 (25.5)            | 6 (17.6)              | 0.029   |
| Tocilizumab, n (%) | 88 (14.2)        | 1 (2.9)              | 22 (13.1)               | 27 (16.5)              | 23 (18.4)               | 11 (11.7)            | 4 (11.8)              | 0.220   |
| Dexamethasone, n (%) | 28 (4.5)         | 0 (0.0)              | 10 (6.0)                | 6 (3.7)                | 7 (5.6)                 | 4 (4.3)              | 1 (2.9)               | 0.655   |
| Room Air, n (%)   | 507 (81.8)       | 31 (88.6)            | 145 (86.3)              | 133 (81.1)             | 95 (76.0)               | 75 (79.8)            | 28 (82.4)             | 0.260   |
| Nasal Cannula, n (%) | 529 (85.3)      | 32 (91.4)            | 150 (89.3)              | 141 (86.0)             | 103 (82.4)              | 75 (79.8)            | 28 (82.4)             | 0.252   |
| Mask, n (%)       | 411 (66.3)       | 25 (71.4)            | 119 (70.8)              | 105 (64.0)             | 79 (63.2)               | 60 (63.8)            | 23 (67.6)             | 0.676   |
| CPAP, n (%)       | 78 (12.6)        | 6 (17.1)             | 22 (13.1)               | 23 (14.0)              | 13 (10.4)               | 12 (12.8)            | 2 (5.9)               | 0.709   |
| BIPAP, n (%)      | 87 (14.0)        | 4 (11.4)             | 24 (14.3)               | 16 (9.8)               | 20 (16.0)               | 17 (18.1)            | 6 (17.6)              | 0.448   |
| High-flow Nasal Cannula, n (%) | 296 (47.7)    | 10 (28.6)            | 56 (33.3)               | 86 (52.4)              | 76 (60.8)               | 50 (53.2)            | 18 (52.9)             | <0.001  |
| Mechanical Ventilation, n (%) | 371 (59.8)     | 23 (65.7)            | 131 (78.0)              | 98 (59.8)              | 65 (52.0)               | 40 (42.6)            | 14 (41.2)             | <0.001  |
| Prone Ventilation, n (%) | 356 (57.4)      | 16 (45.7)            | 97 (57.7)               | 97 (59.1)              | 87 (69.6)               | 47 (50.0)            | 12 (35.3)             | 0.002   |
| Duration of Mechanical Ventilation (days), median (IQR) | 9.1 (4.7–14.4)  | 8.6 (3.5–17.0)       | 9.9 (7.0–15.4)         | 7.4 (4.1–12.1)         | 8.9 (3.9–15.9)        | 8.7 (4.0–15.7)       | 3.9 (2.5–9.6)         | 0.018   |
| ICU LOS (days), median (IQR) | 6.2 (2.7–12.5) | 4.8 (3.4–13.7)       | 9.1 (3.5–13.6)         | 6.0 (2.5–11.4)         | 6.2 (2.3–14.1)         | 5.0 (2.6–9.1)        | 4.0 (1.5–7.4)         | 0.004   |
| LOS (days), median (IQR) | 12.7 (7.5–21.8) | 10.7 (7.1–28.4)      | 14.1 (8.1–23.0)        | 13.6 (8.3–22.1)        | 13.4 (7.2–21.6)        | 10.0 (5.9–17.02)     | 8.7 (5.5–16.1)        | 0.009   |
Table 3
Multivariable logistic regression analyses for independent predictors associated with survival to hospital discharge.

|                                    | Univariate Analysis (n = 620) | Multivariable Analysis | Multivariable Analysis* |
|------------------------------------|------------------------------|------------------------|-------------------------|
|                                    | OR   | Lower 95% CI  | Upper 95% CI | p-value | OR   | Lower 95% CI  | Upper 95% CI | p-value | OR   | Lower 95% CI  | Upper 95% CI | p-value |
| Admission date (bi-weekly)         | 1.07 | 1.00         | 1.14         | 0.042    | 1.11 | 1.02         | 1.20         | 0.017    | 1.09 | 1.00         | 1.19         | 0.049   |
| Age (years)                        | 0.94 | 0.93         | 0.95         | <0.001   | 0.92 | 0.90         | 0.93         | <0.001   | 0.91 | 0.89         | 0.93         | <0.001   |
| Male Sex (Reference: Female)       | 0.92 | 0.64         | 1.32         | 0.648    | 0.88 | 0.55         | 1.40         | 0.596    | 0.90 | 0.56         | 1.47         | 0.687   |
| BMI                                | 0.98 | 0.96         | 1.01         | 0.157    | 0.93 | 0.90         | 0.96         | <0.001   | 0.93 | 0.90         | 0.96         | <0.001   |
| Race and Ethnicity (Reference: White or Caucasian) | | | | | | | | | | | |
| Asian                              | 1.98 | 1.03         | 3.83         | 0.041    | 1.46 | 0.66         | 3.21         | 0.349    | 1.24 | 0.53         | 2.91         | 0.619   |
| Black or African American          | 0.86 | 0.41         | 1.83         | 0.702    | 0.67 | 0.28         | 1.63         | 0.378    | 0.58 | 0.23         | 1.46         | 0.243   |
| Hispanic or Latino                 | 1.63 | 1.09         | 2.43         | 0.017    | 0.65 | 0.38         | 1.10         | 0.108    | 0.69 | 0.39         | 1.23         | 0.207   |
| Other/Unknown                      | 2.01 | 1.18         | 3.43         | 0.010    | 1.69 | 0.85         | 3.37         | 0.136    | 1.74 | 0.84         | 3.59         | 0.135   |
| Median Gross Income ($1,000)       | 1.02 | 1.01         | 1.03         | <0.001   | 1.02 | 1.01         | 1.04         | <0.001   | 1.02 | 1.00         | 1.04         | 0.112   |
| Smoking Status (Reference: Never Smoker) | | | | | | | | | | | |
| Current Smoker                     | 1.23 | 0.53         | 2.82         | 0.633    | 1.13 | 0.4          | 3.19         | 0.819    | 1.18 | 0.40         | 3.50         | 0.764   |
| Former Smoker                      | 0.51 | 0.35         | 0.74         | <0.001   | 0.74 | 0.47         | 1.18         | 0.208    | 0.73 | 0.45         | 1.19         | 0.206   |
| Unknown                            | 0.58 | 0.31         | 1.07         | 0.081    | 0.7  | 0.32         | 1.51         | 0.365    | 0.72 | 0.32         | 1.64         | 0.436   |
| Marital Status (Reference: Not married) | | | | | | | | | | | |
| Married                            | 1.23 | 0.87         | 1.72         | 0.241    | 1.49 | 0.97         | 2.3          | 0.067    | 1.50 | 0.95         | 2.38         | 0.081   |
| Unknown                            | 1.72 | 0.8          | 3.67         | 0.165    | 0.84 | 0.33         | 2.18         | 0.727    | 0.88 | 0.32         | 2.40         | 0.804   |
| Hypertension (Reference: No)       | 0.83 | 0.58         | 1.38         | 0.058    | 1.14 | 0.72         | 1.81         | 0.583    | 1.21 | 0.74         | 2.00         | 0.449   |
| Diabetes (Reference: No)           | 0.81 | 0.56         | 1.26         | 0.147    | 0.42 | 0.51         | 1.32         | 0.422    | 0.84 | 0.50         | 1.38         | 0.485   |
| Chronic Kidney Disease (Reference: No) | 0.58 | 0.35         | 0.96         | 0.033    | 1.49 | 0.79         | 2.81         | 0.223    | 1.56 | 0.80         | 3.03         | 0.188   |
| Coronary Artery Disease (Reference: No) | 0.88 | 0.49         | 1.57         | 0.663    | 1.28 | 0.62         | 2.63         | 0.499    | 1.18 | 0.56         | 2.52         | 0.659   |
| Congestive Heart Failure (Reference: No) | 0.46 | 0.26         | 0.84         | 0.011    | 0.70 | 0.34         | 1.44         | 0.338    | 0.78 | 0.37         | 1.65         | 0.523   |
| COPD (Reference: No)               | 0.6  | 0.32         | 1.11         | 0.104    | 0.90 | 0.41         | 2.00         | 0.804    | 0.90 | 0.39         | 2.09         | 0.800   |
| Asthma (Reference: No)             | 1.98 | 0.84         | 4.67         | 0.1162   | 0.90 | 0.32         | 2.56         | 0.848    | 0.764| 0.263        | 2.222        | 0.621   |
| Initial SOFA Score                 | 0.83 | 0.78         | 0.88         | <0.001   | 0.83 | 0.77         | 0.89         | <0.001   | 0.820| 0.760        | 0.885<        | 0.001   |

*Mixed effects logistic regression model including admission time, baseline patient characteristics as fixed effects, and a hospital indicator variable as a random effect.