BMJ Open

Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality: A Single-network, Retrospective Cohort Study from Pennsylvania State

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042549
Article Type:	Original research
Date Submitted by the Author:	08-Jul-2020
Complete List of Authors:	Gadhiya, Kinjal; UPMC Pinnacle, Department of Internal Medicine Hansrivijit, Panupong ; UPMC Pinnacle, Department of Internal Medicine Gangireddy, Mounika; UPMC Pinnacle, Department of Internal Medicine Goldman, John; UPMC Pinnacle, Department of Infectious Diseases
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTERNAL MEDICINE, MICROBIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality: A Single-network, Retrospective Cohort Study from Pennsylvania State

Kinjal P. Gadhiya,[1*] Panupong Hansrivijit,[1*] Mounika Gangireddy,[1*] John D. Goldman[2]

*equivalent contribution

[1]Department of Internal Medicine, UPMC Pinnacle, Harrisburg, PA 17104, USA;

kinjal268@gmail.com; hansrivijitp@upmc.edu; g.mounikareddy07@gmail.com

[2]Department of Infectious Diseases, UPMC Pinnacle, Harrisburg, PA 17104, USA;

goldmanjd@upmc.edu

Running title: COVID-19 and Clinical Impact: A Retrospective Study from Pennsylvania State

Correspondence

Panupong Hansrivijit, M.D.

205 South Front Street, Suite 3C

Harrisburg, PA 17104

hansrivijitp@upmc.edu

Keywords: COVID-19, coronavirus, SARS-CoV-2, mortality, acute kidney injury

Word count: 3,623 (excl. title page, abstract, legend, declarations, and references)

Funding: None declared.

Disclosure of Potential Conflicts of Interest: The authors declared no potential conflicts of interest.

ABSTRACT

Objective: Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with highest burden in the United States. Data on clinical characteristics of COVID-19 patients in U.S. population are limited. Thus, we aim to determine the clinical characteristics and risk factors for in-hospital mortality from COVID-19.

Design: Retrospective observational study.

Setting: Single-network hospitals in Pennsylvania state.

Participants: Patients with confirmed SARS-CoV-2 infection who were hospitalized from March 1st to May 31st, 2020.

Primary and secondary outcome measures: Primary outcome was in-hospital mortality. Secondary outcomes were complications, such as acute kidney injury and acute respiratory distress syndrome (ARDS).

Results: Of 283 patients, 19.4% were non-survivors. The mean age of all patients was 64.1 ± 15.9 years. 56.2% were male and 50.2% were white. In adjusted multivariate analyses, increasing age (per 1-year increment; OR 1.075), hypoxia (SpO2 < 95%; OR 4.630), opacity/infiltrate on imaging (OR 3.077), leukocytosis (WBC > 10,000 /uL; OR 2.732), ferritin > 336 ng/mL (OR 4.016), lactate dehydrogenase > 200 U/L (OR 7.752), procalcitonin > 0.25 ng/mL (OR 2.404), troponin I > 0.03 ng/mL (OR 2.242), need for advanced oxygen support other than simple nasal cannula (OR 4.608-13.889), ICU admission/transfer (OR 13.699), renal replacement therapy (OR 21.277), need for vasopressor (OR 22.222), acute respiratory distress syndrome (OR 23.810), hydroxychloroquine (OR 2.165), ascorbic acid (OR 2.101), zinc (OR 3.425), convalescent plasma (OR 3.534), steroids therapy (OR 2.825), respiratory acidosis (OR

7.042), acute kidney injury (OR 3.571) and arrhythmias (OR 2.494) were significant risk factors for increased in-hospital death. The median survival time was 25.0 ± 7.0 days.

Conclusion: We reported the characteristics of ethnically diverse, hospitalized patients with COVID-19 from Pennsylvania state.

Strengths and Limitation of This Study

Strength

- This study is first retrospective cohort study of COVID-19 patients from the state of Pennsylvania
- Our study is among one of few studies that reported the associations between ascorbic acid and zinc supplementation and in-hospital mortality from COVID-19
- Multivariate analysis (binary logistic regression model) was used to report the results

Limitation

- Non-randomized design
- Potential confounding factors should be considered

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has become a pandemic in early 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and rapidly escalated to 216 countries within five months with the highest number of infected cases

in the United States.[1] The reported mortality of COVID-19 in the United States was 5.92% as of May 30th, 2020.[1]

Guan, et al first described the clinical characteristics of 1,099 patients infected with SARS-CoV-2 across China.[2] In this study, the overall mortality was 1.4%. However, the association between clinical risk factors and mortality was not described. Later Du et al and Zhou et al demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA) score, D-dimer > 1 μg/mL, cardiac troponin I ≥ 0.05 ng/mL, and pre-existing concurrent cardiovascular and cerebrovascular diseases were significant predictors for increased mortality from COVID-19.[3 4] However, these findings were primarily based on Chinese population; thus, it has been unconfirmed if the results can be applicable to other patient populations.

As of May 30th, 2020, the Department of Health has announced more than 69,916 confirmed cases of COVID-19 leading to 5,555 deaths in the state of Pennsylvania.[5] To date, the characteristics of infected patients in the United States were reported in the state of Washington (n = 21), California (n = 1,299) and New York (n = 5,700) in chronological order.[6-8] The mortality across the U.S. studies ranged from 6.3 to 24%, depending on the severity of COVID-19. However, clinical risk factors for increased mortality in the U.S. population have not been clearly established.

Clinical management of COVID-19 has been dynamic and variable based on available research, which has largely been *in vitro*, such as a combination of hydroxychloroquine and azithromycin,[9] ascorbic acid,[10] ivermectin,[11] and zinc.[12] These therapies have not been proven beneficial in clinical studies. In the current study, we provide our experience on treatment options for patients infected with SARS-CoV-2.

In this retrospective cohort, we aimed to demonstrate the clinical characteristics of COVID-19 patients, treatment outcomes and the impact on in-hospital mortality. This study is intended to serve as one of the earliest cohorts of COVID-19 patients from the United States.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study from seven hospitals under UPMC Pinnacle network located across the state of Pennsylvania. The protocol of this study has been approved by UPMC Pinnacle Institutional Review Board and UPMC Pinnacle Ethic Committee (#20E024). Written informed consent was waived due to the retrospective, observational nature of the study. Our current study followed the Declaration of Helsinki.

Patient and public involvement

No patient involved.

Data source and patient population

Data were collected by extracting electronic medical records from March 1st to May 31th, 2020 through UPMC Pinnacle COVID-19 registry. Adult patients with age ≥ 18 years who were hospitalized with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalized patients, patients < 18 years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-system transfer and patients enrolled in clinical trials. Transfer within the system was considered one admission. For patients with multiple admissions with study period, the first admission for COVID-19 was reviewed.

Data collection

Individual patient charts were reviewed. Collected data was divided into: demographics, comorbidities, signs and symptoms, laboratory findings, radiographic findings, treatments/interventions, complications and outcomes. *Supplemental Documents 1* summarizes the description of each variable in our cohort.

Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation.[13] Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL (27 μmol/L) or ≥ 1.5 times from the baseline value within 48 hours.[14] Chronic kidney disease (CKD) was defined by the Kidney Diseases Improving Global Outcomes guidelines.[15] Patients with history of end stage kidney disease (ESKD) on dialysis prior to admission, were not counted toward 'requirement of renal replacement therapy (RRT)/hemodialysis (HD)' during the hospital stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.[16] Arrhythmias as complications were defined either tachy- or bradyarrhythmia that were new-onset, occurred during hospitalization with COVID-19. In this study, prolongation of QT segment was defined as the QT duration > 500 milliseconds.

Study outcomes

The primary outcome was in-hospital mortality. The secondary outcome included treatment outcomes and complications such as recovery/discharge, AKI, ARDS, arrhythmias, QT prolongation, venous thromboembolism, arterial thrombosis, cerebrovascular events, heart failure, and myocardial infarction.

Statistical analysis

All analyses were conducted using SPSS software version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were reported in percentage for categorical data and in mean ± standard deviation (S.D.) or median (interquartile range; IQR) depending the data distribution.

Comparisons of outcomes for each variable were evaluated using Pearson's χ^2 tests or Fisher-Exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher-Exact tests were opted if the total sample in any cell count was less than five. A p-value less than 0.05 is considered statistically significant.

Logistic regression analysis

Clinical risk factors that were significant from standard analyses were included in univariate binary logistic regression analysis. Odds ratios (OR) were reported along with 95% confidence interval (CI). An 95% CI greater than 1.0 or less than 1.0 is considered statistically significant. Variables that remained statistically significant on univariate analysis were included in multivariate analysis using logistic regression method to adjust for other covariates. For the analyses of overall mortality predictors, Model 1 was adjusted for age, sex, ethnicity and obesity. Model 2 was adjusted for age, sex, ethnicity, obesity and need for oxygen therapy. Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/chronic obstructive pulmonary disease (COPD) and need for oxygen therapy. Model 4 is adjusted for age, sex, ethnicity, obesity, CKD and need for oxygen therapy. Model 5 is adjusted for age, sex, ethnicity, obesity, coronary artery disease, heart failure and history of arrhythmia/conduction disorder.

Sensitivity analysis

The goodness-of-fit tests of logistic regression analyses were evaluated by Hosmer-Lemeshow method. The validity and sustainability of the significant results from multivariate analysis were tested using the bootstrap method to estimate the end point with imputed sample size of 1,000.

Survival analysis

Kaplan-Meier analysis was used to present the survival by plotting between cumulative survival against hospital stay in all included patients and in patients requiring ICU.

RESULTS

Baseline characteristics and patient outcomes

The flowchart of data selection from the UPMC Pinnacle COVID-19 registry is depicted in *Figure 1*. A total of 322 patients with confirmed SARS-CoV-2 infection were identified during the study period. Of 322 patients, 39 patients (12.1%) were outpatient and did not require hospitalization. After excluding these patients, 283 patients were included for further analysis. *Table 1* summarizes the demographics and baseline characteristics of included patients. All patients had confirmed SARS-Cov-2 infection by RT-PCR. Of 283 patients, 80.6% were survivors and 19.4% were non-survivors. The mean age of all patients was 64.1 ± 15.9 years. 56.2% were male and 50.2% were Caucasian. Non-survivors were significantly older and had higher proportion of hypertension, CKD and had lower mean eGFR. Moreover, hypoxia on presentation, rales/crackles on physical examination, leukocytosis, lymphocytopenia, respiratory acidosis, transaminitis, and opacity/infiltrate on imaging were common presentations in non-survivors. Higher inflammatory markers, such as D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive protein, and procalcitonin were significantly prevalent in deceased patients. The need for oxygen therapy regardless of the mode of oxygen delivery was higher among those who did not survive. Furthermore, non-survivors were more likely to have received intensive care unit (ICU) admission/transfer, extracorporeal membrane oxygenation (ECMO), RRT, use of vasopressors, use of antibiotics, azithromycin, hydroxychloroquine, steroids, ascorbic acid, zinc, tocilizumab and convalescent plasma. Of overall complications, the prevalence of AKI, ARDS, arrhythmias

and superimposed bacteremia was significantly higher in non-survivors. There was no significant difference in mean hospital stay between survivors and non-survivors. Up to 78.8% recovered or were discharged from the hospital. Only two patients remained hospitalized as of June 18, 2020. The mean hospital stay was similar between patients who received remdesivir vs. those who did not (9.0 ± 4.7 and 7.6 ± 7.8 days, respectively; p = 0.359). In contrast, patients who received tocilizumab had significantly longer hospital stay compared to those who did not receive tocilizumab (15.3 ± 11.7 and 7.4 ± 7.2 days, respectively; p < 0.001).

Univariate analysis

All factors except superimposed bacteremia remained significant on univariate analysis. The OR of each clinical predictor for overall in-hospital mortality is depicted in *Table 2*. Logistic regression analysis cannot be performed on the following variables: D-dimer (> 500 ng/mL), C-reactive protein (> 1 mg/dL), and the need for ECMO as at least one cell count was zero. Moreover, in a univariate analysis, we found that hydroxychloroquine treatment was associated with increased risk of QT prolongation (OR 3.401; 95%CI 1.473-7.874; p = 0.002).

Multivariate analysis

Variables that were significant on univariate analysis were included in multivariate logistic regression analysis (*Table 3*). In Model 1 (adjusted for age, sex, ethnicity, and obesity), increasing patient age, hypoxia, opacity/infiltrate on imaging, leukocytosis, ferritin > 336 ng/mL, LDH (> 200 U/L), procalcitonin > 0.25 ng/mL, troponin I > 0.03 ng/mL, use of high-flow oxygen nasal cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for increased in-hospital mortality. In Model 2 (adjusted for all variables in Model 1 including the need for oxygen therapy), hydroxychloroquine, ascorbic acid, zinc, and convalescent plasma were

associated with increased mortality. In Model 3 (adjusted for all variables in Model 2 including asthma/COPD), respiratory acidosis and steroid therapy were associated with increased mortality. AKI and arrhythmias were independent risk factors for in-hospital mortality from COVID-19 from Model 4 and 5, respectively. Moreover, we also found that hydroxychloroquine therapy was associated with QT prolongation (OR 2.874; 95% CI 1.189-6.944; p = 0.019) after adjusted for covariates in Model 2. The association of these variables and overall mortality remained significant on bootstrap analysis when the sample size was imputed to 1,000.

Cohort of critically ill patients

A total 89 patients required intensive care during the study period. Of which, 47.2% died. The demographics and clinical characteristics of critically ill patients are demonstrated in *Table 4*. Deceased ICU patients had significantly higher proportion of AKI and ARDS compared to survived ICU patients. The treatments were similar between survivors and non-survivor patients. In multivariate analysis, AKI (OR 3.759, 95% CI 1.342-10.526; p = 0.012) and ARDS (OR 7.937; 95% CI 2.857-21.739; p < 0.001) are significantly predictive of in-hospital mortality among patients admitted the ICU after adjusted for age, sex, and ethnicity.

Survival analysis

Survival analysis was evaluated using Kaplan-Meier curve (*Figure 2*). In our analysis, the cumulative survival declined with increasing length of hospital stay. The median survival time was 25.0 days with standard error of 7.0.

DISCUSSION

In this single-network, retrospective observation study, we found that the overall in-hospital mortality among hospitalized COVID-19 patients was 19.4%. The reported mortality

among Chinese cohorts ranged from 11.7% to 28.2%.[3 4 17] However, our reported mortality rates appeared slightly lower than what previously described from New York City.[8] Richardson et al found that the overall mortality of 5,700 hospitalized COVID-19 patients from 12 hospitals in New York City was 21%. However, one could argue that our study has significantly smaller sample size which might underestimate the actual mortality of COVID-19. Our data need confirmation from other studies with a larger sample size.

We identified several risk factors for mortality from COVID-19 using multivariate logistic regression analysis. Increasing age, hypoxia and opacity/infiltrate on imaging were associated with higher mortality. Moreover, we also found that patient survival diminished as the disease progressed, reflected by advancement in oxygen delivery (high-flow nasal cannula, NIPPV, and mechanical ventilation). Requiring a simple oxygen nasal cannula did not affect mortality. Such findings are similar to previous literature. Older age is an independent risk factor for severe COVID-19 and mortality.[3 18] In line with Zhou et al, increasing oxygen requirement and need for advanced oxygen delivery were predictive of death from COVID-19.[4]

Here, we showed that COVID-19 patients requiring ICU had 13.7-fold increased risk of mortality. Critically ill patients generally had one or more organs in failure, and an increasing number of organ failure has been linked to elevated death in sepsis patients.[19] For COVID-19 patients, we demonstrated that kidney (AKI, and RRT), pulmonary (respiratory acidosis, and ARDS), cardiovascular (arrhythmias, and vasopressor requirement) failure were predictive of in-hospital mortality. These findings are in line with other cohorts and each factor has been demonstrated as an independent risk factor for mortality in critically ill patients.[4 20-24] Although the complications from SARS-CoV-2 infection can be affected by multiple contributing factors, newer evidence has suggested the significance of cytokine storm leading to multi-organ failure.[25]

Here, we showed that elevated ferritin, LDH, procalcitonin, leukocytosis, troponin I and possibly D-dimer were associated with increased death. Although, the odds ratio for D-dimer cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be ignored. Guan et al first demonstrated the importance of elevated inflammatory markers in COVID-19 in Chinese population[2] which has become a standard monitoring parameter for COVID-19 patients.[26] Elevated inflammatory markers should prompt physicians to evaluate and monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated procalcitonin and leukocytosis may indicate concomitant bacterial infection, which has been shown to increase morbidity and mortality of viral pneumonia.[27] Interestingly, our study showed that elevated troponin I level was associated with significantly higher death similar to a recent meta-analysis.[28] Although the etiologies of elevated troponin levels were not determined in our cohort, other studies proposed several mechanisms for elevated troponin level in COVID-19 patients. These include myocarditis, cytokine mediated myocardial injury, microangiopathy of small coronary arteries, or silent coronary artery disease.[24 28]

The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses or bacteria.[29] Cytokine storm is characterized by the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1β resulting in an increased vascular hyperpermeability, and activation of multiple coagulation pathways.[25 30] In light of SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and the protein C system were impaired during active inflammation.[31] These changes lead to thrombin hyperactivity resulting in the development of microthrombosis, disseminated intravascular coagulation (DIC) and sequential multiorgan failure.[25] Moreover, new studies have

revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are beyond the scope of our article.[32] Such syndromes include macrophage activation syndrome, adult-onset Still's disease, and catastrophic anti-phospholipid syndrome.[32]

Hydroxychloroquine therapy was associated with a 3-fold increased risk of QT prolongation and a 2-fold increased risk of death. The concept of using hydroxychloroquine in COVID-19 patients derived from an early *in vitro* study.[33] The results from small non-randomized clinical trials also showed promising effects on viral load reduction.[34 35] However, the clinical benefit of hydroxychloroquine was debated by a large observation study. Of 1,446 patients, Geleris et al observed that hydroxychloroquine had no effect on the death, length of stay or intubation.[36] Thus, the recommendation for use of hydroxychloroquine was recalled by the Infectious Diseases Society of America (IDSA) due to small sample size in previous clinical trials and concern for cardiac adverse effects, such as QT prolongation/torsade de pointe.[37] Whether hydroxychloroquine has clinical benefits is yet to be discovered in a multi-center randomized controlled trial (NCT04370782).

A meta-analysis of four randomized trials and one retrospective study showed that the administration of intravenous vitamin C has vasopressor sparing effects and may reduce the need for mechanical ventilation in critically ill patients while there was no effect on the mortality.[38] However, given the lack of more supporting evidence, the standard use of ascorbic acid is not yet recommended especially in COVID-19 patients. A new clinical trial investigating the treatment outcome of vitamin C in severe COVID-19 is underway (NCT04264533).

Our study is the first cohort showing that zinc supplementation was associated with increased mortality in COVID-19 patients. A Brazilian study revealed that plasma zinc concentration in critically ill patients upon admission to the ICU was low and may make these

patients more susceptible to oxidative stress.[39] Another prospective study showed that zinc supplementation in mechanically ventilated patients was related to less ventilator-associated pneumonia.[40] However, the mean duration of intubation in this study was prolonged (29 days), making it inconclusive if zinc supplementation can prevent pneumonia development in short-term intubation. Thus, the use of zinc supplementation in COVID-19 patients should be discouraged until supporting evidence from randomized controlled trials is available.

Steroid therapy in COVID-19 patients was associated with increased mortality. However, one limitation that a causal relationship between corticosteroids and mortality was difficult to establish given that our deceased patients had been generally more ill and sustained multi-organ failure, which predisposed them to receive several treatment interventions, including corticosteroids, which could result in significant statistical evaluation. A meta-analysis of 42 randomized controlled trials consisting of 10,194 patients has shown that corticosteroids possibly result in a small reduction in mortality and an increased risk of neuromuscular weakness among critically ill patients with sepsis.[41] However, the theoretical concept for corticosteroid use in COVID-19 was to reduce cytokine storm caused by a reaction to SARS-CoV-2 infection.[42] In early April 2020, the IDSA recommended against a routine use of corticosteroids in the treatment of COVID-19 due to lack of evidence.[37] This guidelines was updated on June 25th, 2020 after the result release of the RECOVERY trial showing that patients who received dexamethasone were more likely to be discharged from hospital at 28 days.[43] Thus, currently, the IDSA panel suggests glucocorticoids use in hospitalized patients with severe COVID-19.[37] Here, our findings contradict with the recommendation from the IDSA. The discrepancy could be resulted from several factor, such as selection bias, confounding bias and small sample size.

Our cohort demonstrated that remdesivir and tocilizumab were not associated with mortality and there was no significant improvement in hospital length of stay between in patients receiving these drugs. Recently, the preliminary report from a phase 3 randomized controlled trial revealed that remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19.[44] Several retrospective studies reported that tocilizumab, an IL-6 inhibitor, was shown to reduce the levels of serum inflammatory markers. However, the impact on clinical improvement and mortality remained inconclusive.[45-47] Although we reported no significant clinical benefits from tocilizumab, the consideration for compassionate use of tocilizumab is not discouraged but rather dependent on the judgment of clinicians based on current evidence. A phase 2 (TOCIVID-19; NCT04317092) and 3 randomized controlled trial (COVACTA; NCT04320615) of tocilizumab is being investigated for the treatment of COVID-19 pneumonia. The preliminary results are expected to release in late 2020.

Similarly, although we found that convalescent plasma was predictive of in-hospital mortality, one important limitation should be considered here. The safety of convalescent plasma was demonstrated in a single-center retrospective cohort of 25 patients[48] and in a preprint, non-peer review report.[49] However, the efficacy of convalescent plasma remained undetermined due to lack of control group. At our institution, convalescent plasma is considered if patients have severe symptoms and have contraindications to remdesivir, such as AKI and hepatic dysfunction. With these complications, the mortality is generally higher resulting in potential selection and confounding bias. The IDSA panel has recommended convalescent plasma only in the context of a clinical trials To date, at least one randomized controlled trila (NCT04342182) is being investigated to establish the clinical benefits in hospitalized patients with severe COVID-19.

From our ICU cohort, AKI and ARDS were the only two variables that were predictive of mortality among patients admitted to the ICU. Interestingly, all treatment measures had no effect on mortality once patients were critically ill and required ICU. This could imply that these treatment interventions might be beneficial if given prior to clinical decompensation or ICU transfer. However, interpretation is restricted due to small sample size and examining only critically ill patients. Our hypothesis should be substantiated by studies from other institutions with larger sample sizes.

Our study has some limitations. The observational design made the results susceptible to selection bias. Analyses could be underpowered given the small sample size. However, we improved the validity of the results by performing bootstrapping analysis. Moreover, due to restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir, and convalescent plasma, which may limit the applicability of our findings. More importantly, mortality can be affected by confounding factors. We minimize this risk by applying multivariate analysis. Most of the collected data were cross sectional, thus, making it difficult to conclude the causality between two variables.

In conclusion, COVID-19 is a serious condition with a significant in-hospital mortality rate. Multiple risk factors for in-hospital death were identified. Hydroxychloroquine, ascorbic acid, zinc supplementation, and corticosteroids therapy were not recommended due to increased mortality risk.

Acknowledgement

We would like to thank UPMC Pinnacle IT support for medical record procurement and Mrs. Yijin Wert for constructing the Kaplan-Meier curves.

Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

Figure 2. Survival analysis by Kaplan-Meier curves. **A)** The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. **B)** ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively (p = 0.002).

DECLARATIONS

Funding: None

Disclosure of Potential Conflicts of Interest: The authors declared no potential conflicts of interest.

Ethics Approval: UPMC Pinnacle Ethic Committee approved this study (#20E024).

Informed Consent: Not applicable.

Data sharing statement: No additional data.

Code availability: Not applicable.

Authors' contributions: K.P.G., P.H., M.G. collected the data. P.H. analyzed the data. K.P.G. and P.H. drafted the manuscript. All authors edited and approved the manuscript for submission.

REFERENCES

1. WHO. Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. *Accessed on June 1st* 2020
2. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine* 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032
3. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020;55(5) doi: 10.1183/13993003.00524-2020 [published Online First: 2020/04/10]
4. 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):1054-62. doi: 10.1016/s0140-6736(20)30566-3 [published Online First: 2020/03/15]
5. Department of Health. COVID-19 Data for Pennsylvania. https://www.health.pa.gov/topics/disease/coronavirus/Pages/Cases.aspx. *Accessed on June 1st*
6. 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):1612-14. doi: 10.1001/jama.2020.4326
7. Myers LC, Parodi SM, Escobar GJ, et al. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. *Jama* 2020 doi: 10.1001/jama.2020.7202 [published Online First: 2020/04/25]
8. 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(20):2052-9. doi: 10.1001/jama.2020.6775 [published Online First: 2020/04/23]
9. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949.
10. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *Jama* 2019;322(13):1261-70. doi: 10.1001/jama.2019.11825 [published Online First: 2019/10/02]
11. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020;178:104787. doi: 10.1016/j.antiviral.2020.104787 [published Online First: 2020/04/07]

12. te Velthuis AJ, van den Worm SH, Sims AC, et al. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010;6(11):e1001176. doi: 10.1371/journal.ppat.1001176 [published Online First: 2010/11/17]
13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006 [published Online First: 2009/05/06]
14. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120(4):c179-84. doi: 10.1159/000339789 [published Online First: 2012/08/15]
15. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009(113):S1-130. doi: 10.1038/ki.2009.188 [published Online First: 2009/08/01]
16. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38(10):1573-82. doi: 10.1007/s00134-012-2682-1 [published Online First: 2012/08/29]
17. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;97(5):829-38. doi: 10.1016/j.kint.2020.03.005 [published Online First: 2020/04/06]
18. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020 doi: 10.1016/j.jaci.2020.04.006 [published Online First: 2020/04/16]
19. Gustot T. Multiple organ failure in sepsis: prognosis and role of systemic inflammatory response. *Curr Opin Crit Care* 2011;17(2):153-9. doi: 10.1097/MCC.0b013e328344b446 [published Online First: 2011/02/25]
20. Elseviers MM, Lins RL, Van der Niepen P, et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care* 2010;14(6):R221. doi: 10.1186/cc9355 [published Online First: 2010/12/03]
21. Martin C, Viviand X, Leone M, et al. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000;28(8):2758-65. doi: 10.1097/00003246-200008000-00012 [published Online First: 2000/08/31]
22. Wang CY, Calfee CS, Paul DW, et al. One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014;40(3):388-96. doi: 10.1007/s00134-013-3186-3 [published Online First: 2014/01/18]
23. Combes A, Costa MA, Trouillet JL, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med* 2003;31(5):1373-81. doi: 10.1097/01.Ccm.0000065188.87029.C3 [published Online First: 2003/05/29]
24. Li J-W, Han T-W, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. *Progress in Cardiovascular Diseases* 2020 doi: https://doi.org/10.1016/j.pcad.2020.04.008
25. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8(6):e46-e47. doi: 10.1016/s2213-2600(20)30216-2 [published Online First: 2020/05/01]

26. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2017;45(12):2078-88. doi: 10.1097/ccm.0000000000002737 [published Online First: 2017/09/25]
27. Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. *Front Microbiol* 2017;8:1041. doi: 10.3389/fmicb.2017.01041 [published Online First: 2017/07/12]
28. Vrsalovic M, Vrsalovic Presecki A. Cardiac troponins predict mortality in patients with COVID-19: A meta-analysis of adjusted risk estimates. *J Infect* 2020 doi: 10.1016/j.jinf.2020.05.022 [published Online First: 2020/05/18]
29. Tisoncik JR, Korth MJ, Simmons CP, et al. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012;76(1):16-32. doi: 10.1128/mmbr.05015-11 [published Online First: 2012/03/07]
30. Meduri GU, Kohler G, Headley S, et al. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. *Chest* 1995;108(5):1303-14. doi: 10.1378/chest.108.5.1303 [published Online First: 1995/11/01]
31. José RJ, Williams AE, Chambers RC. Proteinase-activated receptors in fibroproliferative lung disease. *Thorax* 2014;69(2):190-2. doi: 10.1136/thoraxjnl-2013-204367 [published Online First: 2013/11/05]
32. Colafrancesco S, Alessandri C, Conti F, et al. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? *Autoimmun Rev* 2020;19(7):102573. doi: 10.1016/j.autrev.2020.102573 [published Online First: 2020/05/11]
33. Biot C, Daher W, Chavain N, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem* 2006;49(9):2845-9. doi: 10.1021/jm0601856 [published Online First: 2006/04/28]
34. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends* 2020
35. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949. doi: 10.1016/j.ijantimicag.2020.105949 [published Online First: 2020/03/25]
36. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020;382(25):2411-18. doi: 10.1056/NEJMoa2012410 [published Online First: 2020/05/08]
37. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa478 [published Online First: 2020/04/28]
38. Zhang M, Jativa DF. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. *SAGE Open Med* 2018;6:2050312118807615. doi: 10.1177/2050312118807615 [published Online First: 2018/10/27]
39. Cirino Ruocco MA, Pacheco Cechinatti ED, Barbosa F, Jr., et al. Zinc and selenium status in critically ill patients according to severity stratification. *Nutrition* 2018;45:85-89. doi: 10.1016/j.nut.2017.07.009 [published Online First: 2017/11/14]

40. Hasanzadeh Kiabi F, Alipour A, Darvishi-Khezri H, et al. Zinc Supplementation in Adult Mechanically Ventilated Trauma Patients is Associated with Decreased Occurrence of Ventilator-associated Pneumonia: A Secondary Analysis of a Prospective, Observational Study. *Indian J Crit Care Med* 2017;21(1):34-39. doi: 10.4103/0972-5229.198324 [published Online First: 2017/02/16]
41. Annetta M, Maviglia R, Proietti R, et al. Use of corticosteroids in critically ill septic patients : a review of mechanisms of adrenal insufficiency in sepsis and treatment. *Curr Drug Targets* 2009;10(9):887-94. doi: 10.2174/138945009789108792 [published Online First: 2009/10/06]
42. Scaroni C, Armigliato M, Cannavò S. COVID-19 outbreak and steroids administration: are patients treated for Sars-Cov-2 at risk of adrenal insufficiency? *J Endocrinol Invest* 2020:1-2. doi: 10.1007/s40618-020-01253-1 [published Online First: 2020/04/18]
43. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. *medRxiv* 2020:2020.06.22.20137273. doi: 10.1101/2020.06.22.20137273
44. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2007764
45. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* 2020;92(7):814-18. doi: 10.1002/jmv.25801 [published Online First: 2020/04/08]
46. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* 2020 doi: 10.1002/jmv.25964 [published Online First: 2020/05/06]
47. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* 2020;76:43-49. doi: 10.1016/j.ejim.2020.05.021 [published Online First: 2020/06/03]
48. Salazar E, Perez KK, Ashraf M, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. *Am J Pathol* 2020 doi: 10.1016/j.ajpath.2020.05.014 [published Online First: 2020/05/31]
49. Joyner M, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. *medRxiv* 2020:2020.05.12.20099879. doi: 10.1101/2020.05.12.20099879

Table 1. Demographics and baseline characteristics of included patients.

Characteristics	All patients (n = 283)	Survivors (n = 228)	Non-survivors (n = 55)	P-value
Male	159 (56.2)	125 (54.8)	34 (61.8)	0.348
Age (year)	64.1 (15.9)†	61.9 (15.8)†	72.8 (13.5)†	< 0.001*
Ethnicity				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	0.705
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
Co-morbidities				
Obesity (BMI ≥ 30 kg/m²)	132 (46.6)	102 (44.7)	30 (54.5)	0.191
Current/Former smokers	109 (38.5)	88 (38.6)	21 (38.2)	0.955
Hypertension	189 (66.8)	145 (63.6)	44 (80.0)	0.020*
Diabetes mellitus	108 (38.2)	81 (35.5)	27 (49.1)	0.063
Hyperlipidemia	121 (42.8)	94 (41.2)	27 (49.1)	0.290
Coronary artery disease	50 (17.7)	40 (17.5)	10 (18.2)	0.911
Heart failure/cardiomyopathy	53 (18.7)	40 (17.5)	13 (23.6)	0.299
Arrhythmia/conduction disorders	45 (15.9)	36 (15.8)	9 (16.4)	0.917
Chronic kidney disease	66 (23.3)	46 (20.2)	20 (36.4)	0.011*
End-stage kidney disease	13 (4.6)	12 (5.3)	1 (1.8)	0.474
Asthma/COPD	73 (25.8)	54 (23.7)	19 (34.5)	0.098
Cerebrovascular disease	40 (14.1)	32 (14.0)	8 (14.5)	0.922
Signs and symptoms				

Cough	185 (65.4)	149 (65.4)	36 (65.5)	0.988
Dyspnea	203 (71.7)	158 (69.3)	45 (81.8)	0.064
Hypoxia (SpO2 < 95%)	178 (62.9)	130 (57.0)	48 (87.3)	< 0.001*
Rhinorrhea	29 (10.2)	26 (11.4)	3 (5.5)	0.226
Fever/chills	179 (63.3)	143 (62.7)	36 (65.5)	0.706
Chest pain	35 (12.4)	32 (14.0)	3 (5.5)	0.109
Headache	28 (9.9)	26 (11.4)	2 (3.6)	0.128
Gastrointestinal symptoms	79 (27.9)	68 (29.8)	11 (20.0)	0.145
Asymptomatic	8 (2.8)	8 (3.5)	0 (0)	0.361
Rales/crackles	57 (20.1)	40 (17.5)	17 (30.9)	0.027*
Rhonchi	57 (20.1)	45 (19.7)	12 (21.8)	0.730
Reduced breath sound	63 (22.3)	48 (21.1)	15 (27.3)	0.320
Laboratory findings				
Leukopenia (WBC < 4,000 /uL)	56 (19.8)	46 (20.2)	10 (18.2)	0.739
Leukocytosis (WBC > 10,000 /uL)	80 (28.3)	53 (23.2)	27 (49.1)	< 0.001*
Lymphocytopenia (ALC < 1,000 / uL)	109 (38.7)	78 (34.2)	31 (57.4)	0.002*
Thrombocytopenia (< 140,000 /uL)	57 (20.1)	41 (18.0)	16 (29.1)	0.065
Thrombocytosis (> 400,000 /uL)	31 (11.0)	25 (11.0)	6 (10.9)	0.991
Respiratory acidosis	43 (21.3)	18 (11.8)	25 (50.0)	< 0.001*
Transaminitis (ALT > 3X UNL)	33 (12.4)	21 (9.9)	12 (21.8)	0.017*
Serum creatinine (mg/dL) on admission	1.06 (0.72)‡	1.59 (1.88)†	1.64 (1.15)†	0.808
eGFR (mL/min/1.73m^2)	64.2 (51.0)†	66.7 (35.5)†	53.6 (25.3)†	0.002*
Troponin I (> 0.03 ng/mL)	91 (39.1)	61 (33.0)	30 (62.5)	< 0.001*
Inflammatory markers				
D-dimer (> 500 ng/mL)	135 (80.4)	101 (75.4)	34 (100)	< 0.001*
Ferritin (> 336 ng/mL)	109 (65.3)	78 (59.1)	31 (88.6)	0.001*
Lactate dehydrogenase (> 200 U/L)	108 (73.0)	77 (67.0)	31 (93.9)	0.002*
C-reactive protein (> 1 mg/dL)	152 (87.4)	115 (83.9)	37 (100)	0.005*
Procalcitonin (> 0.25 ng/mL)	73 (47.1)	50 (41.7)	23 (65.7)	0.012*
ST-T change on EKG	84 (31.8)	63 (29.7)	21 (40.4)	0.139
Radiographic findings				
Opacity/infiltrate	209 (73.9)	162 (71.1)	47 (85.5)	0.029*
Ground glass appearance	79 (27.9)	65 (28.5)	14 (25.5)	0.650
Pleural effusion	24 (8.5)	17 (7.5)	7 (12.7)	0.208
Pulmonary congestion	30 (10.6)	23 (10.1)	7 (12.7)	0.568
Oxygen therapy/delivery				
Nasal cannula	207 (73.1)	160 (70.2)	47 (85.5)	0.022*
High-flow nasal cannula	36 (12.7)	18 (7.9)	18 (32.7)	< 0.001*
NIPPV	28 (9.9)	10 (4.4)	18 (32.7)	< 0.001*
Mechanical ventilation	58 (20.5)	25 (11.0)	33 (60.0)	< 0.001*
Intervention				
Intensive care unit	89 (31.4)	47 (20.6)	42 (76.4)	< 0.001*
ECMO	2 (0.7)	0 (0)	2 (3.6)	0.037*
RRT	16 (5.7)	3 (1.3)	13 (23.6)	< 0.001*
Vasopressor	53 (18.7)	19 (8.3)	34 (61.8)	< 0.001*
Antibiotics	220 (77.7)	166 (72.8)	54 (98.2)	< 0.001*
Treatment				
Azithromycin	182 (64.3)	139 (61.0)	43 (78.2)	0.017*
Hydroxychloroquine	67 (23.7)	45 (19.7)	22 (40.0)	0.002*
Steroids	46 (16.3)	26 (11.4)	20 (36.4)	< 0.001*
Ascorbic acid	57 (20.1)	38 (16.7)	19 (34.5)	0.003*
Zinc	54 (19.1)	33 (14.5)	21 (38.2)	< 0.001*
Tocilizumab	12 (4.2)	6 (2.6)	6 (10.9)	0.006*

Convalescent plasma	36 (12.7)	19 (8.3)	17 (30.9)	< 0.001*
Remdesivir	25 (8.8)	20 (8.8)	5 (8.8)	0.940
Complications				
Acute kidney injury	115 (40.6)	75 (32.9)	40 (72.7)	< 0.001*
ARDS	53 (18.7)	17 (7.5)	36 (65.5)	< 0.001*
Arrhythmias	31 (11.0)	18 (7.9)	13 (23.6)	0.001*
QT prolongation	25 (8.8)	18 (7.9)	7 (12.7)	0.257
Venous thromboembolism	10 (3.5)	8 (3.5)	2 (3.6)	1.000
Arterial thrombosis	1 (0.4)	1 (0.4)	0 (0)	1.000
Cerebrovascular event	3 (1.1)	3 (1.3)	0 (0)	1.000
Myocardial infection	5 (1.8)	4 (1.8)	1 (1.8)	1.000
Heart failure	16 (5.7)	11 (4.8)	5 (9.1)	0.219
Superimposed bacteremia	19 (6.7)	12 (5.3)	7 (12.7)	0.047*
Hospital stay (day)	6.0 (7.0)‡	7.4 (7.53)†	9.2 (7.7)†	0.125
Outcome				
Recovery/discharge	223 (78.8)			
Remained hospitalized	2 (0.7)			
Death	55 (19.4)			

ALC, absolute lymphocyte count; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extra-corporal membrane oxygenation; eGFR, estimated glomerular filtration rate; EKG, electrocardiography; IQR, interquartile range; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy; SD, standard deviation; SpO2, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.

*statistically significant

†mean (standard deviation)

‡ median (IQR)

Table 2. Clinical risk factors for overall in-hospital mortality using univariate binary logistic regression analysis.

Characteristics	Odds ratio	95% CI	P-value
Age (per 1-year increment)	1.051	1.028-1.075	< 0.001*
Hypertension	2.288	1.121-4.673	0.024*
Chronic kidney disease	2.262	1.195-4.274	0.012*
Hypoxia (SpO2 < 95%)	5.181	2.242-11.905	< 0.001*
Rales/crackles	2.101	1.080-4.098	0.029*
Leukocytosis (WBC > 10,000 /uL)	3.185	1.727-5.882	< 0.001*
Respiratory acidosis	7.463	3.546-15.625	< 0.001*
Transaminitis (ALT > 3X UNL)	2.538	1.160-5.556	0.020*
eGFR (per 1.0 mL/min/1.73m^2 increment)†	0.988	0.980-0.997	0.011*
D-dimer (> 500 ng/mL)‡	-	-	-
Ferritin (> 336 ng/mL)	5.376	1.789-16.129	0.003*
Lactate dehydrogenase (> 200 U/L)	7.634	1.739-33.333	0.007*
C-reactive protein (> 1 mg/dL)‡	-	-	-
Procalcitonin (> 0.25 ng/mL)	2.681	1.222-5.882	0.014*
Troponin I (> 0.03 ng/mL)	3.390	1.751-6.536	< 0.001*
Opacity/infiltrate on imaging	2.392	1.073-5.348	0.033*
Nasal cannula	2.494	1.120-5.556	0.025*
High-flow nasal cannula	5.682	2.703-11.905	< 0.001*
NIPPV	10.638	4.545-2.500	< 0.001*

Mechanical ventilation	12.195	6.173-23.810	< 0.001*
ICU admission/transfer	12.500	6.173-25.000	< 0.001*
ECMO‡	-	-	-
RRT	23.256	6.329-83.333	< 0.001*
Vasopressor	17.857	8.696-37.037	< 0.001*
Antibiotics	20.000	2.732-142.857	0.003*
Azithromycin	2.294	1.147-4.587	0.019*
Hydroxychloroquine	2.710	1.443-5.102	0.002*
Steroids	4.444	2.237-8.772	< 0.001*
Ascorbic acid	2.639	1.370-5.076	0.004*
Zinc	3.650	1.898-7.042	< 0.001*
Tocilizumab	4.525	1.403-14.706	0.012*
Convalescent plasma	4.921	2.348-10.314	< 0.001*
Acute kidney injury	5.435	2.825-10.417	< 0.001*
ARDS	23.256	11.236-50.000	< 0.001*
Arrhythmia	3.610	1.645-7.937	0.001*
Superimposed bacteremia	2.625	0.982-6.993	0.054

ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy.
*statistically significant
†on admission
‡analyses cannot be performed as at least one cell is zero

Table 3. Clinical predictors for overall in-hospital mortality using multivariate binary logistic regression analysis.

	Statistics		
Characteristics	**Odds ratio**	**95% CI**	**P-value**
Model 1			
Age (per 1-year increment)	1.075	1.045-1.105	< 0.001*
Hypertension	1.264	0.572-2.793	0.562
Chronic kidney disease	1.232	0.590-2.571	0.578
Hypoxia (SpO2 < 95%)	4.630	1.934-1.111	0.001*
Rales/crackles	2.016	0.955-4.255	0.066
Leukocytosis (WBC > 10,000 /uL)	2.732	1.412-5.263	0.003*
Transaminitis (ALT > 3X UNL)	2.137	0.890-5.128	0.089
eGFR (per 1.0 mL/min/1.73m^2 decrement)†	1.002	0.990-1.013	0.795
Ferritin (> 336 ng/mL)	4.016	1.195-13.514	0.025*
Lactate dehydrogenase (> 200 U/L)	7.752	1.639-37.037	0.010*
Procalcitonin (> 0.25 ng/mL)	2.404	1.011-5.714	0.047*
Troponin I (> 0.03 ng/mL)	2.242	1.080-4.673	0.030*
Opacity/infiltrate on imaging	3.077	1.276-7.407	0.012*
Nasal cannula	1.883	0.799-4.444	0.148
High-flow nasal cannula	4.608	2.053-10.309	< 0.001*
NIPPV	7.246	2.899-18.182	< 0.001*

Mechanical ventilation	13.889	6.211-31.250	< 0.001*
ICU admission/transfer	13.699	6.135-30.303	< 0.001*
RRT	21.277	5.025-90.909	< 0.001*
Vasopressor	22.222	9.434-52.632	< 0.001*
Antibiotics	17.544	2.309-125.000	0.006*
ARDS	23.810	10.204-55.556	< 0.001*
Superimposed bacteremia	2.041	0.645-6.452	0.224
Model 2			
Azithromycin	2.058	0.918-4.608	0.080
Hydroxychloroquine	2.165	1.052-4.444	0.036*
Ascorbic acid	2.101	1.007-4.386	0.048*
Zinc	3.425	1.629-7.194	0.001*
Tocilizumab	3.279	0.911-11.765	0.069
Convalescent plasma	3.534	1.527-8.130	0.003*
Model 3			
Respiratory acidosis	7.042	2.915-16.949	< 0.001*
Steroids therapy	2.825	1.305-6.098	0.008*
Model 4			
Acute kidney injury	3.571	1.715-7.407	0.001*
Model 5			
Arrhythmias as complications	2.494	1.002-6.211	0.050*

ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy.
*statistically significant
Model 1 is adjusted for age, sex, ethnicity and obesity
Model 2 is adjusted for age, sex, ethnicity, obesity and need for oxygen therapy
Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/COPD and need for oxygen therapy
Model 4 is adjusted for age, sex, ethnicity, obesity, CKD and need for oxygen therapy
Model 5 is adjusted for age, sex, ethnicity, obesity, CAD, heart failure and history of arrhythmia/conduction disorder

Table 4. Demographics and baseline characteristics of critically ill patients (n = 89).

Characteristics	All patients (n = 89)	Survivors (n = 47)	Non-survivors (n = 42)	P-value
Male	61 (68.5)	30 (63.8)	31 (73.8)	0.365
Age (year)	66.0 (14.2)†	69.1 (12.5)†	63.3 (15.2)†	0.052
Ethnicity				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	
African-American	25 (28.1)	12 (25.5)	13 (31.0)	
Hispanic/Latino	12 (13.5)	8 (17.0)	4 (9.5)	0.685
Asian	5 (5.6)	2 (4.3)	3 (7.1)	
Others	-	-	-	
Treatment				
Azithromycin	69 (77.5)	34 (72.3)	35 (83.3)	0.215
Hydroxychloroquine	42 (47.2)	23 (48.9)	19 (45.2)	0.727
Steroids	39 (43.8)	19 (40.4)	20 (47.6)	0.495
Ascorbic acid	39 (43.8)	22 (46.8)	17 (40.5)	0.548
Zinc	40 (44.9)	21 (44.7)	19 (45.2)	0.958
Tocilizumab	11 (12.4)	5 (10.6)	6 (14.3)	0.750
Convalescent plasma	30 (33.7)	14 (29.8)	16 (38.1)	0.408
Remdesivir	11 (12.4)	6 (12.8)	5 (11.9)	1.000
Complications				
Acute kidney injury	56 (62.9)	22 (46.8)	34 (81.0)	0.001*

ARDS	47 (52.8)	15 (31.9)	32 (76.2)	< 0.001*
Arrhythmias	21 (23.6)	10 (21.3)	11 (26.2)	0.586
QT prolongation	16 (18.0)	10 (21.3)	6 (14.3)	0.391
Venous thromboembolism	5 (5.6)	3 (6.4)	2 (4.8)	1.000
Hospital stay (day)	13.1 (9.6)†	10.4 (8.1)†	15.5 (10.3)†	0.125
Outcome				
Recovery/discharge	43 (48.3)			
Remained hospitalized	2 (2.2)			
Death	42 (47.2)			

ARDS, acute respiratory distress syndrome.
*statistically significant
†mean (standard deviation)

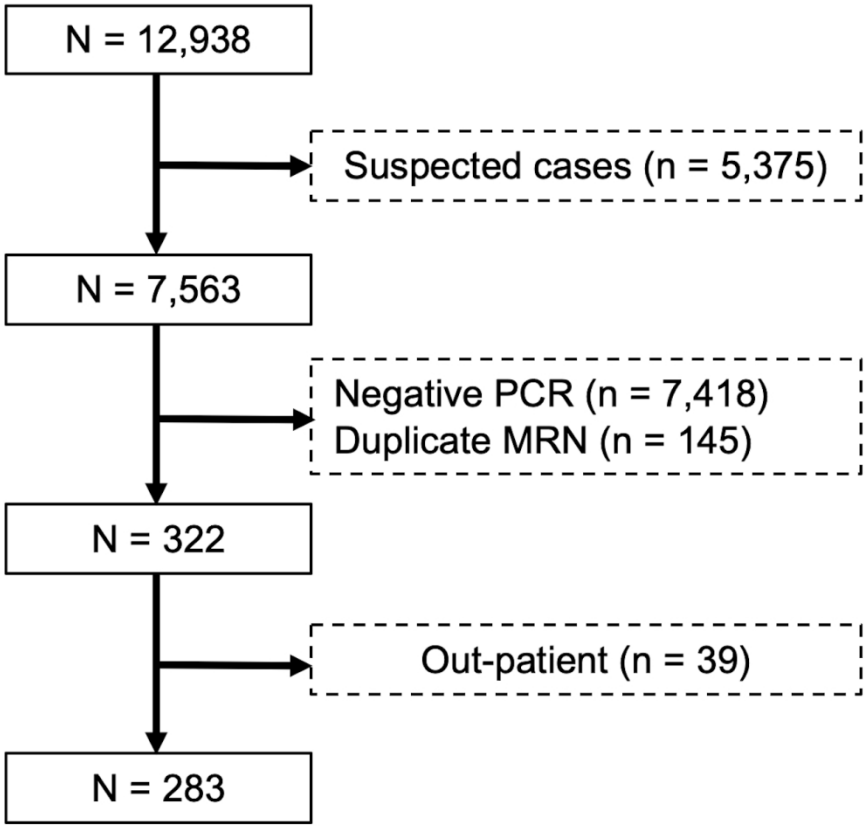

Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

127x117mm (300 x 300 DPI)

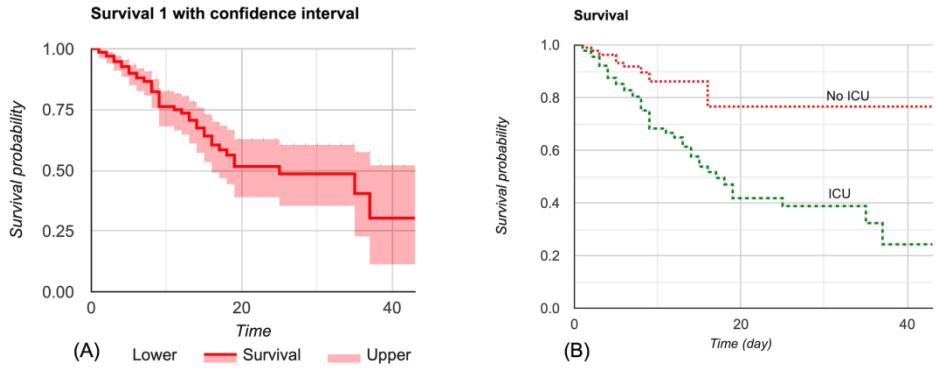

Figure 2. Survival analysis by Kaplan-Meier curves. A) The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. B) ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively (p = 0.002).

203x81mm (300 x 300 DPI)

Data collection (con't):

The demographic data included age, sex, and ethnicity. Co-morbidities included current/prior history of smoking, obesity (BMI ≥ 30 kg/m^2), hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, heart failure/cardiomyopathy, arrhythmia, chronic kidney disease, end-stage kidney disease (ESKD), asthma/chronic pulmonary obstructive disease, and cerebrovascular diseases.

Laboratory findings were recorded: leukocytosis (white blood cells count > 9,500/μL), leukopenia (white blood cells count < 3,900/μL), lymphocytopenia (absolute lymphocytes count < 600/μL), thrombocytosis (platelets > 400,000/μL), and thrombocytopenia (platelets < 140,000/μL), respiratory acidosis (arterial pH < 7.35 and arterial partial pressure of CO_2 > 45 mmHg), transaminitis (alanine transaminase > 3 times of upper normal limit). Serum creatinine (mg/dL) was measured by enzymatic assay. Elevation of serum D-dimer (> 500 ng/mL), ferritin (> 336 ng/mL) lactate dehydrogenase (LDH; > 200 U/L), C-reactive protein (> 1 mg/dL), procalcitonin (> 0.25 ng/mL), and troponin I (> 0.03 ng/mL) were recorded.

BMJ Open

Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality: A Single-network, Retrospective Cohort Study from Pennsylvania State

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042549.R1
Article Type:	Original research
Date Submitted by the Author:	02-Sep-2020
Complete List of Authors:	Gadhiya, Kinjal; UPMC Pinnacle, Department of Internal Medicine Hansrivijit, Panupong ; UPMC Pinnacle, Department of Internal Medicine Gangireddy, Mounika; UPMC Pinnacle, Department of Internal Medicine Goldman, John; UPMC Pinnacle, Department of Infectious Diseases
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTERNAL MEDICINE, MICROBIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality: A Single-network, Retrospective Cohort Study from Pennsylvania State

Kinjal P. Gadhiya,[1*] Panupong Hansrivijit,[1*] Mounika Gangireddy,[1*] John D. Goldman[2]

*equivalent contribution

[1]Department of Internal Medicine, UPMC Pinnacle, Harrisburg, PA 17104, USA;

kinjal268@gmail.com; hansrivijitp@upmc.edu; g.mounikareddy07@gmail.com

[2]Department of Infectious Diseases, UPMC Pinnacle, Harrisburg, PA 17104, USA;

goldmanjd@upmc.edu

Running title: COVID-19 and Clinical Impact: A Retrospective Study from Pennsylvania State

Correspondence

Panupong Hansrivijit, M.D.

205 South Front Street, Suite 3C

Harrisburg, PA 17104

hansrivijitp@upmc.edu

Keywords: COVID-19, coronavirus, SARS-CoV-2, mortality, acute kidney injury

Word count: 3,721 (excl. title page, abstract, legend, declarations, and references)

Funding: None declared.

Disclosure of Potential Conflicts of Interest: The authors declared no potential conflicts of interest.

ABSTRACT

Objective: Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with highest burden in the United States. Data on clinical characteristics of COVID-19 patients in U.S. population are limited. Thus, we aim to determine the clinical characteristics and risk factors for in-hospital mortality from COVID-19.

Design: Retrospective observational study.

Setting: Single-network hospitals in Pennsylvania state.

Participants: Patients with confirmed SARS-CoV-2 infection who were hospitalized from March 1st to May 31st, 2020.

Primary and secondary outcome measures: Primary outcome was in-hospital mortality. Secondary outcomes were complications, such as acute kidney injury and acute respiratory distress syndrome (ARDS).

Results: Of 283 patients, 19.4% were non-survivors. The mean age of all patients was 64.1 ± 15.9 years. 56.2% were male and 50.2% were white. In adjusted multivariate analyses, increasing age (per 1-year increment; OR 1.075), hypoxia (SpO2 < 95%; OR 4.630), opacity/infiltrate on imaging (OR 3.077), leukocytosis (WBC > 10,000 /uL; OR 2.732), ferritin > 336 ng/mL (OR 4.016), lactate dehydrogenase > 200 U/L (OR 7.752), procalcitonin > 0.25 ng/mL (OR 2.404), troponin I > 0.03 ng/mL (OR 2.242), need for advanced oxygen support other than simple nasal cannula (OR 4.608-13.889), ICU admission/transfer (OR 13.699), renal replacement therapy (OR 21.277), need for vasopressor (OR 22.222), acute respiratory distress syndrome (OR 23.810), respiratory acidosis (OR 7.042), and acute kidney injury (OR 3.571).

When critically ill patients were analyzed independently, increasing SOFA score (OR 1.544), AKI (OR 2.128), and ARDS (OR 6.410) were predictive of in-hospital mortality.

Conclusion: We reported the characteristics of ethnically diverse, hospitalized patients with COVID-19 from Pennsylvania state.

Strengths and Limitations of This Study

- Individual patient's chart was reviewed.
- Multivariate analysis (binary logistic regression model) was used to report the results.
- Retrospective, observational design.
- Limited sample size.
- Only hospitalized patients were included in the studies.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has become a pandemic in early 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and rapidly escalated to 216 countries within five months with the highest number of infected cases in the United States.[1] As of August 29th, 2020, the reported cumulated number of confirmed cases in the United States was close to 6 million with a mortality rate of 3.09%.[1]

As of August 29th, 2020, the Pennsylvania Department of Health has announced more than 129,056 confirmed cases of COVID-19 leading to 7,671 deaths, making Pennsylvania the 13th state with the highest confirmed cases.[2] To date, the characteristics of infected patients in the United States were reported in the state of Washington (n = 21), California (n = 1,299) and New York (n = 5,700) in chronological order.[3-5] The mortality across the U.S. studies ranged from 6.3 to 24%, depending on the severity of COVID-19. Although the characteristics of hospitalized COVID-19 patients have been reported in other states, there are some limitations that preclude the generalization of the results toward our patient population. Studies from Washington and California were conducted in pre-remdesivir era and multivariate analysis was not performed in the New York City cohort. The association between clinical characteristics and in-hospital mortality in the U.S. population have not been clearly established.

Guan, et al first described the clinical characteristics of 1,099 patients infected with SARS-CoV-2 across China.[6] In this study, the overall mortality was 1.4%. However, the association between clinical risk factors and mortality was not described. Later Du et al and

Zhou et al demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA) score, D-dimer > 1 μg/mL, cardiac troponin I ≥ 0.05 ng/mL, and pre-existing concurrent cardiovascular and cerebrovascular diseases were significant predictors for increased mortality from COVID-19.[7 8] However, these findings were primarily based on Chinese population; thus, it has been unconfirmed if the results can be applicable to other patient populations.

Clinical management of COVID-19 has been dynamic and variable based on available research, which has largely been *in vitro*, such as a combination of hydroxychloroquine and azithromycin,[9] ascorbic acid,[10] ivermectin,[11] and zinc.[12] These therapies have not been proven beneficial in clinical studies. In the current study, we provide our experience on treatment options for patients infected with SARS-CoV-2.

In this retrospective cohort, we aimed to demonstrate the clinical characteristics of COVID-19 patients, treatment outcomes and the impact on in-hospital mortality in an ethnically diverse population.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study from seven hospitals under UPMC Pinnacle network located across the state of Pennsylvania. The protocol of this study has been approved by UPMC Pinnacle Institutional Review Board and UPMC Pinnacle Ethic Committee (#20E024). Written informed consent was waived due to the retrospective, observational nature of the study. Our current study followed the Declaration of Helsinki.

Patient and public involvement

No patient involvement.

Data source and patient population

Data were collected by extracting electronic medical records from March 1st to May 31th, 2020 through UPMC Pinnacle COVID-19 registry. Adult patients with age ≥ 18 years who were hospitalized with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalized patients, patients < 18 years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-system transfer and patients enrolled in clinical trials. Transfer within the system was considered one admission. For patients with multiple admissions with study period, the first admission for COVID-19 was reviewed.

Data collection

Individual patient charts were reviewed by three independent authors to prevent observer bias. Collected data was divided into: demographics, comorbidities, signs and symptoms, laboratory findings, radiographic findings, treatments/interventions, complications and outcomes. *Supplemental Documents 1* summarizes the description of each variable in our cohort as well as the cutoff values for each variable.

The Sequential Organ failure Assessment (SOFA) score[13] was calculated on the first day of ICU admission. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation.[14] Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL (27 μmol/L) or ≥ 1.5 times from the baseline value within 48 hours.[15] Chronic kidney disease (CKD) was defined by the Kidney Diseases Improving Global Outcomes guidelines.[16] Patients with history of end stage kidney disease (ESKD) on dialysis prior to admission, were not counted toward 'requirement of renal replacement therapy (RRT)/hemodialysis (HD)' during the hospital stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.[17]

Arrhythmias as complications were defined either tachy- or bradyarrhythmia that were new-onset, occurred during hospitalization with COVID-19. In this study, prolongation of QT segment was defined as the QT duration > 500 milliseconds.

Study outcomes

The primary outcome was in-hospital mortality. The secondary outcome included treatment outcomes and complications such as recovery/discharge, AKI, ARDS, arrhythmias, QT prolongation, venous thromboembolism, arterial thrombosis, cerebrovascular events, heart failure, and myocardial infarction.

Statistical analysis

All analyses were conducted using SPSS software version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were reported in percentage for categorical data and in mean ± standard deviation (S.D.) or median (interquartile range; IQR) depending the data distribution. Comparisons of outcomes for each variable were evaluated using Pearson's χ^2 tests or Fisher-Exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher-Exact tests were opted if the total sample in any cell count was less than five. A p-value less than 0.05 is considered statistically significant. Missing data were not included in the analysis.

Logistic regression analysis

Clinical risk factors that were significant from standard analyses (Pearson's χ^2 tests, Fisher-Exact tests, t-tests) were included in univariate binary logistic regression analysis. Odds ratios (OR) were reported along with 95% confidence interval (CI). The analysis is considered statistically significant if the 95% CI crosses 1.0.[18] Variables that remained statistically significant on univariate analysis were included in multivariate analysis using logistic regression method to adjust for other covariates. For the analyses of overall mortality predictors, Model 1 was adjusted

for age, sex, ethnicity and obesity. Model 2 was adjusted for age, sex, ethnicity, obesity and need for oxygen therapy. Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/chronic obstructive pulmonary disease (COPD), the need for oxygen therapy, and ICU admission. Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, the need for oxygen therapy, and ICU admission. Model 5 is adjusted for age, sex, ethnicity, obesity, coronary artery disease, heart failure, history of arrhythmia/conduction disorder, and ICU admission. The rationale for each Model adjustment in multivariate analysis is available in *Supplemental Document 2*.

Sensitivity analysis

The goodness-of-fit tests of logistic regression analyses were evaluated by Hosmer-Lemeshow method. The validity and sustainability of the significant results from multivariate analysis were tested using the bootstrap method to estimate the end point with imputed sample size of 1,000.

Survival analysis

Kaplan-Meier analysis was used to present the survival by plotting between cumulative survival against hospital stay in all included patients and in patients requiring ICU.

RESULTS

Baseline characteristics and patient outcomes

A total of 12,938 patients were identified during the study period. Thirty-nine patients were outpatient and did not require hospitalization. After excluding patients with negative PCR (n = 7,374), duplicate medical records (n = 145), pregnant woman (n = 3), and clinical trial patients (n = 2), 283 patients were included for further analysis. The flowchart of data selection from the UPMC Pinnacle COVID-19 registry is depicted in *Figure 1*. *Table 1* summarizes the demographics

and baseline characteristics of included patients. All patients had confirmed SARS-Cov-2 infection by RT-PCR. Of 283 patients, 80.6% were survivors and 19.4% were non-survivors. The mean age of all patients was 64.1 ± 15.9 years. 56.2% were male and 50.2% were Caucasian. Non-survivors were significantly older and had higher proportion of hypertension, CKD and had lower mean eGFR. Moreover, hypoxia on presentation, rales/crackles on physical examination, leukocytosis, lymphocytopenia, respiratory acidosis, transaminitis, and opacity/infiltrate on imaging were common presentations in non-survivors. Higher inflammatory markers, such as D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive protein, and procalcitonin were significantly prevalent in deceased patients. The need for oxygen therapy regardless of the mode of oxygen delivery was higher among those who did not survive. Furthermore, non-survivors were more likely to have received intensive care unit (ICU) admission/transfer, extracorporeal membrane oxygenation (ECMO), RRT, use of vasopressors, use of antibiotics, azithromycin, hydroxychloroquine, steroids, ascorbic acid, zinc, tocilizumab and convalescent plasma. Of overall complications, the prevalence of AKI, ARDS, arrhythmias and superimposed bacteremia was significantly higher in non-survivors. There was no significant difference in mean hospital stay between survivors and non-survivors. Up to 78.8% recovered or were discharged from the hospital. Only two patients remained hospitalized as of June 18, 2020. The mean hospital stay was similar between patients who received remdesivir vs. those who did not (9.0 ± 4.7 and 7.6 ± 7.8 days, respectively; $p = 0.359$). In contrast, patients who received tocilizumab had significantly longer hospital stay compared to those who did not receive tocilizumab (15.3 ± 11.7 and 7.4 ± 7.2 days, respectively; $p < 0.001$).

Univariate analysis

All factors except superimposed bacteremia remained significant on univariate analysis. The OR of each clinical predictor for overall in-hospital mortality is depicted in *Table 2*. Logistic regression analysis cannot be performed on the following variables: D-dimer (> 500 ng/mL), C-reactive protein (> 1 mg/dL), and the need for ECMO as at least one cell count was zero. Moreover, in a univariate analysis, we found that hydroxychloroquine treatment was associated with increased risk of QT prolongation (OR 3.401; 95%CI 1.473-7.874; p = 0.002).

Multivariate analysis

Variables that were significant on univariate analysis were included in multivariate logistic regression analysis (*Table 3*). In Model 1 (adjusted for age, sex, ethnicity, and obesity), increasing patient age, hypoxia, opacity/infiltrate on imaging, leukocytosis, ferritin > 336 ng/mL, LDH (> 200 U/L), procalcitonin > 0.25 ng/mL, troponin I > 0.03 ng/mL, use of high-flow oxygen nasal cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for increased in-hospital mortality. In Model 2 (adjusted for all variables in Model 1 plus the need for oxygen therapy, and ICU admission), hydroxychloroquine, ascorbic acid, zinc, and convalescent plasma were not associated with increased mortality. In Model 3 (adjusted for all variables in Model 2 plus asthma/COPD), respiratory acidosis was associated with increased mortality. Moreover, AKI was an independent risk factor for in-hospital mortality from COVID-19 from Model 4. In addition, we also found that hydroxychloroquine therapy was associated with QT prolongation (OR 2.874; 95% CI 1.189-6.944; p = 0.019) after adjusted for covariates in Model 2. The association of these variables and overall mortality remained significant on bootstrap analysis when the sample size was imputed to 1,000.

Cohort of critically ill patients

A total 89 patients required intensive care during the study period. Of which, 47.2% died. The demographics and clinical characteristics of critically ill patients are demonstrated in *Table 4*. Deceased ICU patients had significantly higher proportion of AKI and ARDS compared to survived ICU patients. The treatments were similar between survivors and non-survivor patients. In multivariate analysis, each 1-point increment of SOFA score was associated with increased death (OR 1.544; 95% CI 1.168-2.039; p 0.002) after adjusted for age, sex, and ethnicity. Similarly, AKI (OR 2.128, 95% CI 1.111-6.667; p = 0.034) and ARDS (OR 6.410; 95% CI 2.237-18.182; p = 0.023) are significantly predictive of in-hospital mortality among patients admitted the ICU after adjusted for age, sex, ethnicity, and SOFA score.

Survival analysis

Survival analyses were evaluated using Kaplan-Meier curve (*Figure 2*). In our analysis, the cumulative survival declined with increasing length of hospital stay. The median survival time was 25.0 days with standard error of 7.0.

DISCUSSION

In this single-network, retrospective observation study, we found that the overall in-hospital mortality among hospitalized COVID-19 patients was 19.4%. The reported mortality among Chinese cohorts ranged from 11.7% to 28.2%.[7 8 19] However, our reported mortality rates appeared slightly lower than what previously described from New York City.[5] Richardson et al found that the overall mortality of 5,700 hospitalized COVID-19 patients from 12 hospitals in New York City was 21%. However, one could argue that our study has significantly smaller sample size which might underestimate the actual mortality of COVID-19. Our data need confirmation from other studies with a larger sample size.

We identified several risk factors for mortality from COVID-19 using multivariate logistic regression analysis. Increasing age, hypoxia and opacity/infiltrate on imaging were associated with higher mortality. Moreover, we also found that patient survival diminished as the disease progressed, reflected by advancement in oxygen delivery (high-flow nasal cannula, NIPPV, and mechanical ventilation). Requiring a simple oxygen nasal cannula did not affect mortality. Such findings are similar to previous literature. Older age is an independent risk factor for severe COVID-19 and mortality.[7 20] In line with Zhou et al, increasing oxygen requirement and need for advanced oxygen delivery were predictive of death from COVID-19.[8]

Here, we showed that COVID-19 patients requiring ICU had 13.7-fold increased risk of mortality. Critically ill patients generally had one or more organs in failure, and an increasing number of organ failure has been linked to elevated death in sepsis patients.[21] For COVID-19 patients, we demonstrated that kidney (AKI, and RRT), pulmonary (respiratory acidosis, and ARDS), cardiovascular (vasopressor requirement) failure were predictive of in-hospital mortality. These findings are in line with other cohorts and each factor has been demonstrated as an independent risk factor for mortality in critically ill patients.[8 22-26] Although the complications from SARS-CoV-2 infection can be affected by multiple contributing factors, newer evidence has suggested the significance of cytokine storm leading to multi-organ failure.[27]

Here, we showed that elevated ferritin, LDH, procalcitonin, leukocytosis, troponin I and possibly D-dimer were associated with increased death. Although, the odds ratio for D-dimer cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be ignored. Guan et al first demonstrated the importance of elevated inflammatory markers in COVID-19 in Chinese population[6] which has become a standard monitoring parameter for

COVID-19 patients.[28] Elevated inflammatory markers should prompt physicians to evaluate and monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated procalcitonin and leukocytosis may indicate concomitant bacterial infection, which has been shown to increase morbidity and mortality of viral pneumonia.[29] Interestingly, our study showed that elevated troponin I level was associated with significantly higher death similar to a recent meta-analysis.[30] Although the etiologies of elevated troponin levels were not determined in our cohort, other studies proposed several mechanisms for elevated troponin level in COVID-19 patients. These include myocarditis, cytokine mediated myocardial injury, microangiopathy of small coronary arteries, or silent coronary artery disease.[26 30]

The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses or bacteria.[31] Cytokine storm is characterized by the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1β resulting in an increased vascular hyperpermeability, and activation of multiple coagulation pathways.[27 32] In light of SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and the protein C system were impaired during active inflammation.[33] These changes lead to thrombin hyperactivity resulting in the development of microthrombosis, disseminated intravascular coagulation (DIC) and sequential multiorgan failure.[27] Moreover, new studies have revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are beyond the scope of our article.[34] Such syndromes include macrophage activation syndrome, adult-onset Still's disease, and catastrophic anti-phospholipid syndrome.[34]

Hydroxychloroquine therapy was associated with a 3-fold increased risk of QT prolongation but not associated with increased risk of death. The concept of using hydroxychloroquine in COVID-19 patients derived from an early *in vitro* study.[35] The results

from small non-randomized clinical trials also showed promising effects on viral load reduction.[36 37] However, the clinical benefit of hydroxychloroquine was debated by a large observation study. Of 1,446 patients, Geleris et al observed that hydroxychloroquine had no effect on the death, length of stay or intubation.[38] Later, the efficacy of hydroxychloroquine with or without azithromycin has been demonstrated in a recent multicenter, randomized, open-label, controlled trial in hospitalized patients with mild-to-moderate COVID-19.[39] In this study, the authors found that the use of hydroxychloroquine, alone or with azithromycin did not improve the clinical outcome at 15 days compared to the standard treatment. Thus, the recommendation for use of hydroxychloroquine was recalled by the Infectious Diseases Society of America (IDSA) due to small sample size in previous clinical trials and concern for cardiac adverse effects, such as QT prolongation/torsade de pointe.[40]

A meta-analysis of four randomized trials and one retrospective study showed that the administration of intravenous vitamin C has vasopressor sparing effects and may reduce the need for mechanical ventilation in critically ill patients while there was no effect on the mortality.[41] However, given the lack of more supporting evidence, the standard use of ascorbic acid is not yet recommended especially in COVID-19 patients. A new clinical trial investigating the treatment outcome of vitamin C in severe COVID-19 is underway (NCT04264533).

Although our study also showed that zinc supplementation was not associated with increased mortality in COVID-19 patients, the routine use of zinc supplementation could not be supported due to lack of randomized controlled trials. A Brazilian study revealed that plasma zinc concentration in critically ill patients upon admission to the ICU was low and may make these patients more susceptible to oxidative stress.[42] Another prospective study showed that zinc supplementation in mechanically ventilated patients was related to less ventilator-associated

pneumonia.[43] However, the mean duration of intubation in this study was prolonged (29 days), making it inconclusive if zinc supplementation can prevent pneumonia development in short-term intubation.

Steroid therapy in COVID-19 patients was not associated with increased mortality. A meta-analysis of 42 randomized controlled trials consisting of 10,194 patients has shown that corticosteroids possibly result in a small reduction in mortality and an increased risk of neuromuscular weakness among critically ill patients with sepsis.[44] However, the theoretical concept for corticosteroid use in COVID-19 was to reduce cytokine storm caused by a reaction to SARS-CoV-2 infection.[45] In early April 2020, the IDSA recommended against a routine use of corticosteroids in the treatment of COVID-19 due to lack of evidence.[40] This guidelines was updated on June 25th, 2020 after the results of the RECOVERY trial was released showing that patients who received dexamethasone were more likely to be discharged from hospital at 28 days compared to non-steroids group.[46] Thus, currently, the IDSA panel suggests glucocorticoids use in hospitalized patients with severe COVID-19.[40] Here, our study is in line with the recommendation from the IDSA.

We have observed that remdesivir and tocilizumab were not associated with mortality and there was no significant improvement in hospital length of stay between patients receiving these drugs. However, given the observational, non-randomized design of this study, it is difficult to determine the efficacy of such treatment. Recently, the preliminary report from a phase 3 randomized controlled trial revealed that remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19.[47] Several retrospective studies reported that tocilizumab, an IL-6 inhibitor, was shown to reduce the levels of serum inflammatory markers. However, the impact on clinical improvement and mortality remained

inconclusive.[48-50] Although we reported no significant clinical benefits from tocilizumab, the consideration for compassionate use of tocilizumab is not discouraged but rather dependent on the judgment of clinicians based on current evidence. A phase 2 (TOCIVID-19; NCT04317092) and 3 randomized controlled trial (COVACTA; NCT04320615) of tocilizumab is being investigated for the treatment of COVID-19 pneumonia. The preliminary results are expected to release in late 2020.

Similarly, we found that convalescent plasma was not associated with in-hospital mortality. The safety of convalescent plasma was demonstrated in a single-center retrospective cohort of 25 patients[51] and in a preprint, non-peer review report.[52] However, the efficacy of convalescent plasma remained undetermined due to lack of control group. The IDSA panel has recommended convalescent plasma only in the context of a clinical trials. However, at our institution, convalescent plasma is considered if patients have severe symptoms and have contraindications to remdesivir, such as AKI and hepatic dysfunction. Although we did not observe mortality adverse effect from convalescent plasma, the final recommendations on its efficacy and safety are dependent on the randomized controlled trials. To date, at least one randomized controlled trial (NCT04342182) is being investigated to establish the clinical benefits in hospitalized patients with severe COVID-19.

From our ICU cohort, the SOFA score, AKI and ARDS were the only variables that were predictive of mortality among patients admitted to the ICU. Interestingly, all treatment measures had no effect on mortality once patients were critically ill and required ICU. This could imply that these treatment interventions might be beneficial if given prior to clinical decompensation or ICU transfer. However, interpretation is restricted due to small sample size and examining only

critically ill patients. Our hypothesis should be substantiated by studies from other institutions with larger sample sizes.

Our study has some limitations. The observational design made the results susceptible to selection bias. Analyses could be underpowered given the small sample size. However, we improved the validity of the results by performing bootstrapping analysis. Moreover, due to restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir, and convalescent plasma, which may limit the applicability of our findings. More importantly, the mortality can be affected by confounding factors. We minimize this risk by applying multivariate analysis. Most of the collected data were cross sectional, thus, making it difficult to conclude the causality between the two variables. Furthermore, our binary logistic regression analyses may not strictly follow the one-in-ten rule which may lead to over-fitting effect. However, our statistical rationale is supported by newer simulation studies by McCulloch et al.,[53] and Smeden et al.[54] Moreover, we advised the readers to consider their patient population to determine the applicability of our results.

In conclusion, COVID-19 is a serious condition with a significant in-hospital mortality rate. Multiple risk factors for in-hospital death were identified. Increasing SOFA score, AKI and ARDS are significant risk factors for increased death in critically ill patients.

Acknowledgement

We would like to thank UPMC Pinnacle IT support for medical record procurement and Mrs. Yijin Wert for constructing the Kaplan-Meier curves.

Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

Figure 2. Survival analysis by Kaplan-Meier curves. **A)** The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. **B)** ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively (p = 0.002). **C)** The cumulative survival between ICU patients with and without acute respiratory distress syndrome (p = 0.302). **D)** The cumulative survival between ICU patients with and without acute kidney injury (p = 0.504).

DECLARATIONS

Funding: None

Disclosure of Potential Conflicts of Interest: The authors declared no potential conflicts of interest.

Ethics Approval: UPMC Pinnacle Ethic Committee approved this study (#20E024).

Informed Consent: Not applicable.

Data availability: Raw data are available upon reasonable request.

Authors' contributions: K.P.G., P.H., M.G. collected the data. P.H. analyzed the data. K.P.G., P.H., and J.D.G. drafted the manuscript. All authors edited and approved the manuscript for submission.

REFERENCES

1. WHO. Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. *Accessed on August 29th* 2020
2. Department of Health. COVID-19 Data for Pennsylvania. https://www.health.pa.gov/topics/disease/coronavirus/Pages/Cases.aspx. *Accessed on August 29th*
3. 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):1612-14. doi: 10.1001/jama.2020.4326
4. Myers LC, Parodi SM, Escobar GJ, et al. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. *Jama* 2020 doi: 10.1001/jama.2020.7202 [published Online First: 2020/04/25]
5. 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(20):2052-9. doi: 10.1001/jama.2020.6775 [published Online First: 2020/04/23]
6. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine* 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032
7. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020;55(5) doi: 10.1183/13993003.00524-2020 [published Online First: 2020/04/10]
8. 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):1054-62. doi: 10.1016/s0140-6736(20)30566-3 [published Online First: 2020/03/15]
9. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949.
10. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *Jama* 2019;322(13):1261-70. doi: 10.1001/jama.2019.11825 [published Online First: 2019/10/02]

11. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020;178:104787. doi: 10.1016/j.antiviral.2020.104787 [published Online First: 2020/04/07]
12. te Velthuis AJ, van den Worm SH, Sims AC, et al. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010;6(11):e1001176. doi: 10.1371/journal.ppat.1001176 [published Online First: 2010/11/17]
13. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *Jama* 2001;286(14):1754-8. doi: 10.1001/jama.286.14.1754 [published Online First: 2001/10/12]
14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006 [published Online First: 2009/05/06]
15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120(4):c179-84. doi: 10.1159/000339789 [published Online First: 2012/08/15]
16. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009(113):S1-130. doi: 10.1038/ki.2009.188 [published Online First: 2009/08/01]
17. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38(10):1573-82. doi: 10.1007/s00134-012-2682-1 [published Online First: 2012/08/29]
18. Hazra A. Using the confidence interval confidently. *J Thorac Dis* 2017;9(10):4125-30. doi: 10.21037/jtd.2017.09.14
19. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;97(5):829-38. doi: 10.1016/j.kint.2020.03.005 [published Online First: 2020/04/06]
20. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020 doi: 10.1016/j.jaci.2020.04.006 [published Online First: 2020/04/16]
21. Gustot T. Multiple organ failure in sepsis: prognosis and role of systemic inflammatory response. *Curr Opin Crit Care* 2011;17(2):153-9. doi: 10.1097/MCC.0b013e328344b446 [published Online First: 2011/02/25]
22. Elseviers MM, Lins RL, Van der Niepen P, et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care* 2010;14(6):R221. doi: 10.1186/cc9355 [published Online First: 2010/12/03]
23. Martin C, Viviand X, Leone M, et al. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000;28(8):2758-65. doi: 10.1097/00003246-200008000-00012 [published Online First: 2000/08/31]
24. Wang CY, Calfee CS, Paul DW, et al. One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014;40(3):388-96. doi: 10.1007/s00134-013-3186-3 [published Online First: 2014/01/18]
25. Combes A, Costa MA, Trouillet JL, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med*

2003;31(5):1373-81. doi: 10.1097/01.Ccm.0000065188.87029.C3 [published Online First: 2003/05/29]
26. Li J-W, Han T-W, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. *Progress in Cardiovascular Diseases* 2020 doi: https://doi.org/10.1016/j.pcad.2020.04.008
27. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8(6):e46-e47. doi: 10.1016/s2213-2600(20)30216-2 [published Online First: 2020/05/01]
28. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2017;45(12):2078-88. doi: 10.1097/ccm.0000000000002737 [published Online First: 2017/09/25]
29. Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. *Front Microbiol* 2017;8:1041. doi: 10.3389/fmicb.2017.01041 [published Online First: 2017/07/12]
30. Vrsalovic M, Vrsalovic Presecki A. Cardiac troponins predict mortality in patients with COVID-19: A meta-analysis of adjusted risk estimates. *J Infect* 2020 doi: 10.1016/j.jinf.2020.05.022 [published Online First: 2020/05/18]
31. Tisoncik JR, Korth MJ, Simmons CP, et al. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012;76(1):16-32. doi: 10.1128/mmbr.05015-11 [published Online First: 2012/03/07]
32. Meduri GU, Kohler G, Headley S, et al. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. *Chest* 1995;108(5):1303-14. doi: 10.1378/chest.108.5.1303 [published Online First: 1995/11/01]
33. José RJ, Williams AE, Chambers RC. Proteinase-activated receptors in fibroproliferative lung disease. *Thorax* 2014;69(2):190-2. doi: 10.1136/thoraxjnl-2013-204367 [published Online First: 2013/11/05]
34. Colafrancesco S, Alessandri C, Conti F, et al. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? *Autoimmun Rev* 2020;19(7):102573. doi: 10.1016/j.autrev.2020.102573 [published Online First: 2020/05/11]
35. Biot C, Daher W, Chavain N, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem* 2006;49(9):2845-9. doi: 10.1021/jm0601856 [published Online First: 2006/04/28]
36. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends* 2020
37. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949. doi: 10.1016/j.ijantimicag.2020.105949 [published Online First: 2020/03/25]
38. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020;382(25):2411-18. doi: 10.1056/NEJMoa2012410 [published Online First: 2020/05/08]

39. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2019014
40. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa478 [published Online First: 2020/04/28]
41. Zhang M, Jativa DF. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. *SAGE Open Med* 2018;6:2050312118807615. doi: 10.1177/2050312118807615 [published Online First: 2018/10/27]
42. Cirino Ruocco MA, Pacheco Cechinatti ED, Barbosa F, Jr., et al. Zinc and selenium status in critically ill patients according to severity stratification. *Nutrition* 2018;45:85-89. doi: 10.1016/j.nut.2017.07.009 [published Online First: 2017/11/14]
43. Hasanzadeh Kiabi F, Alipour A, Darvishi-Khezri H, et al. Zinc Supplementation in Adult Mechanically Ventilated Trauma Patients is Associated with Decreased Occurrence of Ventilator-associated Pneumonia: A Secondary Analysis of a Prospective, Observational Study. *Indian J Crit Care Med* 2017;21(1):34-39. doi: 10.4103/0972-5229.198324 [published Online First: 2017/02/16]
44. Annetta M, Maviglia R, Proietti R, et al. Use of corticosteroids in critically ill septic patients : a review of mechanisms of adrenal insufficiency in sepsis and treatment. *Curr Drug Targets* 2009;10(9):887-94. doi: 10.2174/138945009789108792 [published Online First: 2009/10/06]
45. Scaroni C, Armigliato M, Cannavò S. COVID-19 outbreak and steroids administration: are patients treated for Sars-Cov-2 at risk of adrenal insufficiency? *J Endocrinol Invest* 2020:1-2. doi: 10.1007/s40618-020-01253-1 [published Online First: 2020/04/18]
46. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2021436
47. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2007764
48. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* 2020;92(7):814-18. doi: 10.1002/jmv.25801 [published Online First: 2020/04/08]
49. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* 2020 doi: 10.1002/jmv.25964 [published Online First: 2020/05/06]
50. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* 2020;76:43-49. doi: 10.1016/j.ejim.2020.05.021 [published Online First: 2020/06/03]
51. Salazar E, Perez KK, Ashraf M, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. *Am J Pathol* 2020 doi: 10.1016/j.ajpath.2020.05.014 [published Online First: 2020/05/31]
52. Joyner M, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. *medRxiv* 2020:2020.05.12.20099879. doi: 10.1101/2020.05.12.20099879

53. Vittinghoff E, McCulloch CE. Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. *American Journal of Epidemiology* 2007;165(6):710-18. doi: 10.1093/aje/kwk052
54. van Smeden M, de Groot JAH, Moons KGM, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC Medical Research Methodology* 2016;16(1):163. doi: 10.1186/s12874-016-0267-3

Table 1. Demographics and baseline characteristics of included patients.

Characteristics	All patients (n = 283)	Survivors (n = 228)	Non-survivors (n = 55)	P-value
Male	159 (56.2)	125 (54.8)	34 (61.8)	0.348
Age (year)	64.1 (15.9)†	61.9 (15.8)†	72.8 (13.5)†	< 0.001*
Ethnicity				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	0.705
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
Co-morbidities				
Obesity (BMI ≥ 30 kg/m²)	132 (46.6)	102 (44.7)	30 (54.5)	0.191
Current/Former smokers	109 (38.5)	88 (38.6)	21 (38.2)	0.955
Hypertension	189 (66.8)	145 (63.6)	44 (80.0)	0.020*
Diabetes mellitus	108 (38.2)	81 (35.5)	27 (49.1)	0.063
Hyperlipidemia	121 (42.8)	94 (41.2)	27 (49.1)	0.290
Coronary artery disease	50 (17.7)	40 (17.5)	10 (18.2)	0.911
Heart failure/cardiomyopathy	53 (18.7)	40 (17.5)	13 (23.6)	0.299
Arrhythmia/conduction disorders	45 (15.9)	36 (15.8)	9 (16.4)	0.917
Chronic kidney disease	66 (23.3)	46 (20.2)	20 (36.4)	0.011*
End-stage kidney disease	13 (4.6)	12 (5.3)	1 (1.8)	0.474
Asthma/COPD	73 (25.8)	54 (23.7)	19 (34.5)	0.098
Cerebrovascular disease	40 (14.1)	32 (14.0)	8 (14.5)	0.922
Signs and symptoms				
Cough	185 (65.4)	149 (65.4)	36 (65.5)	0.988
Dyspnea	203 (71.7)	158 (69.3)	45 (81.8)	0.064
Hypoxia (SpO2 < 95%)	178 (62.9)	130 (57.0)	48 (87.3)	< 0.001*
Rhinorrhea	29 (10.2)	26 (11.4)	3 (5.5)	0.226
Fever/chills	179 (63.3)	143 (62.7)	36 (65.5)	0.706
Chest pain	35 (12.4)	32 (14.0)	3 (5.5)	0.109
Headache	28 (9.9)	26 (11.4)	2 (3.6)	0.128
Gastrointestinal symptoms	79 (27.9)	68 (29.8)	11 (20.0)	0.145
Asymptomatic	8 (2.8)	8 (3.5)	0 (0)	0.361
Rales/crackles	57 (20.1)	40 (17.5)	17 (30.9)	0.027*

Rhonchi	57 (20.1)	45 (19.7)	12 (21.8)	0.730
Reduced breath sound	63 (22.3)	48 (21.1)	15 (27.3)	0.320
Laboratory findings				
Leukopenia (WBC < 4,000 /uL)	56 (19.8)	46 (20.2)	10 (18.2)	0.739
Leukocytosis (WBC > 10,000 /uL)	80 (28.3)	53 (23.2)	27 (49.1)	< 0.001*
Lymphocytopenia (ALC < 1,000 / uL)	109 (38.7)	78 (34.2)	31 (57.4)	0.002*
Thrombocytopenia (< 140,000 /uL)	57 (20.1)	41 (18.0)	16 (29.1)	0.065
Thrombocytosis (> 400,000 /uL)	31 (11.0)	25 (11.0)	6 (10.9)	0.991
Respiratory acidosis	43 (21.3)	18 (11.8)	25 (50.0)	< 0.001*
Transaminitis (ALT > 3X UNL)	33 (12.4)	21 (9.9)	12 (21.8)	0.017*
Serum creatinine (mg/dL) on admission	1.06 (0.72)‡	1.59 (1.88)†	1.64 (1.15)†	0.808
eGFR (mL/min/1.73m^2)	64.2 (51.0)†	66.7 (35.5)†	53.6 (25.3)†	0.002*
Troponin I (> 0.03 ng/mL)	91 (39.1)	61 (33.0)	30 (62.5)	< 0.001*
Inflammatory markers				
D-dimer (> 500 ng/mL)	135 (80.4)	101 (75.4)	34 (100)	< 0.001*
Ferritin (> 336 ng/mL)	109 (65.3)	78 (59.1)	31 (88.6)	0.001*
Lactate dehydrogenase (> 200 U/L)	108 (73.0)	77 (67.0)	31 (93.9)	0.002*
C-reactive protein (> 1 mg/dL)	152 (87.4)	115 (83.9)	37 (100)	0.005*
Procalcitonin (> 0.25 ng/mL)	73 (47.1)	50 (41.7)	23 (65.7)	0.012*
ST-T change on EKG	84 (31.8)	63 (29.7)	21 (40.4)	0.139
Radiographic findings				
Opacity/infiltrate	209 (73.9)	162 (71.1)	47 (85.5)	0.029*
Ground glass appearance	79 (27.9)	65 (28.5)	14 (25.5)	0.650
Pleural effusion	24 (8.5)	17 (7.5)	7 (12.7)	0.208
Pulmonary congestion	30 (10.6)	23 (10.1)	7 (12.7)	0.568
Oxygen therapy/delivery				
Nasal cannula	207 (73.1)	160 (70.2)	47 (85.5)	0.022*
High-flow nasal cannula	36 (12.7)	18 (7.9)	18 (32.7)	< 0.001*
NIPPV	28 (9.9)	10 (4.4)	18 (32.7)	< 0.001*
Mechanical ventilation	58 (20.5)	25 (11.0)	33 (60.0)	< 0.001*
Intervention				
Intensive care unit	89 (31.4)	47 (20.6)	42 (76.4)	< 0.001*
ECMO	2 (0.7)	0 (0)	2 (3.6)	0.037*
RRT	16 (5.7)	3 (1.3)	13 (23.6)	< 0.001*
Vasopressor	53 (18.7)	19 (8.3)	34 (61.8)	< 0.001*
Antibiotics	220 (77.7)	166 (72.8)	54 (98.2)	< 0.001*
Treatment				
Azithromycin	182 (64.3)	139 (61.0)	43 (78.2)	0.017*
Hydroxychloroquine	67 (23.7)	45 (19.7)	22 (40.0)	0.002*
Steroids	46 (16.3)	26 (11.4)	20 (36.4)	< 0.001*
Ascorbic acid	57 (20.1)	38 (16.7)	19 (34.5)	0.003*
Zinc	54 (19.1)	33 (14.5)	21 (38.2)	< 0.001*
Tocilizumab	12 (4.2)	6 (2.6)	6 (10.9)	0.006*
Convalescent plasma	36 (12.7)	19 (8.3)	17 (30.9)	< 0.001*
Remdesivir	25 (8.8)	20 (8.8)	5 (8.8)	0.940
Complications				
Acute kidney injury	115 (40.6)	75 (32.9)	40 (72.7)	< 0.001*
ARDS	53 (18.7)	17 (7.5)	36 (65.5)	< 0.001*
Arrhythmias	31 (11.0)	18 (7.9)	13 (23.6)	0.001*
QT prolongation	25 (8.8)	18 (7.9)	7 (12.7)	0.257
Venous thromboembolism	10 (3.5)	8 (3.5)	2 (3.6)	1.000
Arterial thrombosis	1 (0.4)	1 (0.4)	0 (0)	1.000

Cerebrovascular event	3 (1.1)	3 (1.3)	0 (0)	1.000
Myocardial infection	5 (1.8)	4 (1.8)	1 (1.8)	1.000
Heart failure	16 (5.7)	11 (4.8)	5 (9.1)	0.219
Superimposed bacteremia	19 (6.7)	12 (5.3)	7 (12.7)	0.047*
Hospital stay (day)	6.0 (7.0)‡	7.4 (7.53)†	9.2 (7.7)†	0.125
Outcome				
Recovery/discharge	223 (78.8)			
Remained hospitalized	2 (0.7)			
Death	55 (19.4)			

ALC, absolute lymphocyte count; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extra-corporal membrane oxygenation; eGFR, estimated glomerular filtration rate; EKG, electrocardiography; IQR, interquartile range; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy; SD, standard deviation; SpO2, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.
*statistically significant
†mean (standard deviation)
‡ median (IQR)

Table 2. Clinical risk factors for overall in-hospital mortality using univariate binary logistic regression analysis.

Characteristics	Odds ratio	95% CI	P-value
Age (per 1-year increment)	1.051	1.028-1.075	< 0.001*
Hypertension	2.288	1.121-4.673	0.024*
Chronic kidney disease	2.262	1.195-4.274	0.012*
Hypoxia (SpO2 < 95%)	5.181	2.242-11.905	< 0.001*
Rales/crackles	2.101	1.080-4.098	0.029*
Leukocytosis (WBC > 10,000 /uL)	3.185	1.727-5.882	< 0.001*
Respiratory acidosis	7.463	3.546-15.625	< 0.001*
Transaminitis (ALT > 3X UNL)	2.538	1.160-5.556	0.020*
eGFR (per 1.0 mL/min/1.73m^2 increment)†	0.988	0.980-0.997	0.011*
D-dimer (> 500 ng/mL)‡	-	-	-
Ferritin (> 336 ng/mL)	5.376	1.789-16.129	0.003*
Lactate dehydrogenase (> 200 U/L)	7.634	1.739-33.333	0.007*
C-reactive protein (> 1 mg/dL)‡	-	-	-
Procalcitonin (> 0.25 ng/mL)	2.681	1.222-5.882	0.014*
Troponin I (> 0.03 ng/mL)	3.390	1.751-6.536	< 0.001*
Opacity/infiltrate on imaging	2.392	1.073-5.348	0.033*
Nasal cannula	2.494	1.120-5.556	0.025*
High-flow nasal cannula	5.682	2.703-11.905	< 0.001*
NIPPV	10.638	4.545-2.500	< 0.001*
Mechanical ventilation	12.195	6.173-23.810	< 0.001*
ICU admission/transfer	12.500	6.173-25.000	< 0.001*
ECMO‡	-	-	-
RRT	23.256	6.329-83.333	< 0.001*
Vasopressor	17.857	8.696-37.037	< 0.001*
Antibiotics	20.000	2.732-142.857	0.003*
Azithromycin	2.294	1.147-4.587	0.019*

Hydroxychloroquine	2.710	1.443-5.102	0.002*
Steroids	4.444	2.237-8.772	< 0.001*
Ascorbic acid	2.639	1.370-5.076	0.004*
Zinc	3.650	1.898-7.042	< 0.001*
Tocilizumab	4.525	1.403-14.706	0.012*
Convalescent plasma	4.921	2.348-10.314	< 0.001*
Acute kidney injury	5.435	2.825-10.417	< 0.001*
ARDS	23.256	11.236-50.000	< 0.001*
Arrhythmia	3.610	1.645-7.937	0.001*
Superimposed bacteremia	2.625	0.982-6.993	0.054

ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy.
*statistically significant
†on admission
‡analyses cannot be performed as at least one cell is zero

Table 3. Clinical predictors for overall in-hospital mortality using multivariate binary logistic regression analysis.

	Statistics		
Characteristics	**Odds ratio**	**95% CI**	**P-value**
Model 1			
Age (per 1-year increment)	1.075	1.045-1.105	< 0.001*
Hypertension	1.264	0.572-2.793	0.562
Chronic kidney disease	1.232	0.590-2.571	0.578
Hypoxia (SpO2 < 95%)	4.630	1.934-1.111	0.001*
Rales/crackles	2.016	0.955-4.255	0.066
Leukocytosis (WBC > 10,000 /uL)	2.732	1.412-5.263	0.003*
Transaminitis (ALT > 3X UNL)	2.137	0.890-5.128	0.089
eGFR (per 1.0 mL/min/1.73m^2 decrement)†	1.002	0.990-1.013	0.795
Ferritin (> 336 ng/mL)	4.016	1.195-13.514	0.025*
Lactate dehydrogenase (> 200 U/L)	7.752	1.639-37.037	0.010*
Procalcitonin (> 0.25 ng/mL)	2.404	1.011-5.714	0.047*
Troponin I (> 0.03 ng/mL)	2.242	1.080-4.673	0.030*
Opacity/infiltrate on imaging	3.077	1.276-7.407	0.012*
Nasal cannula	1.883	0.799-4.444	0.148
High-flow nasal cannula	4.608	2.053-10.309	< 0.001*
NIPPV	7.246	2.899-18.182	< 0.001*
Mechanical ventilation	13.889	6.211-31.250	< 0.001*
ICU admission/transfer	13.699	6.135-30.303	< 0.001*
RRT	21.277	5.025-90.909	< 0.001*
Vasopressor	22.222	9.434-52.632	< 0.001*
Antibiotics	17.544	2.309-125.000	0.006*
ARDS	23.810	10.204-55.556	< 0.001*
Superimposed bacteremia	2.041	0.645-6.452	0.224

Model 2			
Azithromycin	1.916	0.788-4.651	0.152
Hydroxychloroquine	1.057	0.467-2.392	0.894
Ascorbic acid	1.008	0.440-2.313	0.985
Zinc	1.517	0.651-3.546	0.334
Tocilizumab	1.499	0.381-5.917	0.562
Convalescent plasma	1.513	0.600-3.817	0.381
Model 3			
Respiratory acidosis	3.745	1.443-9.709	0.007*
Steroids therapy	1.107	0.459-2.667	0.821
Model 4			
Acute kidney injury	2.268	1.025-5.025	0.043*
Model 5			
Arrhythmias as complications	1.161	0.428-3.155	0.769

ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy.
*statistically significant
Model 1 is adjusted for age, sex, ethnicity and obesity
Model 2 is adjusted for age, sex, ethnicity, obesity, need for oxygen therapy, and ICU admission
Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/COPD, need for oxygen therapy, and ICU admission
Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, need for oxygen therapy, and ICU admission
Model 5 is adjusted for age, sex, ethnicity, obesity, CAD, heart failure, history of arrhythmia/conduction disorder, and ICU admission

Table 4. Demographics and baseline characteristics of critically ill patients (n = 89).

Characteristics	All patients (n = 89)	Survivors (n = 47)	Non-survivors (n = 42)	P-value
Male	61 (68.5)	30 (63.8)	31 (73.8)	0.365
Age (year)	66.0 (14.2)†	69.1 (12.5)†	63.3 (15.2)†	0.052
SOFA score†‡	4.3 (2.0)	3.6 (1.7)	5.1 (1.9)	< 0.001*
Ethnicity				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	
African-American	25 (28.1)	12 (25.5)	13 (31.0)	
Hispanic/Latino	12 (13.5)	8 (17.0)	4 (9.5)	0.685
Asian	5 (5.6)	2 (4.3)	3 (7.1)	
Others	-	-	-	
Treatment				
Azithromycin	69 (77.5)	34 (72.3)	35 (83.3)	0.215
Hydroxychloroquine	42 (47.2)	23 (48.9)	19 (45.2)	0.727
Steroids	39 (43.8)	19 (40.4)	20 (47.6)	0.495
Ascorbic acid	39 (43.8)	22 (46.8)	17 (40.5)	0.548
Zinc	40 (44.9)	21 (44.7)	19 (45.2)	0.958
Tocilizumab	11 (12.4)	5 (10.6)	6 (14.3)	0.750
Convalescent plasma	30 (33.7)	14 (29.8)	16 (38.1)	0.408
Remdesivir	11 (12.4)	6 (12.8)	5 (11.9)	1.000
Complications				
Acute kidney injury	56 (62.9)	22 (46.8)	34 (81.0)	0.001*
ARDS	47 (52.8)	15 (31.9)	32 (76.2)	< 0.001*
Arrhythmias	21 (23.6)	10 (21.3)	11 (26.2)	0.586
QT prolongation	16 (18.0)	10 (21.3)	6 (14.3)	0.391
Venous thromboembolism	5 (5.6)	3 (6.4)	2 (4.8)	1.000
Hospital stay (day)	13.1 (9.6)†	10.4 (8.1)†	15.5 (10.3)†	0.125
Outcome				

Recovery/discharge	43 (48.3)
Remained hospitalized	2 (2.2)
Death	42 (47.2)

ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment
*statistically significant
†mean (standard deviation)
‡collected on the first day of ICU admission

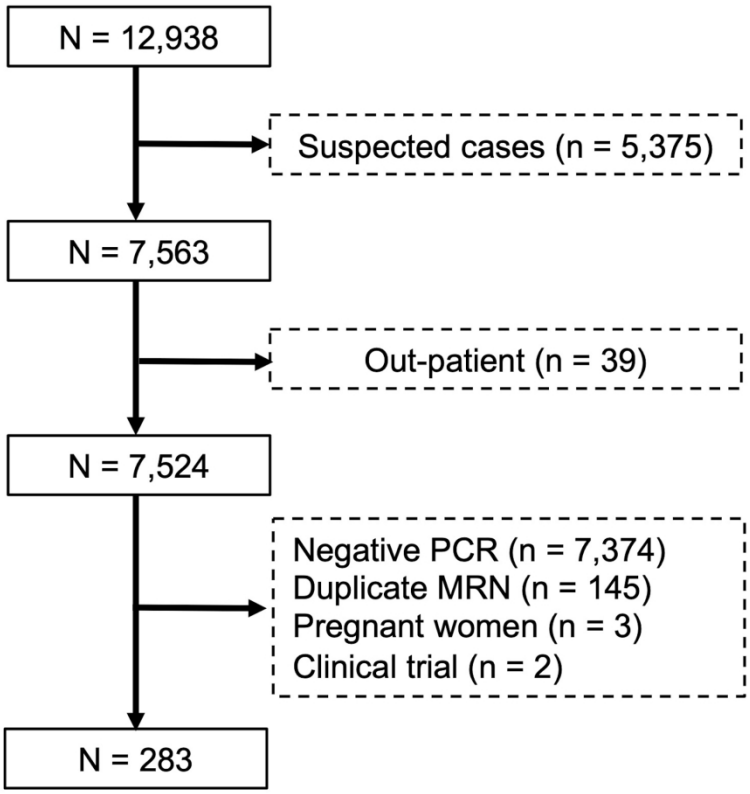

Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

203x185mm (300 x 300 DPI)

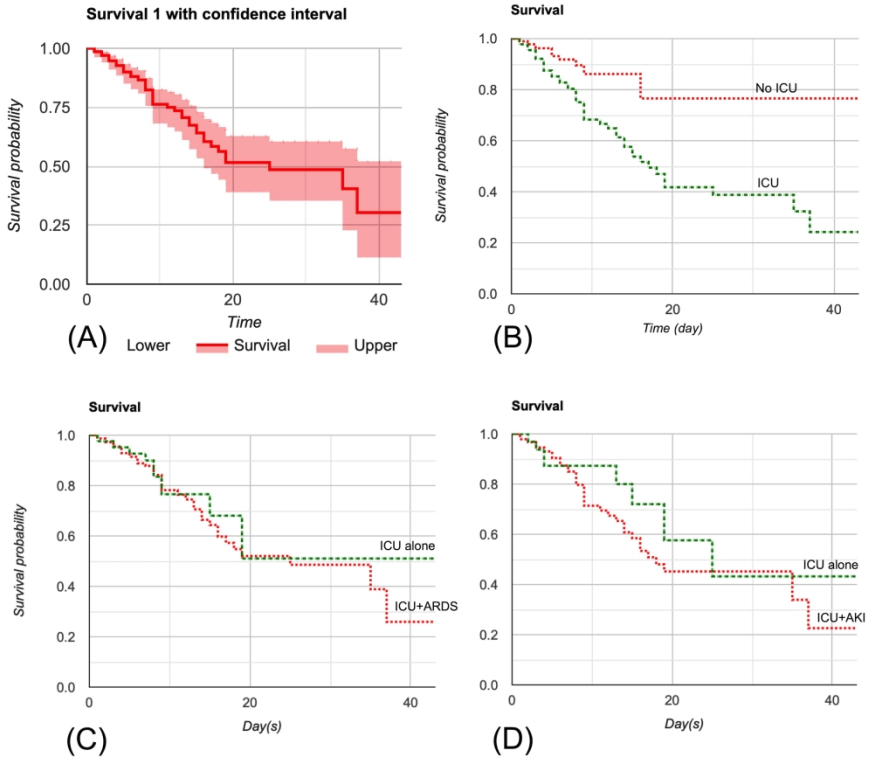

Figure 2. Survival analysis by Kaplan-Meier curves. A) The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. B) ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively (p = 0.002). C) The cumulative survival between ICU patients with and without acute respiratory distress syndrome (p = 0.302). D) The cumulative survival between ICU patients with and without acute kidney injury (p = 0.504).

254x228mm (300 x 300 DPI)

Data collection (con't):

The demographic data included age, sex, and ethnicity. Co-morbidities included current/prior history of smoking, obesity (BMI ≥ 30 kg/m^2), hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, heart failure/cardiomyopathy, arrhythmia, chronic kidney disease, end-stage kidney disease (ESKD), asthma/chronic pulmonary obstructive disease, and cerebrovascular diseases.

Laboratory findings were recorded: leukocytosis (white blood cells count > 9,500/μL), leukopenia (white blood cells count < 3,900/μL), lymphocytopenia (absolute lymphocytes count < 600/μL), thrombocytosis (platelets > 400,000/μL), and thrombocytopenia (platelets < 140,000/μL), respiratory acidosis (arterial pH < 7.35 and arterial partial pressure of CO_2 > 45 mmHg), transaminitis (alanine transaminase > 3 times of upper normal limit). Serum creatinine (mg/dL) was measured by enzymatic assay. Elevation of serum D-dimer (> 500 ng/mL), ferritin (> 336 ng/mL) lactate dehydrogenase (LDH; > 200 U/L), C-reactive protein (> 1 mg/dL), procalcitonin (> 0.25 ng/mL), and troponin I (> 0.03 ng/mL; Backman Coulter DxI).

Please note that the cutoff values were determined by the National Reference Laboratory.

Rationale for multivariate analysis models

Model 1 is adjusted for the baseline co-morbidities (age, sex, ethnicity, obesity). Some of these co-variates showed significant association with death on univariate analysis. Without these adjustments, the aforementioned co-variates will act as confounding factors.

Model 2 is adjusted for all factors in Model 1 plus "the need for oxygen therapy" because the interventions included in Model 2 (azithromycin, hydroxychloroquine, ascorbic acid, zinc, tocilizumab, convalescent plasma) were usually given in patients who required oxygen therapy. Thus, in this Model, "the need for oxygen therapy" was held constant allowing us to determine if these interventions were associated with death.

For Model 3, "respiratory acidosis, and steroids therapy" are usually seen in patients with asthma, COPD, critical illnesses and those who required oxygen therapy. These factors are potential confounders. Thus, we adjusted this Model for "asthma/COPD"; "the need for oxygen therapy"; and "ICU admission" to determine the true association between the variables and death.

In Model 4, "acute kidney injury" is defined by serum creatinine elevation. Patients with CKD would also have some elevation of serum creatinine levels. Thus, CKD would be a potential confounder. That is why we adjusted the Model for "CKD"; "need for oxygen therapy"; and "ICU admission" as all of these factors may contribute to death.

In Model 5, “arrhythmias” is a cardiac complication, hence we adjusted for every variable that could be the confounding factor, such as CAD, heart failure, history of arrhythmia/conduction disorder, and ICU admission.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, Line 31-32
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, Line 129-131
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5, Line 134
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6, Line 159-166
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6, Line 159-166
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6, Line 168-183 Supplemental Document 1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supplemental Document 1
Bias	9	Describe any efforts to address potential sources of bias	Page 6, Line 168-169
Study size	10	Explain how the study size was arrived at	Page 6, Line 159-166
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7, Line 190-196
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8, Line 189-221
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	Page 7, Line 196
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A

		(*e*) Describe any sensitivity analyses	Page 8, Line 215-218
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8, Line 225-228
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2-3
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11, Line 271-302
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11-16, Line 309-467
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16-17, Line 468-491
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17, Line 490-491
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 19, Line 538

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality: A Single-network, Retrospective Cohort Study from Pennsylvania State

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042549.R2
Article Type:	Original research
Date Submitted by the Author:	07-Oct-2020
Complete List of Authors:	Gadhiya, Kinjal; UPMC Pinnacle, Department of Internal Medicine Hansrivijit, Panupong ; UPMC Pinnacle, Department of Internal Medicine Gangireddy, Mounika; UPMC Pinnacle, Department of Internal Medicine Goldman, John; UPMC Pinnacle, Department of Infectious Diseases
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTERNAL MEDICINE, MICROBIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality: A Single-network, Retrospective Cohort Study from Pennsylvania State

Kinjal P. Gadhiya,[1*] Panupong Hansrivijit,[1*] Mounika Gangireddy,[1*] John D. Goldman[2]

*equivalent contribution

[1]Department of Internal Medicine, UPMC Pinnacle, Harrisburg, PA 17104, USA;

kinjal268@gmail.com; hansrivijitp@upmc.edu; g.mounikareddy07@gmail.com

[2]Department of Infectious Diseases, UPMC Pinnacle, Harrisburg, PA 17104, USA;

goldmanjd@upmc.edu

Running title: COVID-19 and Clinical Impact: A Retrospective Study from Pennsylvania State

Correspondence

Panupong Hansrivijit, M.D.

205 South Front Street, Suite 3C

Harrisburg, PA 17104

hansrivijitp@upmc.edu

Keywords: COVID-19, coronavirus, SARS-CoV-2, mortality, acute kidney injury

Word count: 3,708 (excl. title page, abstract, legend, declarations, and references)

Funding: None declared.

Disclosure of Potential Conflicts of Interest: The authors declared no potential conflicts of interest.

ABSTRACT

Objective: Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with highest burden in the United States. Data on clinical characteristics of COVID-19 patients in U.S. population are limited. Thus, we aim to determine the clinical characteristics and risk factors for in-hospital mortality from COVID-19.

Design: Retrospective observational study.

Setting: Single-network hospitals in Pennsylvania state.

Participants: Patients with confirmed SARS-CoV-2 infection who were hospitalized from March 1st to May 31st, 2020.

Primary and secondary outcome measures: Primary outcome was in-hospital mortality. Secondary outcomes were complications, such as acute kidney injury and acute respiratory distress syndrome (ARDS).

Results: Of 283 patients, 19.4% were non-survivors. The mean age of all patients was 64.1 ± 15.9 years. 56.2% were male and 50.2% were white. Several factors were identified from our adjusted multivariate analyses to be associated with in-hospital mortality: increasing age (per 1-year increment; OR 1.07 [1.045-1.105]), hypoxia (SpO2 < 95%; OR 4.630 [1.934-1.111]), opacity/infiltrate on imaging (OR 3.077 [1.276-7.407]), leukocytosis (WBC > 10,000 /uL; OR 2.732 [1.412-5.263]), ferritin > 336 ng/mL (OR 4.016 [1.195-13.514]), lactate dehydrogenase > 200 U/L (OR 7.752 [1.639-37.037]), procalcitonin > 0.25 ng/mL (OR 2.404 [1.011-5.714]), troponin I > 0.03 ng/mL (OR 2.242 [1.080-4.673]), need for advanced oxygen support other than simple nasal cannula (OR 4.608-13.889 [2.053-31.250]), ICU admission/transfer (OR 13.699 [6.135-30.303]), renal replacement therapy (OR 21.277 [5.025-90.909]), need for vasopressor

(OR 22.222 [9.434-52.632]), acute respiratory distress syndrome (OR 23.810 [10.204-55.556]), respiratory acidosis (OR 7.042 [2.915-16.949]), and acute kidney injury (OR 3.571 [1.715-7.407]). When critically ill patients were analyzed independently, increasing SOFA score (OR 1.544 [1.168-2.039]), AKI (OR 2.128 [1.111-6.667]), and ARDS (OR 6.410 [2.237-18.182]) were predictive of in-hospital mortality.

Conclusion: We reported the characteristics of ethnically diverse, hospitalized patients with COVID-19 from Pennsylvania state.

Strengths and Limitations of This Study

- Individual patient's chart was reviewed.
- Multivariate analysis (binary logistic regression model) was used to report the results.
- Retrospective, observational design.
- Limited sample size.
- Only hospitalized patients were included in the studies.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has become a pandemic in early 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and rapidly escalated to 216 countries within five months with the highest number of infected cases in the United States.[1] As of August 29th, 2020, the reported cumulated number of confirmed cases in the United States was close to 6 million with a mortality rate of 3.09%.[1]

As of August 29th, 2020, the Pennsylvania Department of Health has announced more than 129,056 confirmed cases of COVID-19 leading to 7,671 deaths, making Pennsylvania the 13th state with the highest confirmed cases.[2] To date, the characteristics of infected patients in the United States were reported in the state of Washington (n = 21), California (n = 1,299) and New York (n = 5,700) in chronological order.[3-5] The mortality across the U.S. studies ranged from 6.3 to 24%, depending on the severity of COVID-19. Although the characteristics of hospitalized COVID-19 patients have been reported in other states, there are some limitations that preclude the generalization of the results toward our patient population. Studies from Washington and California were conducted and published during an early stage of the pandemic where treatment options, such as remdesivir, or dexamethasone were not recommended as the standard of care. In addition, multivariate analysis was not performed in the New York City cohort. The association between clinical characteristics and in-hospital mortality in the U.S. population have not been clearly established.

Guan, et al first described the clinical characteristics of 1,099 patients infected with SARS-CoV-2 across China.[6] In this study, the overall mortality was 1.4%. However, the association between clinical risk factors and mortality was not described. Later Du et al and

Zhou et al demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA) score, D-dimer > 1 μg/mL, cardiac troponin I ≥ 0.05 ng/mL, and pre-existing concurrent cardiovascular and cerebrovascular diseases were significant predictors for increased mortality from COVID-19.[7 8] However, these findings were primarily based on Chinese population; thus, it has been unconfirmed if the results can be applicable to other patient populations.

Clinical management of COVID-19 has been dynamic and variable based on available research, which has largely been *in vitro*, such as a combination of hydroxychloroquine and azithromycin,[9] ascorbic acid,[10] ivermectin,[11] and zinc.[12] These therapies have not been proven beneficial in clinical studies. In the current study, we provide our experience on treatment options for patients infected with SARS-CoV-2.

In this retrospective cohort, we aimed to demonstrate the clinical characteristics of COVID-19 patients, treatment outcomes and the impact on in-hospital mortality in an ethnically diverse population.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study from seven hospitals under UPMC Pinnacle network located across the state of Pennsylvania. The protocol of this study has been approved by UPMC Pinnacle Institutional Review Board and UPMC Pinnacle Ethic Committee (#20E024). Written informed consent was waived due to the retrospective, observational nature of the study. Our current study followed the Declaration of Helsinki.

Patient and public involvement

No patient involvement.

Data source and patient population

Data were collected by extracting electronic medical records from March 1st to May 31th, 2020 through UPMC Pinnacle COVID-19 registry. Adult patients with age ≥ 18 years who were hospitalized with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalized patients, patients < 18 years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-system transfer and patients enrolled in clinical trials. Transfer within the system was considered one admission. For patients with multiple admissions with study period, the first admission for COVID-19 was reviewed.

Data collection

Individual patient charts were reviewed by three independent authors to prevent observer bias. Collected data was divided into: demographics, comorbidities, signs and symptoms, laboratory findings, radiographic findings, treatments/interventions, complications and outcomes. *Supplemental Documents 1* summarizes the description of each variable in our cohort as well as the cutoff values for each variable.

The Sequential Organ failure Assessment (SOFA) score[13] was calculated on the first day of ICU admission. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation.[14] Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL (27 μmol/L) or ≥ 1.5 times from the baseline value within 48 hours.[15] Chronic kidney disease (CKD) was defined by the Kidney Diseases Improving Global Outcomes guidelines.[16] Patients with history of end stage kidney disease (ESKD) on dialysis prior to admission, were not counted toward 'requirement of renal replacement therapy (RRT)/hemodialysis (HD)' during the hospital stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.[17]

Arrhythmias as complications were defined either tachy- or bradyarrhythmia that were new-onset, occurred during hospitalization with COVID-19. In this study, prolongation of QT segment was defined as the QT duration > 500 milliseconds.

Study outcomes

The primary outcome was in-hospital mortality. The secondary outcome included treatment outcomes and complications such as recovery/discharge, AKI, ARDS, arrhythmias, QT prolongation, venous thromboembolism, arterial thrombosis, cerebrovascular events, heart failure, and myocardial infarction.

Statistical analysis

All analyses were conducted using SPSS software version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses were reported in percentage for categorical data and in mean ± standard deviation (S.D.) or median (interquartile range; IQR) depending the data distribution. Comparisons of outcomes for each variable were evaluated using Pearson's χ^2 tests or Fisher-Exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher-Exact tests were opted if the total sample in any cell count was less than five. A p-value less than 0.05 is considered statistically significant. Missing data were not included in the analysis.

Logistic regression analysis

Clinical risk factors that were significant from standard analyses (Pearson's χ^2 tests, Fisher-Exact tests, t-tests) were included in univariate binary logistic regression analysis. Odds ratios (OR) were reported along with 95% confidence interval (CI). A 95% CI that crosses 1.0 and a p-value of less than 0.05 is considered statistically significant.[18] Variables that remained statistically significant on univariate analysis were included in multivariate analysis using logistic regression method to adjust for other covariates. For the analyses of overall mortality predictors, each variable

was analyzed by only one model that was adjusted for several potential confounding factors for that particular variable. Model 1 was adjusted for age, sex, ethnicity and obesity. Model 2 was adjusted for age, sex, ethnicity, obesity and need for oxygen therapy. Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/chronic obstructive pulmonary disease (COPD), the need for oxygen therapy, and ICU admission. Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, the need for oxygen therapy, and ICU admission. Model 5 is adjusted for age, sex, ethnicity, obesity, coronary artery disease, heart failure, history of arrhythmia/conduction disorder, and ICU admission. The rationale for each Model adjustment in multivariate analysis is available in *Supplemental Document 2*.

Survival analysis

Kaplan-Meier analysis was used to present the survival by plotting between cumulative survival against hospital stay in all included patients and in patients requiring ICU.

RESULTS

Baseline characteristics and patient outcomes

A total of 12,938 patients were identified during the study period. Thirty-nine patients were outpatient and did not require hospitalization. After excluding patients with negative PCR (n = 7,374), duplicate medical records (n = 145), pregnant woman (n = 3), and clinical trial patients (n = 2), 283 patients were included for further analysis. The flowchart of data selection from the UPMC Pinnacle COVID-19 registry is depicted in *Figure 1*. *Table 1* summarizes the demographics and baseline characteristics of included patients. All patients had confirmed SARS-Cov-2 infection by RT-PCR. Of 283 patients, 80.6% were survivors and 19.4% were non-survivors. The mean age of all patients was 64.1 ± 15.9 years. 56.2% were male and 50.2% were Caucasian. Non-survivors

were significantly older and had higher proportion of hypertension, CKD and had lower mean eGFR. Moreover, hypoxia on presentation, rales/crackles on physical examination, leukocytosis, lymphocytopenia, respiratory acidosis, transaminitis, and opacity/infiltrate on imaging were common presentations in non-survivors. Higher inflammatory markers, such as D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive protein, and procalcitonin were significantly prevalent in deceased patients. The need for oxygen therapy regardless of the mode of oxygen delivery was higher among those who did not survive. Furthermore, non-survivors were more likely to have received intensive care unit (ICU) admission/transfer, extracorporeal membrane oxygenation (ECMO), RRT, use of vasopressors, use of antibiotics, azithromycin, hydroxychloroquine, steroids, ascorbic acid, zinc, tocilizumab and convalescent plasma. Of overall complications, the prevalence of AKI, ARDS, arrhythmias and superimposed bacteremia was significantly higher in non-survivors. There was no significant difference in mean hospital stay between survivors and non-survivors. Up to 78.8% recovered or were discharged from the hospital. Only two patients remained hospitalized as of June 18, 2020. The mean hospital stay was similar between patients who received remdesivir vs. those who did not (9.0 ± 4.7 and 7.6 ± 7.8 days, respectively; $p = 0.359$). In contrast, patients who received tocilizumab had significantly longer hospital stay compared to those who did not receive tocilizumab (15.3 ± 11.7 and 7.4 ± 7.2 days, respectively; $p < 0.001$).

Univariate analysis

All factors except superimposed bacteremia remained significant on univariate analysis. The OR of each clinical predictor for overall in-hospital mortality is depicted in *Table 2*. Logistic regression analysis cannot be performed on the following variables: D-dimer (> 500 ng/mL), C-reactive protein (> 1 mg/dL), and the need for ECMO as at least one cell count was zero.

Moreover, in a univariate analysis, we found that hydroxychloroquine treatment was associated with increased risk of QT prolongation (OR 3.401; 95%CI 1.473-7.874; p = 0.002).

Multivariate analysis

Variables that were significant on univariate analysis were included in multivariate logistic regression analysis (*Table 3*). In Model 1 (adjusted for age, sex, ethnicity, and obesity), increasing patient age, hypoxia, opacity/infiltrate on imaging, leukocytosis, ferritin > 336 ng/mL, LDH (> 200 U/L), procalcitonin > 0.25 ng/mL, troponin I > 0.03 ng/mL, use of high-flow oxygen nasal cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for increased in-hospital mortality. In Model 2 (adjusted for all variables in Model 1 plus the need for oxygen therapy, and ICU admission), hydroxychloroquine, ascorbic acid, zinc, and convalescent plasma were not associated with increased mortality. In Model 3 (adjusted for all variables in Model 2 plus asthma/COPD), respiratory acidosis was associated with increased mortality. Moreover, AKI was an independent risk factor for in-hospital mortality from COVID-19 from Model 4. In addition, we also found that hydroxychloroquine therapy was associated with QT prolongation (OR 2.874; 95% CI 1.189-6.944; p = 0.019) after adjusted for covariates in Model 2.

Cohort of critically ill patients

A total 89 patients required intensive care during the study period. Of which, 47.2% died. The demographics and clinical characteristics of critically ill patients are demonstrated in *Table 4*. Deceased ICU patients had significantly higher proportion of AKI and ARDS compared to survived ICU patients. The treatments were similar between survivors and non-survivor patients. In multivariate analysis, each 1-point increment of SOFA score was associated with increased death (OR 1.544; 95% CI 1.168-2.039; p 0.002) after adjusted for age, sex, and ethnicity.

Similarly, AKI (OR 2.128, 95% CI 1.111-6.667; p = 0.034) and ARDS (OR 6.410; 95% CI 2.237-18.182; p = 0.023) are significantly predictive of in-hospital mortality among patients admitted the ICU after adjusted for age, sex, ethnicity, and SOFA score.

Survival analysis

Survival analyses were evaluated using Kaplan-Meier curve of all patients were presented in *Figure 2A*. The median survival time was 25.0 days with standard error of 7.0. The Kaplan-Meier curves for ICU and no ICU patients were illustrated in *Figure 2B*.

DISCUSSION

In this single-network, retrospective observation study, we found that the overall in-hospital mortality among hospitalized COVID-19 patients was 19.4%. The reported mortality among Chinese cohorts ranged from 11.7% to 28.2%.[7 8 19] However, our reported mortality rates appeared slightly lower than what previously described from New York City.[5] Richardson et al found that the overall mortality of 5,700 hospitalized COVID-19 patients from 12 hospitals in New York City was 21%. However, one could argue that our study has a significantly smaller sample size. Our data need confirmation from other studies with a larger sample size.

We identified several risk factors for mortality from COVID-19 using multivariate logistic regression analysis. Increasing age, hypoxia and opacity/infiltrate on imaging were associated with higher mortality. Moreover, we also found that patient survival diminished as the disease progressed, reflected by advancement in oxygen delivery (high-flow nasal cannula, NIPPV, and mechanical ventilation). Requiring a simple oxygen nasal cannula did not affect mortality. Such findings are similar to previous literature. Older age is an independent risk factor

for severe COVID-19 and mortality.[7 20] In line with Zhou et al, increasing oxygen requirement and need for advanced oxygen delivery were predictive of death from COVID-19.[8]

Here, we showed that COVID-19 patients requiring ICU had 13.7-fold increased risk of mortality. Critically ill patients generally had one or more organs in failure, and an increasing number of organ failure has been linked to elevated death in sepsis patients.[21] For COVID-19 patients, we demonstrated that kidney (AKI, and RRT), pulmonary (respiratory acidosis, and ARDS), cardiovascular (vasopressor requirement) failure were predictive of in-hospital mortality. These findings are in line with other cohorts and each factor has been demonstrated as an independent risk factor for mortality in critically ill patients.[8 22-26] Although the complications from SARS-CoV-2 infection can be affected by multiple contributing factors, newer evidence has suggested the significance of cytokine storm leading to multi-organ failure.[27]

Here, we showed that elevated ferritin, LDH, procalcitonin, leukocytosis, troponin I and possibly D-dimer were associated with increased death. Although, the odds ratio for D-dimer cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be ignored. Guan et al first demonstrated the importance of elevated inflammatory markers in COVID-19 in Chinese population[6] which has become a standard monitoring parameter for COVID-19 patients.[28] Elevated inflammatory markers should prompt physicians to evaluate and monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated procalcitonin and leukocytosis may indicate concomitant bacterial infection, which has been shown to increase morbidity and mortality of viral pneumonia.[29] Interestingly, our study showed that elevated troponin I level was associated with significantly higher death similar to a recent meta-analysis.[30] Although the etiologies of elevated troponin levels were not determined in our

cohort, other studies proposed several mechanisms for elevated troponin level in COVID-19 patients. These include myocarditis, cytokine mediated myocardial injury, microangiopathy of small coronary arteries, or silent coronary artery disease.[26 30]

The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses or bacteria.[31] Cytokine storm is characterized by the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1β resulting in an increased vascular hyperpermeability, and activation of multiple coagulation pathways.[27 32] In light of SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and the protein C system were impaired during active inflammation.[33] These changes lead to thrombin hyperactivity resulting in the development of microthrombosis, disseminated intravascular coagulation (DIC) and sequential multiorgan failure.[27] Moreover, new studies have revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are beyond the scope of our article.[34] Such syndromes include macrophage activation syndrome, adult-onset Still's disease, and catastrophic anti-phospholipid syndrome.[34]

Hydroxychloroquine therapy was associated with a 3-fold increased risk of QT prolongation but not associated with increased risk of death. The concept of using hydroxychloroquine in COVID-19 patients derived from an early *in vitro* study.[35] The results from small non-randomized clinical trials also showed promising effects on viral load reduction.[36 37] However, the clinical benefit of hydroxychloroquine was debated by a large observation study. Of 1,446 patients, Geleris et al observed that hydroxychloroquine had no effect on the death, length of stay or intubation.[38] A recent multicenter, randomized, open-label, controlled trial in hospitalized patients with mild-to-moderate COVID-19 found that the use of hydroxychloroquine, alone or with azithromycin did not improve the clinical outcome at 15 days

compared to the standard treatment.[39] Thus, the recommendation for use of hydroxychloroquine was recalled by the Infectious Diseases Society of America (IDSA) due to small sample size in previous clinical trials and concern for cardiac adverse effects, such as QT prolongation/torsade de pointe.[40]

A meta-analysis of four randomized trials and one retrospective study showed that the administration of intravenous vitamin C has vasopressor sparing effects and may reduce the need for mechanical ventilation in critically ill patients while there was no effect on the mortality.[41] However, given the lack of more supporting evidence, the standard use of ascorbic acid is not yet recommended especially in COVID-19 patients. A new clinical trial investigating the treatment outcome of vitamin C in severe COVID-19 is underway (NCT04264533).

Although our study also showed that zinc supplementation was not associated with increased mortality in COVID-19 patients, the routine use of zinc supplementation could not be supported due to lack of randomized controlled trials. A Brazilian study revealed that plasma zinc concentration in critically ill patients upon admission to the ICU was low and may make these patients more susceptible to oxidative stress.[42] Another prospective study showed that zinc supplementation in mechanically ventilated patients was related to less ventilator-associated pneumonia.[43] However, the mean duration of intubation in this study was prolonged (29 days), making it inconclusive if zinc supplementation can prevent pneumonia development in short-term intubation.

Steroid therapy in COVID-19 patients was not associated with increased mortality. A meta-analysis of 42 randomized controlled trials consisting of 10,194 patients has shown that corticosteroids possibly result in a small reduction in mortality and an increased risk of neuromuscular weakness among critically ill patients with sepsis.[44] However, the theoretical

concept for corticosteroid use in COVID-19 was to reduce cytokine storm caused by a reaction to SARS-CoV-2 infection.[45] In early April 2020, the IDSA recommended against a routine use of corticosteroids in the treatment of COVID-19 due to lack of evidence.[40] This guidelines was updated on June 25th, 2020 after the results of the RECOVERY trial was released showing that patients who received dexamethasone were more likely to be discharged from hospital at 28 days compared to non-steroids group.[46] Thus, currently, the IDSA panel suggests glucocorticoids use in hospitalized patients with severe COVID-19.[40] Here, our study is in line with the recommendation from the IDSA.

We have observed that remdesivir and tocilizumab were not associated with mortality and there was no significant improvement in hospital length of stay between patients receiving these drugs. However, given the observational, non-randomized design of this study, it is difficult to determine the efficacy of such treatment. Recently, the preliminary report from a phase III randomized controlled trial revealed that remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19.[47] Several retrospective studies reported that tocilizumab, an IL-6 inhibitor, was shown to reduce the levels of serum inflammatory markers. However, the impact on clinical improvement and mortality remained inconclusive.[48-50] Although we reported no significant clinical benefits from tocilizumab, the consideration for compassionate use of tocilizumab is not discouraged but rather dependent on the judgment of clinicians based on current evidence. A phase 2 (TOCIVID-19; NCT04317092) and 3 randomized controlled trial (COVACTA; NCT04320615) of tocilizumab is being investigated for the treatment of COVID-19 pneumonia. The preliminary results are expected to release in late 2020.

Similarly, we found that convalescent plasma was not associated with in-hospital mortality. The safety of convalescent plasma was demonstrated in a single-center retrospective cohort of 25 patients[51] and in a preprint, non-peer review report.[52] However, the efficacy of convalescent plasma remained undetermined due to lack of control group. The IDSA panel has recommended convalescent plasma only in the context of a clinical trials. However, at our institution, convalescent plasma is considered if patients have severe symptoms and have contraindications to remdesivir, such as AKI and hepatic dysfunction. Although we did not observe mortality adverse effect from convalescent plasma, the final recommendations on its efficacy and safety are dependent on the randomized controlled trials. To date, at least one randomized controlled trial (NCT04342182) is being investigated to establish the clinical benefits in hospitalized patients with severe COVID-19.

From our ICU cohort, the SOFA score, AKI and ARDS were the only variables that were predictive of mortality among patients admitted to the ICU. Interestingly, all treatment measures had no effect on mortality once patients were critically ill and required ICU. This could imply that these treatment interventions might be beneficial if given prior to clinical decompensation or ICU transfer. However, interpretation is restricted due to small sample size and examining only critically ill patients. Our hypothesis should be substantiated by studies from other institutions with larger sample sizes.

Our study has some limitations. The observational design made the results susceptible to selection bias. Analyses could be underpowered given the small sample size. Moreover, due to restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir, and convalescent plasma, which may limit the applicability of our findings. More importantly, the mortality can be affected by confounding factors. We minimize this risk by applying multivariate

analysis with models designed to cover all possible confounding factors for each analyzed variable. Most of the collected data were cross sectional, thus, making it difficult to conclude the causality between the two variables. Furthermore, our binary logistic regression analyses may not strictly follow the one-in-ten rule which may lead to over-fitting effect. However, our statistical rationale is supported by newer simulation studies by McCulloch et al.,[53] and Smeden et al.[54] The length of stay was computed in the Kaplan-Meier analysis to represent the time to death. It is worth noting that the non-survivors had a curtailed length of stay. Moreover, we advised the readers to consider their patient population to determine the applicability of our results.

In conclusion, COVID-19 is a serious condition with a significant in-hospital mortality rate. Multiple risk factors for in-hospital death were identified. Increasing SOFA score, AKI and ARDS are significant risk factors for increased death in critically ill patients.

Acknowledgement

We would like to thank UPMC Pinnacle IT support for medical record procurement and Mrs. Yijin Wert for constructing the Kaplan-Meier curves.

Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

Figure 2. Survival analysis by Kaplan-Meier curves. **A)** The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. **B)** ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively (p = 0.002). **C)** The cumulative survival between ICU patients with and without acute respiratory distress syndrome (p = 0.302). **D)** The cumulative survival between ICU patients with and without acute kidney injury (p = 0.504).

DECLARATIONS

Funding: None

Disclosure of Potential Conflicts of Interest: The authors declared no potential conflicts of interest.

Ethics Approval: UPMC Pinnacle Ethic Committee approved this study (#20E024).

Informed Consent: Not applicable.

Data availability: Raw data are available upon reasonable request.

Authors' contributions: K.P.G., P.H., M.G. collected the data. P.H. analyzed the data. K.P.G., P.H., and J.D.G. drafted the manuscript. All authors edited and approved the manuscript for submission.

REFERENCES

1. WHO. Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. *Accessed on August 29th* 2020
2. Department of Health. COVID-19 Data for Pennsylvania. https://www.health.pa.gov/topics/disease/coronavirus/Pages/Cases.aspx. *Accessed on August 29th*
3. 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):1612-14. doi: 10.1001/jama.2020.4326
4. Myers LC, Parodi SM, Escobar GJ, et al. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. *Jama* 2020 doi: 10.1001/jama.2020.7202 [published Online First: 2020/04/25]
5. 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(20):2052-9. doi: 10.1001/jama.2020.6775 [published Online First: 2020/04/23]
6. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine* 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032
7. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020;55(5) doi: 10.1183/13993003.00524-2020 [published Online First: 2020/04/10]
8. 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):1054-62. doi: 10.1016/s0140-6736(20)30566-3 [published Online First: 2020/03/15]
9. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949.
10. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *Jama* 2019;322(13):1261-70. doi: 10.1001/jama.2019.11825 [published Online First: 2019/10/02]
11. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020;178:104787. doi: 10.1016/j.antiviral.2020.104787 [published Online First: 2020/04/07]
12. te Velthuis AJ, van den Worm SH, Sims AC, et al. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010;6(11):e1001176. doi: 10.1371/journal.ppat.1001176 [published Online First: 2010/11/17]

13. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *Jama* 2001;286(14):1754-8. doi: 10.1001/jama.286.14.1754 [published Online First: 2001/10/12]
14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006 [published Online First: 2009/05/06]
15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120(4):c179-84. doi: 10.1159/000339789 [published Online First: 2012/08/15]
16. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009(113):S1-130. doi: 10.1038/ki.2009.188 [published Online First: 2009/08/01]
17. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38(10):1573-82. doi: 10.1007/s00134-012-2682-1 [published Online First: 2012/08/29]
18. Hazra A. Using the confidence interval confidently. *J Thorac Dis* 2017;9(10):4125-30. doi: 10.21037/jtd.2017.09.14
19. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;97(5):829-38. doi: 10.1016/j.kint.2020.03.005 [published Online First: 2020/04/06]
20. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020 doi: 10.1016/j.jaci.2020.04.006 [published Online First: 2020/04/16]
21. Gustot T. Multiple organ failure in sepsis: prognosis and role of systemic inflammatory response. *Curr Opin Crit Care* 2011;17(2):153-9. doi: 10.1097/MCC.0b013e328344b446 [published Online First: 2011/02/25]
22. Elseviers MM, Lins RL, Van der Niepen P, et al. Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care* 2010;14(6):R221. doi: 10.1186/cc9355 [published Online First: 2010/12/03]
23. Martin C, Viviand X, Leone M, et al. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000;28(8):2758-65. doi: 10.1097/00003246-200008000-00012 [published Online First: 2000/08/31]
24. Wang CY, Calfee CS, Paul DW, et al. One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014;40(3):388-96. doi: 10.1007/s00134-013-3186-3 [published Online First: 2014/01/18]
25. Combes A, Costa MA, Trouillet JL, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med* 2003;31(5):1373-81. doi: 10.1097/01.Ccm.0000065188.87029.C3 [published Online First: 2003/05/29]
26. Li J-W, Han T-W, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. *Progress in Cardiovascular Diseases* 2020 doi: https://doi.org/10.1016/j.pcad.2020.04.008
27. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8(6):e46-e47. doi: 10.1016/s2213-2600(20)30216-2 [published Online First: 2020/05/01]

28. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2017;45(12):2078-88. doi: 10.1097/ccm.0000000000002737 [published Online First: 2017/09/25]
29. Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. *Front Microbiol* 2017;8:1041. doi: 10.3389/fmicb.2017.01041 [published Online First: 2017/07/12]
30. Vrsalovic M, Vrsalovic Presecki A. Cardiac troponins predict mortality in patients with COVID-19: A meta-analysis of adjusted risk estimates. *J Infect* 2020 doi: 10.1016/j.jinf.2020.05.022 [published Online First: 2020/05/18]
31. Tisoncik JR, Korth MJ, Simmons CP, et al. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012;76(1):16-32. doi: 10.1128/mmbr.05015-11 [published Online First: 2012/03/07]
32. Meduri GU, Kohler G, Headley S, et al. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. *Chest* 1995;108(5):1303-14. doi: 10.1378/chest.108.5.1303 [published Online First: 1995/11/01]
33. José RJ, Williams AE, Chambers RC. Proteinase-activated receptors in fibroproliferative lung disease. *Thorax* 2014;69(2):190-2. doi: 10.1136/thoraxjnl-2013-204367 [published Online First: 2013/11/05]
34. Colafrancesco S, Alessandri C, Conti F, et al. COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? *Autoimmun Rev* 2020;19(7):102573. doi: 10.1016/j.autrev.2020.102573 [published Online First: 2020/05/11]
35. Biot C, Daher W, Chavain N, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem* 2006;49(9):2845-9. doi: 10.1021/jm0601856 [published Online First: 2006/04/28]
36. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends* 2020
37. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949. doi: 10.1016/j.ijantimicag.2020.105949 [published Online First: 2020/03/25]
38. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020;382(25):2411-18. doi: 10.1056/NEJMoa2012410 [published Online First: 2020/05/08]
39. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2019014
40. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020 doi: 10.1093/cid/ciaa478 [published Online First: 2020/04/28]
41. Zhang M, Jativa DF. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. *SAGE Open Med* 2018;6:2050312118807615. doi: 10.1177/2050312118807615 [published Online First: 2018/10/27]

42. Cirino Ruocco MA, Pacheco Cechinatti ED, Barbosa F, Jr., et al. Zinc and selenium status in critically ill patients according to severity stratification. *Nutrition* 2018;45:85-89. doi: 10.1016/j.nut.2017.07.009 [published Online First: 2017/11/14]
43. Hasanzadeh Kiabi F, Alipour A, Darvishi-Khezri H, et al. Zinc Supplementation in Adult Mechanically Ventilated Trauma Patients is Associated with Decreased Occurrence of Ventilator-associated Pneumonia: A Secondary Analysis of a Prospective, Observational Study. *Indian J Crit Care Med* 2017;21(1):34-39. doi: 10.4103/0972-5229.198324 [published Online First: 2017/02/16]
44. Annetta M, Maviglia R, Proietti R, et al. Use of corticosteroids in critically ill septic patients : a review of mechanisms of adrenal insufficiency in sepsis and treatment. *Curr Drug Targets* 2009;10(9):887-94. doi: 10.2174/138945009789108792 [published Online First: 2009/10/06]
45. Scaroni C, Armigliato M, Cannavò S. COVID-19 outbreak and steroids administration: are patients treated for Sars-Cov-2 at risk of adrenal insufficiency? *J Endocrinol Invest* 2020:1-2. doi: 10.1007/s40618-020-01253-1 [published Online First: 2020/04/18]
46. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2021436
47. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020 doi: 10.1056/NEJMoa2007764
48. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* 2020;92(7):814-18. doi: 10.1002/jmv.25801 [published Online First: 2020/04/08]
49. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* 2020 doi: 10.1002/jmv.25964 [published Online First: 2020/05/06]
50. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med* 2020;76:43-49. doi: 10.1016/j.ejim.2020.05.021 [published Online First: 2020/06/03]
51. Salazar E, Perez KK, Ashraf M, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. *Am J Pathol* 2020 doi: 10.1016/j.ajpath.2020.05.014 [published Online First: 2020/05/31]
52. Joyner M, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. *medRxiv* 2020:2020.05.12.20099879. doi: 10.1101/2020.05.12.20099879
53. Vittinghoff E, McCulloch CE. Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. *American Journal of Epidemiology* 2007;165(6):710-18. doi: 10.1093/aje/kwk052
54. van Smeden M, de Groot JAH, Moons KGM, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC Medical Research Methodology* 2016;16(1):163. doi: 10.1186/s12874-016-0267-3

Table 1. Demographics and baseline characteristics of included patients.

Characteristics	All patients (n = 283)	Survivors (n = 228)	Non-survivors (n = 55)	P-value
Male	159 (56.2)	125 (54.8)	34 (61.8)	0.348
Age (year)	64.1 (15.9)†	61.9 (15.8)†	72.8 (13.5)†	< 0.001*
Ethnicity				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	0.705
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
Co-morbidities				
Obesity (BMI ≥ 30 kg/m^2)	132 (46.6)	102 (44.7)	30 (54.5)	0.191
Current/Former smokers	109 (38.5)	88 (38.6)	21 (38.2)	0.955
Hypertension	189 (66.8)	145 (63.6)	44 (80.0)	0.020*
Diabetes mellitus	108 (38.2)	81 (35.5)	27 (49.1)	0.063
Hyperlipidemia	121 (42.8)	94 (41.2)	27 (49.1)	0.290
Coronary artery disease	50 (17.7)	40 (17.5)	10 (18.2)	0.911
Heart failure/cardiomyopathy	53 (18.7)	40 (17.5)	13 (23.6)	0.299
Arrhythmia/conduction disorders	45 (15.9)	36 (15.8)	9 (16.4)	0.917
Chronic kidney disease	66 (23.3)	46 (20.2)	20 (36.4)	0.011*
End-stage kidney disease	13 (4.6)	12 (5.3)	1 (1.8)	0.474
Asthma/COPD	73 (25.8)	54 (23.7)	19 (34.5)	0.098
Cerebrovascular disease	40 (14.1)	32 (14.0)	8 (14.5)	0.922
Signs and symptoms				
Cough	185 (65.4)	149 (65.4)	36 (65.5)	0.988
Dyspnea	203 (71.7)	158 (69.3)	45 (81.8)	0.064
Hypoxia (SpO2 < 95%)	178 (62.9)	130 (57.0)	48 (87.3)	< 0.001*
Rhinorrhea	29 (10.2)	26 (11.4)	3 (5.5)	0.226
Fever/chills	179 (63.3)	143 (62.7)	36 (65.5)	0.706
Chest pain	35 (12.4)	32 (14.0)	3 (5.5)	0.109
Headache	28 (9.9)	26 (11.4)	2 (3.6)	0.128
Gastrointestinal symptoms	79 (27.9)	68 (29.8)	11 (20.0)	0.145
Asymptomatic	8 (2.8)	8 (3.5)	0 (0)	0.361
Rales/crackles	57 (20.1)	40 (17.5)	17 (30.9)	0.027*
Rhonchi	57 (20.1)	45 (19.7)	12 (21.8)	0.730
Reduced breath sound	63 (22.3)	48 (21.1)	15 (27.3)	0.320
Laboratory findings				
Leukopenia (WBC < 4,000 /uL)	56 (19.8)	46 (20.2)	10 (18.2)	0.739
Leukocytosis (WBC > 10,000 /uL)	80 (28.3)	53 (23.2)	27 (49.1)	< 0.001*
Lymphocytopenia (ALC < 1,000 / uL)	109 (38.7)	78 (34.2)	31 (57.4)	0.002*
Thrombocytopenia (< 140,000 /uL)	57 (20.1)	41 (18.0)	16 (29.1)	0.065
Thrombocytosis (> 400,000 /uL)	31 (11.0)	25 (11.0)	6 (10.9)	0.991
Respiratory acidosis	43 (21.3)	18 (11.8)	25 (50.0)	< 0.001*
Transaminitis (ALT > 3X UNL)	33 (12.4)	21 (9.9)	12 (21.8)	0.017*
Serum creatinine (mg/dL) on admission	1.06 (0.72)‡	1.59 (1.88)†	1.64 (1.15)†	0.808
eGFR (mL/min/1.73m^2)	64.2 (51.0)†	66.7 (35.5)†	53.6 (25.3)†	0.002*
Troponin I (> 0.03 ng/mL)	91 (39.1)	61 (33.0)	30 (62.5)	< 0.001*

Inflammatory markers				
D-dimer (> 500 ng/mL)	135 (80.4)	101 (75.4)	34 (100)	< 0.001*
Ferritin (> 336 ng/mL)	109 (65.3)	78 (59.1)	31 (88.6)	0.001*
Lactate dehydrogenase (> 200 U/L)	108 (73.0)	77 (67.0)	31 (93.9)	0.002*
C-reactive protein (> 1 mg/dL)	152 (87.4)	115 (83.9)	37 (100)	0.005*
Procalcitonin (> 0.25 ng/mL)	73 (47.1)	50 (41.7)	23 (65.7)	0.012*
ST-T change on EKG	84 (31.8)	63 (29.7)	21 (40.4)	0.139
Radiographic findings				
Opacity/infiltrate	209 (73.9)	162 (71.1)	47 (85.5)	0.029*
Ground glass appearance	79 (27.9)	65 (28.5)	14 (25.5)	0.650
Pleural effusion	24 (8.5)	17 (7.5)	7 (12.7)	0.208
Pulmonary congestion	30 (10.6)	23 (10.1)	7 (12.7)	0.568
Oxygen therapy/delivery				
Nasal cannula	207 (73.1)	160 (70.2)	47 (85.5)	0.022*
High-flow nasal cannula	36 (12.7)	18 (7.9)	18 (32.7)	< 0.001*
NIPPV	28 (9.9)	10 (4.4)	18 (32.7)	< 0.001*
Mechanical ventilation	58 (20.5)	25 (11.0)	33 (60.0)	< 0.001*
Intervention				
Intensive care unit	89 (31.4)	47 (20.6)	42 (76.4)	< 0.001*
ECMO	2 (0.7)	0 (0)	2 (3.6)	0.037*
RRT	16 (5.7)	3 (1.3)	13 (23.6)	< 0.001*
Vasopressor	53 (18.7)	19 (8.3)	34 (61.8)	< 0.001*
Antibiotics	220 (77.7)	166 (72.8)	54 (98.2)	< 0.001*
Treatment				
Azithromycin	182 (64.3)	139 (61.0)	43 (78.2)	0.017*
Hydroxychloroquine	67 (23.7)	45 (19.7)	22 (40.0)	0.002*
Steroids	46 (16.3)	26 (11.4)	20 (36.4)	< 0.001*
Ascorbic acid	57 (20.1)	38 (16.7)	19 (34.5)	0.003*
Zinc	54 (19.1)	33 (14.5)	21 (38.2)	< 0.001*
Tocilizumab	12 (4.2)	6 (2.6)	6 (10.9)	0.006*
Convalescent plasma	36 (12.7)	19 (8.3)	17 (30.9)	< 0.001*
Remdesivir	25 (8.8)	20 (8.8)	5 (8.8)	0.940
Complications				
Acute kidney injury	115 (40.6)	75 (32.9)	40 (72.7)	< 0.001*
ARDS	53 (18.7)	17 (7.5)	36 (65.5)	< 0.001*
Arrhythmias	31 (11.0)	18 (7.9)	13 (23.6)	0.001*
QT prolongation	25 (8.8)	18 (7.9)	7 (12.7)	0.257
Venous thromboembolism	10 (3.5)	8 (3.5)	2 (3.6)	1.000
Arterial thrombosis	1 (0.4)	1 (0.4)	0 (0)	1.000
Cerebrovascular event	3 (1.1)	3 (1.3)	0 (0)	1.000
Myocardial infection	5 (1.8)	4 (1.8)	1 (1.8)	1.000
Heart failure	16 (5.7)	11 (4.8)	5 (9.1)	0.219
Superimposed bacteremia	19 (6.7)	12 (5.3)	7 (12.7)	0.047*
Hospital stay (day)	6.0 (7.0)‡	7.4 (7.53)†	9.2 (7.7)†	0.125
Outcome				
Recovery/discharge	223 (78.8)			
Remained hospitalized	2 (0.7)			
Death	55 (19.4)			

ALC, absolute lymphocyte count; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extra-corporal membrane oxygenation; eGFR, estimated glomerular filtration rate; EKG, electrocardiography; IQR, interquartile range; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy; SD, standard deviation; SpO2, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.

*statistically significant

†mean (standard deviation)

‡ median (IQR)

Table 2. Clinical risk factors for overall in-hospital mortality using univariate binary logistic regression analysis.

Characteristics	Odds ratio	95% CI	P-value
Age (per 1-year increment)	1.051	1.028-1.075	< 0.001*
Hypertension	2.288	1.121-4.673	0.024*
Chronic kidney disease	2.262	1.195-4.274	0.012*
Hypoxia (SpO2 < 95%)	5.181	2.242-11.905	< 0.001*
Rales/crackles	2.101	1.080-4.098	0.029*
Leukocytosis (WBC > 10,000 /uL)	3.185	1.727-5.882	< 0.001*
Respiratory acidosis	7.463	3.546-15.625	< 0.001*
Transaminitis (ALT > 3X UNL)	2.538	1.160-5.556	0.020*
eGFR (per 1.0 mL/min/1.73m^2 increment)†	0.988	0.980-0.997	0.011*
D-dimer (> 500 ng/mL)‡	-	-	-
Ferritin (> 336 ng/mL)	5.376	1.789-16.129	0.003*
Lactate dehydrogenase (> 200 U/L)	7.634	1.739-33.333	0.007*
C-reactive protein (> 1 mg/dL)‡	-	-	-
Procalcitonin (> 0.25 ng/mL)	2.681	1.222-5.882	0.014*
Troponin I (> 0.03 ng/mL)	3.390	1.751-6.536	< 0.001*
Opacity/infiltrate on imaging	2.392	1.073-5.348	0.033*
Nasal cannula	2.494	1.120-5.556	0.025*
High-flow nasal cannula	5.682	2.703-11.905	< 0.001*
NIPPV	10.638	4.545-2.500	< 0.001*
Mechanical ventilation	12.195	6.173-23.810	< 0.001*
ICU admission/transfer	12.500	6.173-25.000	< 0.001*
ECMO‡	-	-	-
RRT	23.256	6.329-83.333	< 0.001*
Vasopressor	17.857	8.696-37.037	< 0.001*
Antibiotics	20.000	2.732-142.857	0.003*
Azithromycin	2.294	1.147-4.587	0.019*
Hydroxychloroquine	2.710	1.443-5.102	0.002*
Steroids	4.444	2.237-8.772	< 0.001*
Ascorbic acid	2.639	1.370-5.076	0.004*
Zinc	3.650	1.898-7.042	< 0.001*
Tocilizumab	4.525	1.403-14.706	0.012*
Convalescent plasma	4.921	2.348-10.314	< 0.001*
Acute kidney injury	5.435	2.825-10.417	< 0.001*
ARDS	23.256	11.236-50.000	< 0.001*
Arrhythmia	3.610	1.645-7.937	0.001*
Superimposed bacteremia	2.625	0.982-6.993	0.054

ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy.
*statistically significant
†on admission
‡analyses cannot be performed as at least one cell is zero

Table 3. Clinical predictors for overall in-hospital mortality using multivariate binary logistic regression analysis.

	Statistics		
Characteristics	**Odds ratio**	**95% CI**	**P-value**
Model 1			
Age (per 1-year increment)	1.075	1.045-1.105	< 0.001*
Hypertension	1.264	0.572-2.793	0.562
Chronic kidney disease	1.232	0.590-2.571	0.578
Hypoxia (SpO2 < 95%)	4.630	1.934-1.111	0.001*
Rales/crackles	2.016	0.955-4.255	0.066
Leukocytosis (WBC > 10,000 /uL)	2.732	1.412-5.263	0.003*
Transaminitis (ALT > 3X UNL)	2.137	0.890-5.128	0.089
eGFR (per 1.0 mL/min/1.73m^2 decrement)†	1.002	0.990-1.013	0.795
Ferritin (> 336 ng/mL)	4.016	1.195-13.514	0.025*
Lactate dehydrogenase (> 200 U/L)	7.752	1.639-37.037	0.010*
Procalcitonin (> 0.25 ng/mL)	2.404	1.011-5.714	0.047*
Troponin I (> 0.03 ng/mL)	2.242	1.080-4.673	0.030*
Opacity/infiltrate on imaging	3.077	1.276-7.407	0.012*
Nasal cannula	1.883	0.799-4.444	0.148
High-flow nasal cannula	4.608	2.053-10.309	< 0.001*
NIPPV	7.246	2.899-18.182	< 0.001*
Mechanical ventilation	13.889	6.211-31.250	< 0.001*
ICU admission/transfer	13.699	6.135-30.303	< 0.001*
RRT	21.277	5.025-90.909	< 0.001*
Vasopressor	22.222	9.434-52.632	< 0.001*
Antibiotics	17.544	2.309-125.000	0.006*
ARDS	23.810	10.204-55.556	< 0.001*
Superimposed bacteremia	2.041	0.645-6.452	0.224
Model 2			
Azithromycin	1.916	0.788-4.651	0.152
Hydroxychloroquine	1.057	0.467-2.392	0.894
Ascorbic acid	1.008	0.440-2.313	0.985
Zinc	1.517	0.651-3.546	0.334
Tocilizumab	1.499	0.381-5.917	0.562
Convalescent plasma	1.513	0.600-3.817	0.381
Model 3			
Respiratory acidosis	3.745	1.443-9.709	0.007*
Steroids therapy	1.107	0.459-2.667	0.821

Model 4			
Acute kidney injury	2.268	1.025-5.025	0.043*
Model 5			
Arrhythmias as complications	1.161	0.428-3.155	0.769

ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy.
*statistically significant
Model 1 is adjusted for age, sex, ethnicity and obesity
Model 2 is adjusted for age, sex, ethnicity, obesity, need for oxygen therapy, and ICU admission
Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/COPD, need for oxygen therapy, and ICU admission
Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, need for oxygen therapy, and ICU admission
Model 5 is adjusted for age, sex, ethnicity, obesity, CAD, heart failure, history of arrhythmia/conduction disorder, and ICU admission

Table 4. Demographics and baseline characteristics of critically ill patients (n = 89).

Characteristics	All patients (n = 89)	Survivors (n = 47)	Non-survivors (n = 42)	P-value
Male	61 (68.5)	30 (63.8)	31 (73.8)	0.365
Age (year)	66.0 (14.2)†	69.1 (12.5)†	63.3 (15.2)†	0.052
SOFA score†‡	4.3 (2.0)	3.6 (1.7)	5.1 (1.9)	< 0.001*
Ethnicity				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	
African-American	25 (28.1)	12 (25.5)	13 (31.0)	
Hispanic/Latino	12 (13.5)	8 (17.0)	4 (9.5)	0.685
Asian	5 (5.6)	2 (4.3)	3 (7.1)	
Others	-	-	-	
Treatment				
Azithromycin	69 (77.5)	34 (72.3)	35 (83.3)	0.215
Hydroxychloroquine	42 (47.2)	23 (48.9)	19 (45.2)	0.727
Steroids	39 (43.8)	19 (40.4)	20 (47.6)	0.495
Ascorbic acid	39 (43.8)	22 (46.8)	17 (40.5)	0.548
Zinc	40 (44.9)	21 (44.7)	19 (45.2)	0.958
Tocilizumab	11 (12.4)	5 (10.6)	6 (14.3)	0.750
Convalescent plasma	30 (33.7)	14 (29.8)	16 (38.1)	0.408
Remdesivir	11 (12.4)	6 (12.8)	5 (11.9)	1.000
Complications				
Acute kidney injury	56 (62.9)	22 (46.8)	34 (81.0)	0.001*
ARDS	47 (52.8)	15 (31.9)	32 (76.2)	< 0.001*
Arrhythmias	21 (23.6)	10 (21.3)	11 (26.2)	0.586
QT prolongation	16 (18.0)	10 (21.3)	6 (14.3)	0.391
Venous thromboembolism	5 (5.6)	3 (6.4)	2 (4.8)	1.000
Hospital stay (day)	13.1 (9.6)†	10.4 (8.1)†	15.5 (10.3)†	0.125
Outcome				
Recovery/discharge	43 (48.3)			
Remained hospitalized	2 (2.2)			
Death	42 (47.2)			

ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment
*statistically significant
†mean (standard deviation)
‡collected on the first day of ICU admission

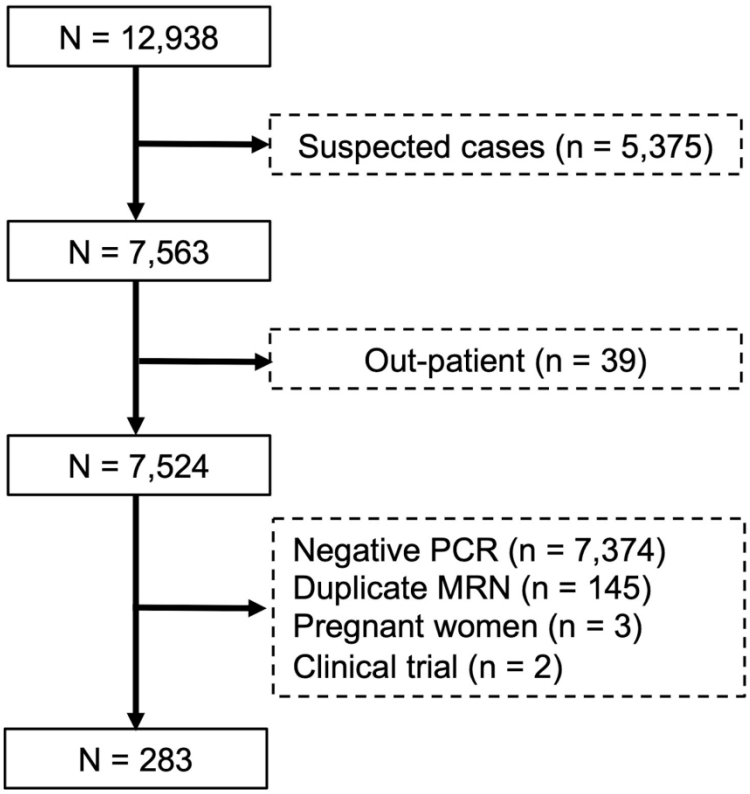

Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

203x185mm (300 x 300 DPI)

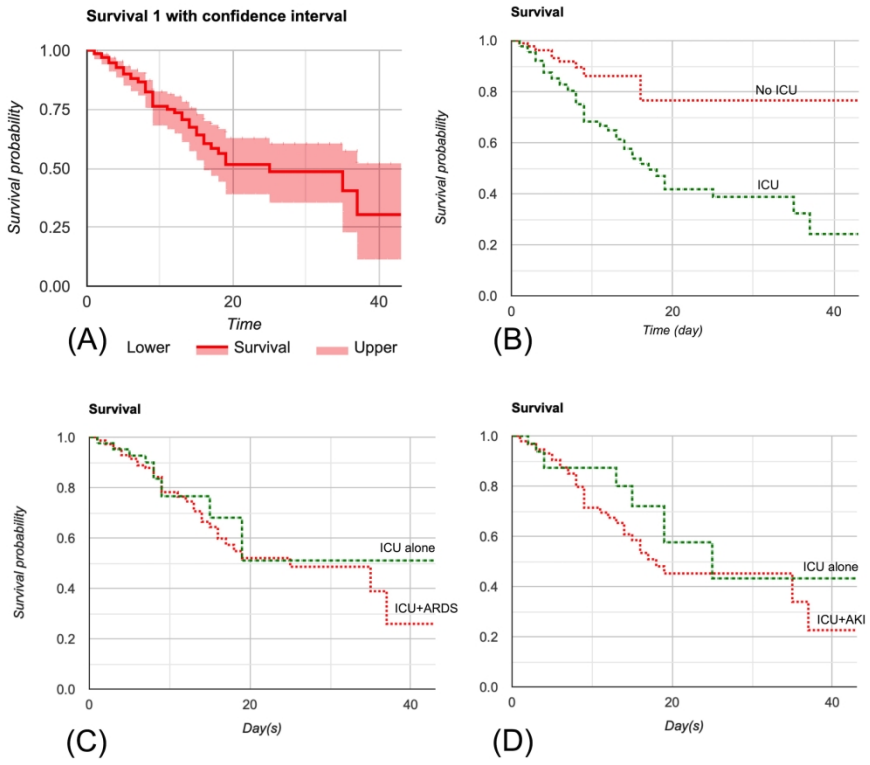

Figure 2. Survival analysis by Kaplan-Meier curves. A) The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. B) ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively (p = 0.002). C) The cumulative survival between ICU patients with and without acute respiratory distress syndrome (p = 0.302). D) The cumulative survival between ICU patients with and without acute kidney injury (p = 0.504).

254x228mm (300 x 300 DPI)

Data collection (con't):

The demographic data included age, sex, and ethnicity. Co-morbidities included current/prior history of smoking, obesity (BMI ≥ 30 kg/m^2), hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, heart failure/cardiomyopathy, arrhythmia, chronic kidney disease, end-stage kidney disease (ESKD), asthma/chronic pulmonary obstructive disease, and cerebrovascular diseases.

Laboratory findings were recorded: leukocytosis (white blood cells count > 9,500/μL), leukopenia (white blood cells count < 3,900/μL), lymphocytopenia (absolute lymphocytes count < 600/μL), thrombocytosis (platelets > 400,000/μL), and thrombocytopenia (platelets < 140,000/μL), respiratory acidosis (arterial pH < 7.35 and arterial partial pressure of CO_2 > 45 mmHg), transaminitis (alanine transaminase > 3 times of upper normal limit). Serum creatinine (mg/dL) was measured by enzymatic assay. Elevation of serum D-dimer (> 500 ng/mL), ferritin (> 336 ng/mL) lactate dehydrogenase (LDH; > 200 U/L), C-reactive protein (> 1 mg/dL), procalcitonin (> 0.25 ng/mL), and troponin I (> 0.03 ng/mL; Backman Coulter DxI).

Please note that the cutoff values were determined by the National Reference Laboratory.

Rationale for multivariate analysis models

Model 1 is adjusted for the baseline co-morbidities (age, sex, ethnicity, obesity). Some of these co-variates showed significant association with death on univariate analysis. Without these adjustments, the aforementioned co-variates will act as confounding factors.

Model 2 is adjusted for all factors in Model 1 plus "the need for oxygen therapy" because the interventions included in Model 2 (azithromycin, hydroxychloroquine, ascorbic acid, zinc, tocilizumab, convalescent plasma) were usually given in patients who required oxygen therapy. Thus, in this Model, "the need for oxygen therapy" was held constant allowing us to determine if these interventions were associated with death.

For Model 3, "respiratory acidosis, and steroids therapy" are usually seen in patients with asthma, COPD, critical illnesses and those who required oxygen therapy. These factors are potential confounders. Thus, we adjusted this Model for "asthma/COPD"; "the need for oxygen therapy"; and "ICU admission" to determine the true association between the variables and death.

In Model 4, "acute kidney injury" is defined by serum creatinine elevation. Patients with CKD would also have some elevation of serum creatinine levels. Thus, CKD would be a potential confounder. That is why we adjusted the Model for "CKD"; "need for oxygen therapy"; and "ICU admission" as all of these factors may contribute to death.

In Model 5, “arrhythmias” is a cardiac complication, hence we adjusted for every variable that could be the confounding factor, such as CAD, heart failure, history of arrhythmia/conduction disorder, and ICU admission.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, Line 31-32
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, Line 129-131
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5, Line 134
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6, Line 159-166
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6, Line 159-166
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6, Line 168-183 Supplemental Document 1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supplemental Document 1
Bias	9	Describe any efforts to address potential sources of bias	Page 6, Line 168-169
Study size	10	Explain how the study size was arrived at	Page 6, Line 159-166
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7, Line 190-196
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7-8, Line 189-221
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	Page 7, Line 196
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A

		(*e*) Describe any sensitivity analyses	Page 8, Line 215-218
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8, Line 225-228
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2-3
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 10-11, Line 271-302
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 11-16, Line 309-467
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 16-17, Line 468-491
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17, Line 490-491
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 19, Line 538

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.