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

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3 **Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality:**  
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5 **A Single-network, Retrospective Cohort Study from Pennsylvania State**  
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7  
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36

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## 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 1<sup>st</sup> to May 31<sup>st</sup>, 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  $64.1 \pm 15.9$  years. 56.2% were male and 50.2% were white. In adjusted multivariate analyses, increasing age (per 1-year increment; OR 1.075), hypoxia ( $\text{SpO}_2 < 95\%$ ; OR 4.630), opacity/infiltrate on imaging (OR 3.077), leukocytosis ( $\text{WBC} > 10,000/\mu\text{L}$ ; 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

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3 7.042), acute kidney injury (OR 3.571) and arrhythmias (OR 2.494) were significant risk factors  
4  
5 for increased in-hospital death. The median survival time was  $25.0 \pm 7.0$  days.  
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8 **Conclusion:** We reported the characteristics of ethnically diverse, hospitalized patients with  
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10 COVID-19 from Pennsylvania state.  
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### 17 **Strengths and Limitation of This Study**

#### 18 *Strength*

- 19 - This study is first retrospective cohort study of COVID-19 patients from the state of  
20  
21 Pennsylvania  
22  
23 - Our study is among one of few studies that reported the associations between ascorbic  
24  
25 acid and zinc supplementation and in-hospital mortality from COVID-19  
26  
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28  
29 - Multivariate analysis (binary logistic regression model) was used to report the results  
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#### 33 *Limitation*

- 34 - Non-randomized design  
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37 - Potential confounding factors should be considered  
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## 44 **INTRODUCTION**

45  
46 Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute  
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48 Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has become a pandemic in early  
49  
50 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and  
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52 rapidly escalated to 216 countries within five months with the highest number of infected cases  
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3 in the United States.<sup>1</sup> The reported mortality of COVID-19 in the United States was 5.92% as of  
4  
5 May 30<sup>th</sup>, 2020.<sup>1</sup>  
6

7  
8 Guan, et al first described the clinical characteristics of 1,099 patients infected with  
9  
10 SARS-CoV-2 across China.<sup>2</sup> In this study, the overall mortality was 1.4%. However, the  
11  
12 association between clinical risk factors and mortality was not described. Later Du et al and  
13  
14 Zhou et al demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA)  
15  
16 score, D-dimer > 1 µg/mL, cardiac troponin I ≥ 0.05 ng/mL, and pre-existing concurrent  
17  
18 cardiovascular and cerebrovascular diseases were significant predictors for increased mortality  
19  
20 from COVID-19.<sup>3 4</sup> However, these findings were primarily based on Chinese population; thus, it  
21  
22 has been unconfirmed if the results can be applicable to other patient populations.  
23  
24

25  
26 As of May 30<sup>th</sup>, 2020, the Department of Health has announced more than 69,916  
27  
28 confirmed cases of COVID-19 leading to 5,555 deaths in the state of Pennsylvania.<sup>5</sup> To date, the  
29  
30 characteristics of infected patients in the United States were reported in the state of Washington  
31  
32 (n = 21), California (n = 1,299) and New York (n = 5,700) in chronological order.<sup>6-8</sup> The  
33  
34 mortality across the U.S. studies ranged from 6.3 to 24%, depending on the severity of COVID-  
35  
36 19. However, clinical risk factors for increased mortality in the U.S. population have not been  
37  
38 clearly established.  
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42 Clinical management of COVID-19 has been dynamic and variable based on available  
43  
44 research, which has largely been *in vitro*, such as a combination of hydroxychloroquine and  
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46 azithromycin,<sup>9</sup> ascorbic acid,<sup>10</sup> ivermectin,<sup>11</sup> and zinc.<sup>12</sup> These therapies have not been proven  
47  
48 beneficial in clinical studies. In the current study, we provide our experience on treatment options  
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50 for patients infected with SARS-CoV-2.  
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3 In this retrospective cohort, we aimed to demonstrate the clinical characteristics of COVID-  
4 19 patients, treatment outcomes and the impact on in-hospital mortality. This study is intended to  
5 serve as one of the earliest cohorts of COVID-19 patients from the United States.  
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## 11 **MATERIALS AND METHODS**

### 12 ***Study design***

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

29 No patient involved.  
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32

### 33 ***Data source and patient population***

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35 Data were collected by extracting electronic medical records from March 1<sup>st</sup> to May 31<sup>th</sup>,  
36 2020 through UPMC Pinnacle COVID-19 registry. Adult patients with age  $\geq 18$  years who were  
37 hospitalized with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-  
38 PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalized  
39 patients, patients  $< 18$  years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-  
40 system transfer and patients enrolled in clinical trials. Transfer within the system was considered  
41 one admission. For patients with multiple admissions with study period, the first admission for  
42 COVID-19 was reviewed.  
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### 53 ***Data collection***



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3 Individual patient charts were reviewed. Collected data was divided into: demographics,  
4 comorbidities, signs and symptoms, laboratory findings, radiographic findings,  
5  
6 treatments/interventions, complications and outcomes. *Supplemental Documents 1* summarizes the  
7  
8 description of each variable in our cohort.  
9  
10

11  
12 Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation.<sup>13</sup>  
13  
14 Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL (27  
15  $\mu\text{mol/L}$ ) or  $\geq 1.5$  times from the baseline value within 48 hours.<sup>14</sup> Chronic kidney disease (CKD)  
16  
17 was defined by the Kidney Diseases Improving Global Outcomes guidelines.<sup>15</sup> Patients with  
18  
19 history of end stage kidney disease (ESKD) on dialysis prior to admission, were not counted  
20  
21 toward 'requirement of renal replacement therapy (RRT)/hemodialysis (HD)' during the hospital  
22  
23 stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.<sup>16</sup>  
24  
25 Arrhythmias as complications were defined either tachy- or bradyarrhythmia that were new-onset,  
26  
27 occurred during hospitalization with COVID-19. In this study, prolongation of QT segment was  
28  
29 defined as the QT duration  $> 500$  milliseconds.  
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### 34 ***Study outcomes***

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36 The primary outcome was in-hospital mortality. The secondary outcome included  
37  
38 treatment outcomes and complications such as recovery/discharge, AKI, ARDS, arrhythmias, QT  
39  
40 prolongation, venous thromboembolism, arterial thrombosis, cerebrovascular events, heart  
41  
42 failure, and myocardial infarction.  
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### 45 ***Statistical analysis***

46  
47 All analyses were conducted using SPSS software version 23.0 (IBM Corp., Armonk,  
48  
49 NY, USA). Descriptive analyses were reported in percentage for categorical data and in mean  $\pm$   
50  
51 standard deviation (S.D.) or median (interquartile range; IQR) depending the data distribution.  
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3 Comparisons of outcomes for each variable were evaluated using Pearson's  $\chi^2$  tests or Fisher-  
4 Exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher-  
5 Exact tests were opted if the total sample in any cell count was less than five. A p-value less than  
6 0.05 is considered statistically significant.  
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### 12 ***Logistic regression analysis***

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

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

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

### 11 *Baseline characteristics and patient outcomes*

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14 The flowchart of data selection from the UPMC Pinnacle COVID-19 registry is depicted  
15 in *Figure 1*. A total of 322 patients with confirmed SARS-CoV-2 infection were identified during  
16 the study period. Of 322 patients, 39 patients (12.1%) were outpatient and did not require  
17 hospitalization. After excluding these patients, 283 patients were included for further analysis.  
18  
19 *Table 1* summarizes the demographics and baseline characteristics of included patients. All  
20 patients had confirmed SARS-Cov-2 infection by RT-PCR. Of 283 patients, 80.6% were survivors  
21 and 19.4% were non-survivors. The mean age of all patients was  $64.1 \pm 15.9$  years. 56.2% were  
22 male and 50.2% were Caucasian. Non-survivors were significantly older and had higher proportion  
23 of hypertension, CKD and had lower mean eGFR. Moreover, hypoxia on presentation,  
24 rales/crackles on physical examination, leukocytosis, lymphocytopenia, respiratory acidosis,  
25 transaminitis, and opacity/infiltrate on imaging were common presentations in non-survivors.  
26 Higher inflammatory markers, such as D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive  
27 protein, and procalcitonin were significantly prevalent in deceased patients. The need for oxygen  
28 therapy regardless of the mode of oxygen delivery was higher among those who did not survive.  
29 Furthermore, non-survivors were more likely to have received intensive care unit (ICU)  
30 admission/transfer, extracorporeal membrane oxygenation (ECMO), RRT, use of vasopressors,  
31 use of antibiotics, azithromycin, hydroxychloroquine, steroids, ascorbic acid, zinc, tocilizumab  
32 and convalescent plasma. Of overall complications, the prevalence of AKI, ARDS, arrhythmias  
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3 and superimposed bacteremia was significantly higher in non-survivors. There was no significant  
4 difference in mean hospital stay between survivors and non-survivors. Up to 78.8% recovered or  
5 were discharged from the hospital. Only two patients remained hospitalized as of June 18, 2020.  
6  
7 The mean hospital stay was similar between patients who received remdesivir vs. those who did  
8 not ( $9.0 \pm 4.7$  and  $7.6 \pm 7.8$  days, respectively;  $p = 0.359$ ). In contrast, patients who received  
9 tocilizumab had significantly longer hospital stay compared to those who did not receive  
10 tocilizumab ( $15.3 \pm 11.7$  and  $7.4 \pm 7.2$  days, respectively;  $p < 0.001$ ).

### 19 ***Univariate analysis***

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

### 35 ***Multivariate analysis***

37 Variables that were significant on univariate analysis were included in multivariate logistic  
38 regression analysis (*Table 3*). In Model 1 (adjusted for age, sex, ethnicity, and obesity), increasing  
39 patient age, hypoxia, opacity/infiltrate on imaging, leukocytosis, ferritin  $> 336$  ng/mL, LDH ( $>$   
40  $200$  U/L), procalcitonin  $> 0.25$  ng/mL, troponin I  $> 0.03$  ng/mL, use of high-flow oxygen nasal  
41 cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU  
42 admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for  
43 increased in-hospital mortality. In Model 2 (adjusted for all variables in Model 1 including the  
44 need for oxygen therapy), hydroxychloroquine, ascorbic acid, zinc, and convalescent plasma were  
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3 associated with increased mortality. In Model 3 (adjusted for all variables in Model 2 including  
4 asthma/COPD), respiratory acidosis and steroid therapy were associated with increased mortality.  
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6 AKI and arrhythmias were independent risk factors for in-hospital mortality from COVID-19 from  
7  
8 Model 4 and 5, respectively. Moreover, we also found that hydroxychloroquine therapy was  
9  
10 associated with QT prolongation (OR 2.874; 95% CI 1.189-6.944;  $p = 0.019$ ) after adjusted for  
11  
12 covariates in Model 2. The association of these variables and overall mortality remained significant  
13  
14 on bootstrap analysis when the sample size was imputed to 1,000.  
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### 18 19 *Cohort of critically ill patients*

20  
21 A total 89 patients required intensive care during the study period. Of which, 47.2% died.  
22  
23 The demographics and clinical characteristics of critically ill patients are demonstrated in *Table*  
24  
25 4. Deceased ICU patients had significantly higher proportion of AKI and ARDS compared to  
26  
27 survived ICU patients. The treatments were similar between survivors and non-survivor patients.  
28  
29 In multivariate analysis, AKI (OR 3.759, 95% CI 1.342-10.526;  $p = 0.012$ ) and ARDS (OR  
30  
31 7.937; 95% CI 2.857-21.739;  $p < 0.001$ ) are significantly predictive of in-hospital mortality  
32  
33 among patients admitted the ICU after adjusted for age, sex, and ethnicity.  
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### 37 38 *Survival analysis*

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

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51 In this single-network, retrospective observation study, we found that the overall in-  
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53 hospital mortality among hospitalized COVID-19 patients was 19.4%. The reported mortality  
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3 among Chinese cohorts ranged from 11.7% to 28.2%.<sup>3 4 17</sup> However, our reported mortality rates  
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5 appeared slightly lower than what previously described from New York City.<sup>8</sup> Richardson et al  
6  
7 found that the overall mortality of 5,700 hospitalized COVID-19 patients from 12 hospitals in  
8  
9 New York City was 21%. However, one could argue that our study has significantly smaller  
10  
11 sample size which might underestimate the actual mortality of COVID-19. Our data need  
12  
13 confirmation from other studies with a larger sample size.  
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16  
17 We identified several risk factors for mortality from COVID-19 using multivariate  
18  
19 logistic regression analysis. Increasing age, hypoxia and opacity/infiltrate on imaging were  
20  
21 associated with higher mortality. Moreover, we also found that patient survival diminished as the  
22  
23 disease progressed, reflected by advancement in oxygen delivery (high-flow nasal cannula,  
24  
25 NIPPV, and mechanical ventilation). Requiring a simple oxygen nasal cannula did not affect  
26  
27 mortality. Such findings are similar to previous literature. Older age is an independent risk factor  
28  
29 for severe COVID-19 and mortality.<sup>3 18</sup> In line with Zhou et al, increasing oxygen requirement  
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31 and need for advanced oxygen delivery were predictive of death from COVID-19.<sup>4</sup>  
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36 Here, we showed that COVID-19 patients requiring ICU had 13.7-fold increased risk of  
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38 mortality. Critically ill patients generally had one or more organs in failure, and an increasing  
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40 number of organ failure has been linked to elevated death in sepsis patients.<sup>19</sup> For COVID-19  
41  
42 patients, we demonstrated that kidney (AKI, and RRT), pulmonary (respiratory acidosis, and  
43  
44 ARDS), cardiovascular (arrhythmias, and vasopressor requirement) failure were predictive of in-  
45  
46 hospital mortality. These findings are in line with other cohorts and each factor has been  
47  
48 demonstrated as an independent risk factor for mortality in critically ill patients.<sup>4 20-24</sup> Although  
49  
50 the complications from SARS-CoV-2 infection can be affected by multiple contributing factors,  
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52 newer evidence has suggested the significance of cytokine storm leading to multi-organ failure.<sup>25</sup>  
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3 Here, we showed that elevated ferritin, LDH, procalcitonin, leukocytosis, troponin I and  
4 possibly D-dimer were associated with increased death. Although, the odds ratio for D-dimer  
5 cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-  
6 dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be  
7 ignored. Guan et al first demonstrated the importance of elevated inflammatory markers in  
8 COVID-19 in Chinese population<sup>2</sup> which has become a standard monitoring parameter for  
9 COVID-19 patients.<sup>26</sup> Elevated inflammatory markers should prompt physicians to evaluate and  
10 monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated  
11 procalcitonin and leukocytosis may indicate concomitant bacterial infection, which has been  
12 shown to increase morbidity and mortality of viral pneumonia.<sup>27</sup> Interestingly, our study showed  
13 that elevated troponin I level was associated with significantly higher death similar to a recent  
14 meta-analysis.<sup>28</sup> Although the etiologies of elevated troponin levels were not determined in our  
15 cohort, other studies proposed several mechanisms for elevated troponin level in COVID-19  
16 patients. These include myocarditis, cytokine mediated myocardial injury, microangiopathy of  
17 small coronary arteries, or silent coronary artery disease.<sup>24 28</sup>

18  
19 The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses  
20 or bacteria.<sup>29</sup> Cytokine storm is characterized by the overproduction of pro-inflammatory  
21 cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1 $\beta$  resulting in an increased  
22 vascular hyperpermeability, and activation of multiple coagulation pathways.<sup>25 30</sup> In light of  
23 SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and  
24 the protein C system were impaired during active inflammation.<sup>31</sup> These changes lead to  
25 thrombin hyperactivity resulting in the development of microthrombosis, disseminated  
26 intravascular coagulation (DIC) and sequential multiorgan failure.<sup>25</sup> Moreover, new studies have

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2  
3 revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are  
4 beyond the scope of our article.<sup>32</sup> Such syndromes include macrophage activation syndrome,  
5  
6 adult-onset Still's disease, and catastrophic anti-phospholipid syndrome.<sup>32</sup>  
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10 Hydroxychloroquine therapy was associated with a 3-fold increased risk of QT  
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12 prolongation and a 2-fold increased risk of death. The concept of using hydroxychloroquine in  
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14 COVID-19 patients derived from an early *in vitro* study.<sup>33</sup> The results from small non-  
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16 randomized clinical trials also showed promising effects on viral load reduction.<sup>34 35</sup> However,  
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18 the clinical benefit of hydroxychloroquine was debated by a large observation study. Of 1,446  
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20 patients, Geleris et al observed that hydroxychloroquine had no effect on the death, length of stay  
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22 or intubation.<sup>36</sup> Thus, the recommendation for use of hydroxychloroquine was recalled by the  
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24 Infectious Diseases Society of America (IDSA) due to small sample size in previous clinical  
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26 trials and concern for cardiac adverse effects, such as QT prolongation/torsade de pointe.<sup>37</sup>  
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29 Whether hydroxychloroquine has clinical benefits is yet to be discovered in a multi-center  
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31 randomized controlled trial (NCT04370782).  
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35 A meta-analysis of four randomized trials and one retrospective study showed that the  
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37 administration of intravenous vitamin C has vasopressor sparing effects and may reduce the need  
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39 for mechanical ventilation in critically ill patients while there was no effect on the mortality.<sup>38</sup>  
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42 However, given the lack of more supporting evidence, the standard use of ascorbic acid is not yet  
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44 recommended especially in COVID-19 patients. A new clinical trial investigating the treatment  
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46 outcome of vitamin C in severe COVID-19 is underway (NCT04264533).  
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49 Our study is the first cohort showing that zinc supplementation was associated with  
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51 increased mortality in COVID-19 patients. A Brazilian study revealed that plasma zinc  
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53 concentration in critically ill patients upon admission to the ICU was low and may make these  
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3 patients more susceptible to oxidative stress.<sup>39</sup> Another prospective study showed that zinc  
4 supplementation in mechanically ventilated patients was related to less ventilator-associated  
5 pneumonia.<sup>40</sup> However, the mean duration of intubation in this study was prolonged (29 days),  
6 making it inconclusive if zinc supplementation can prevent pneumonia development in short-  
7 term intubation. Thus, the use of zinc supplementation in COVID-19 patients should be  
8 discouraged until supporting evidence from randomized controlled trials is available.  
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17 Steroid therapy in COVID-19 patients was associated with increased mortality. However,  
18 one limitation that a causal relationship between corticosteroids and mortality was difficult to  
19 establish given that our deceased patients had been generally more ill and sustained multi-organ  
20 failure, which predisposed them to receive several treatment interventions, including  
21 corticosteroids, which could result in significant statistical evaluation. A meta-analysis of 42  
22 randomized controlled trials consisting of 10,194 patients has shown that corticosteroids possibly  
23 result in a small reduction in mortality and an increased risk of neuromuscular weakness among  
24 critically ill patients with sepsis.<sup>41</sup> However, the theoretical concept for corticosteroid use in  
25 COVID-19 was to reduce cytokine storm caused by a reaction to SARS-CoV-2 infection.<sup>42</sup> In  
26 early April 2020, the IDSA recommended against a routine use of corticosteroids in the  
27 treatment of COVID-19 due to lack of evidence.<sup>37</sup> This guidelines was updated on June 25<sup>th</sup>,  
28 2020 after the result release of the RECOVERY trial showing that patients who received  
29 dexamethasone were more likely to be discharged from hospital at 28 days.<sup>43</sup> Thus, currently, the  
30 IDSA panel suggests glucocorticoids use in hospitalized patients with severe COVID-19.<sup>37</sup> Here,  
31 our findings contradict with the recommendation from the IDSA. The discrepancy could be  
32 resulted from several factor, such as selection bias, confounding bias and small sample size.  
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3 Our cohort demonstrated that remdesivir and tocilizumab were not associated with  
4 mortality and there was no significant improvement in hospital length of stay between in patients  
5 receiving these drugs. Recently, the preliminary report from a phase 3 randomized controlled  
6 trial revealed that remdesivir was superior to placebo in shortening the time to recovery in adults  
7 hospitalized with COVID-19.<sup>44</sup> Several retrospective studies reported that tocilizumab, an IL-6  
8 inhibitor, was shown to reduce the levels of serum inflammatory markers. However, the impact  
9 on clinical improvement and mortality remained inconclusive.<sup>45-47</sup> Although we reported no  
10 significant clinical benefits from tocilizumab, the consideration for compassionate use of  
11 tocilizumab is not discouraged but rather dependent on the judgment of clinicians based on  
12 current evidence. A phase 2 (TOCIVID-19; NCT04317092) and 3 randomized controlled trial  
13 (COVACTA; NCT04320615) of tocilizumab is being investigated for the treatment of COVID-  
14 19 pneumonia. The preliminary results are expected to release in late 2020.

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17 Similarly, although we found that convalescent plasma was predictive of in-hospital  
18 mortality, one important limitation should be considered here. The safety of convalescent plasma  
19 was demonstrated in a single-center retrospective cohort of 25 patients<sup>48</sup> and in a preprint, non-  
20 peer review report.<sup>49</sup> However, the efficacy of convalescent plasma remained undetermined due  
21 to lack of control group. At our institution, convalescent plasma is considered if patients have  
22 severe symptoms and have contraindications to remdesivir, such as AKI and hepatic dysfunction.  
23 With these complications, the mortality is generally higher resulting in potential selection and  
24 confounding bias. The IDSA panel has recommended convalescent plasma only in the context of  
25 a clinical trials To date, at least one randomized controlled trila (NCT04342182) is being  
26 investigated to establish the clinical benefits in hospitalized patients with severe COVID-19.  
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3 From our ICU cohort, AKI and ARDS were the only two variables that were predictive of  
4 mortality among patients admitted to the ICU. Interestingly, all treatment measures had no effect  
5 on mortality once patients were critically ill and required ICU. This could imply that these  
6 treatment interventions might be beneficial if given prior to clinical decompensation or ICU  
7 transfer. However, interpretation is restricted due to small sample size and examining only  
8 critically ill patients. Our hypothesis should be substantiated by studies from other institutions  
9 with larger sample sizes.  
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19 Our study has some limitations. The observational design made the results susceptible to  
20 selection bias. Analyses could be underpowered given the small sample size. However, we  
21 improved the validity of the results by performing bootstrapping analysis. Moreover, due to  
22 restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir,  
23 and convalescent plasma, which may limit the applicability of our findings. More importantly,  
24 mortality can be affected by confounding factors. We minimize this risk by applying multivariate  
25 analysis. Most of the collected data were cross sectional, thus, making it difficult to conclude the  
26 causality between two variables.  
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38 In conclusion, COVID-19 is a serious condition with a significant in-hospital mortality  
39 rate. Multiple risk factors for in-hospital death were identified. Hydroxychloroquine, ascorbic  
40 acid, zinc supplementation, and corticosteroids therapy were not recommended due to increased  
41 mortality risk.  
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50  
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52 Yijin Wert for constructing the Kaplan-Meier curves.  
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12 **Figure 1.** Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1  
13 to May 31, 2020.  
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17 **Figure 2.** Survival analysis by Kaplan-Meier curves. **A)** The cumulative survival declined with  
18 increasing length of hospital stay. The median survival time was 25 days with standard error (SE)  
19 of 7.0. **B)** ICU patients significantly lower survival probability with mean survival time of 22.3  
20 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively ( $p = 0.002$ ).  
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## DECLARATIONS

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**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.

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**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) <sup>†</sup>	61.9 (15.8) <sup>†</sup>	72.8 (13.5) <sup>†</sup>	< 0.001*
<i>Ethnicity</i>				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	0.705
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
<i>Co-morbidities</i>				
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )	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
<i>Signs and symptoms</i>				

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 (SpO <sub>2</sub> < 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
<b>Laboratory findings</b>				
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 <sup>2</sup> )	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*
<b>Inflammatory markers</b>				
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
<b>Radiographic findings</b>				
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
<b>Oxygen therapy/delivery</b>				
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*
<b>Intervention</b>				
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*
<b>Treatment</b>				
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
<b>Complications</b>				
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
<b>Outcome</b>				
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-corporeal 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; SpO<sub>2</sub>, 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 (SpO <sub>2</sub> < 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 <sup>2</sup> 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.

Characteristics	Statistics		
	Odds ratio	95% CI	P-value
<b>Model 1</b>			
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 (SpO <sub>2</sub> < 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 <sup>2</sup> 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
<b>Model 2</b>			
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*
<b>Model 3</b>			
Respiratory acidosis	7.042	2.915-16.949	< 0.001*
Steroids therapy	2.825	1.305-6.098	0.008*
<b>Model 4</b>			
Acute kidney injury	3.571	1.715-7.407	0.001*
<b>Model 5</b>			
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) <sup>†</sup>	69.1 (12.5) <sup>†</sup>	63.3 (15.2) <sup>†</sup>	0.052
<i>Ethnicity</i>				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	0.685
African-American	25 (28.1)	12 (25.5)	13 (31.0)	
Hispanic/Latino	12 (13.5)	8 (17.0)	4 (9.5)	
Asian	5 (5.6)	2 (4.3)	3 (7.1)	
Others	-	-	-	
<i>Treatment</i>				
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
<i>Complications</i>				
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
<b>Outcome</b>				
Recovery/discharge	43 (48.3)			
Remained hospitalized	2 (2.2)			
Death	42 (47.2)			

ARDS, acute respiratory distress syndrome.

\*statistically significant

†mean (standard deviation)



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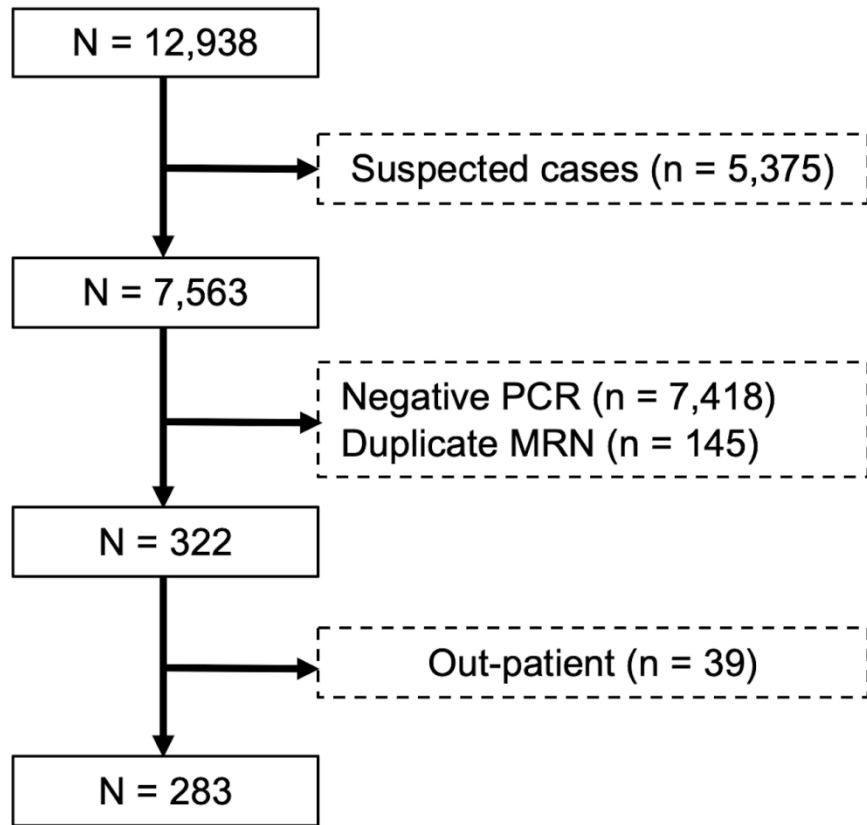


Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

127x117mm (300 x 300 DPI)

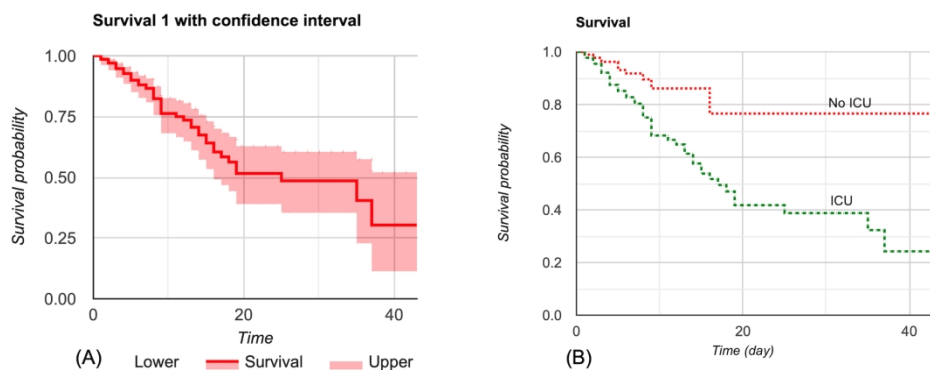


Figure 2. Survival analysis by Kaplan-Meier curves. A) The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. B) ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) 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  $\geq 30$  kg/m<sup>2</sup>), 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  $> 9,500/\mu\text{L}$ ), leukopenia (white blood cells count  $< 3,900/\mu\text{L}$ ), lymphocytopenia (absolute lymphocytes count  $< 600/\mu\text{L}$ ), thrombocytosis (platelets  $> 400,000/\mu\text{L}$ ), and thrombocytopenia (platelets  $< 140,000/\mu\text{L}$ ), respiratory acidosis (arterial pH  $< 7.35$  and arterial partial pressure of CO<sub>2</sub>  $> 45$  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

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<b>Primary Subject Heading</b>:	Infectious diseases
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3 **1 Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality:**  
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5 **2 A Single-network, Retrospective Cohort Study from Pennsylvania State**  
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3 **24 ABSTRACT**  
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5 **25 Objective:** Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by severe  
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8 **26** acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with highest burden in the United  
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11 **27** States. Data on clinical characteristics of COVID-19 patients in U.S. population are limited.  
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13 **28** Thus, we aim to determine the clinical characteristics and risk factors for in-hospital mortality  
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15 **29** from COVID-19.

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17 **30 Design:** Retrospective observational study.

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19 **31 Setting:** Single-network hospitals in Pennsylvania state.

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21 **32 Participants:** Patients with confirmed SARS-CoV-2 infection who were hospitalized from  
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24 **33** March 1<sup>st</sup> to May 31<sup>st</sup>, 2020.

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26 **34 Primary and secondary outcome measures:** Primary outcome was in-hospital mortality.  
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29 **35** Secondary outcomes were complications, such as acute kidney injury and acute respiratory  
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31 **36** distress syndrome (ARDS).

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33 **37 Results:** Of 283 patients, 19.4% were non-survivors. The mean age of all patients was  $64.1 \pm$   
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35 **38** 15.9 years. 56.2% were male and 50.2% were white. In adjusted multivariate analyses,  
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38 **39** increasing age (per 1-year increment; OR 1.075), hypoxia (SpO<sub>2</sub> < 95%; OR 4.630),  
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40 **40** opacity/infiltrate on imaging (OR 3.077), leukocytosis (WBC > 10,000 /uL; OR 2.732), ferritin >  
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42 **41** 336 ng/mL (OR 4.016), lactate dehydrogenase > 200 U/L (OR 7.752), procalcitonin > 0.25  
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44 **42** ng/mL (OR 2.404), troponin I > 0.03 ng/mL (OR 2.242), need for advanced oxygen support  
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47 **43** other than simple nasal cannula (OR 4.608-13.889), ICU admission/transfer (OR 13.699), renal  
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49 **44** replacement therapy (OR 21.277), need for vasopressor (OR 22.222), acute respiratory distress  
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51 **45** syndrome (OR 23.810), respiratory acidosis (OR 7.042), and acute kidney injury (OR 3.571).  
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3 46 When critically ill patients were analyzed independently, increasing SOFA score (OR 1.544),  
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5 47 AKI (OR 2.128), and ARDS (OR 6.410) were predictive of in-hospital mortality.  
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8 48 **Conclusion:** We reported the characteristics of ethnically diverse, hospitalized patients with  
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10 49 COVID-19 from Pennsylvania state.  
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## 17 52 **Strengths and Limitations of This Study**

- 19 53 - Individual patient's chart was reviewed.
  - 21 54 - Multivariate analysis (binary logistic regression model) was used to report the results.
  - 23 55 - Retrospective, observational design.
  - 25 56 - Limited sample size.
  - 27 57 - Only hospitalized patients were included in the studies.
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## 71 INTRODUCTION

72           Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute  
73 Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has become a pandemic in early  
74 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and  
75 rapidly escalated to 216 countries within five months with the highest number of infected cases  
76 in the United States.<sup>1</sup> As of August 29<sup>th</sup>, 2020, the reported cumulated number of confirmed  
77 cases in the United States was close to 6 million with a mortality rate of 3.09%.<sup>1</sup>

78           As of August 29<sup>th</sup>, 2020, the Pennsylvania Department of Health has announced more  
79 than 129,056 confirmed cases of COVID-19 leading to 7,671 deaths, making Pennsylvania the  
80 13<sup>th</sup> state with the highest confirmed cases.<sup>2</sup> To date, the characteristics of infected patients in the  
81 United States were reported in the state of Washington (n = 21), California (n = 1,299) and New  
82 York (n = 5,700) in chronological order.<sup>3-5</sup> The mortality across the U.S. studies ranged from 6.3  
83 to 24%, depending on the severity of COVID-19. Although the characteristics of hospitalized  
84 COVID-19 patients have been reported in other states, there are some limitations that preclude  
85 the generalization of the results toward our patient population. Studies from Washington and  
86 California were conducted in pre-remdesivir era and multivariate analysis was not performed in  
87 the New York City cohort. The association between clinical characteristics and in-hospital  
88 mortality in the U.S. population have not been clearly established.

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

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3 92 Zhou et al demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA)  
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5 93 score, D-dimer > 1 µg/mL, cardiac troponin I ≥ 0.05 ng/mL, and pre-existing concurrent  
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8 94 cardiovascular and cerebrovascular diseases were significant predictors for increased mortality  
9  
10 95 from COVID-19.<sup>7 8</sup> However, these findings were primarily based on Chinese population; thus, it  
11  
12 96 has been unconfirmed if the results can be applicable to other patient populations.

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14  
15 97 Clinical management of COVID-19 has been dynamic and variable based on available  
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17 98 research, which has largely been *in vitro*, such as a combination of hydroxychloroquine and  
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19 99 azithromycin,<sup>9</sup> ascorbic acid,<sup>10</sup> ivermectin,<sup>11</sup> and zinc.<sup>12</sup> These therapies have not been proven  
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21  
22 100 beneficial in clinical studies. In the current study, we provide our experience on treatment options  
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24 101 for patients infected with SARS-CoV-2.

25  
26 102 In this retrospective cohort, we aimed to demonstrate the clinical characteristics of COVID-  
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28 103 19 patients, treatment outcomes and the impact on in-hospital mortality in an ethnically diverse  
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31 104 population.

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## 34 35 106 **MATERIALS AND METHODS**

### 36 37 107 ***Study design***

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40 108 This is a retrospective cohort study from seven hospitals under UPMC Pinnacle network  
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42 109 located across the state of Pennsylvania. The protocol of this study has been approved by UPMC  
43  
44  
45 110 Pinnacle Institutional Review Board and UPMC Pinnacle Ethic Committee (#20E024). Written  
46  
47 111 informed consent was waived due to the retrospective, observational nature of the study. Our  
48  
49 112 current study followed the Declaration of Helsinki.

### 50 51 113 ***Patient and public involvement***

52  
53  
54 114 No patient involvement.

### 115 ***Data source and patient population***

116 Data were collected by extracting electronic medical records from March 1<sup>st</sup> to May 31<sup>th</sup>,  
117 2020 through UPMC Pinnacle COVID-19 registry. Adult patients with age  $\geq 18$  years who were  
118 hospitalized with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-  
119 PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalized  
120 patients, patients  $< 18$  years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-  
121 system transfer and patients enrolled in clinical trials. Transfer within the system was considered  
122 one admission. For patients with multiple admissions with study period, the first admission for  
123 COVID-19 was reviewed.

### 124 ***Data collection***

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

130 The Sequential Organ failure Assessment (SOFA) score<sup>13</sup> was calculated on the first day  
131 of ICU admission. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI  
132 equation.<sup>14</sup> Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL  
133 (27  $\mu\text{mol/L}$ ) or  $\geq 1.5$  times from the baseline value within 48 hours.<sup>15</sup> Chronic kidney disease  
134 (CKD) was defined by the Kidney Diseases Improving Global Outcomes guidelines.<sup>16</sup> Patients  
135 with history of end stage kidney disease (ESKD) on dialysis prior to admission, were not counted  
136 toward 'requirement of renal replacement therapy (RRT)/hemodialysis (HD)' during the hospital  
137 stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.<sup>17</sup>

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2  
3 138 Arrhythmias as complications were defined either tachy- or bradyarrhythmia that were new-onset,  
4  
5 139 occurred during hospitalization with COVID-19. In this study, prolongation of QT segment was  
6  
7 140 defined as the QT duration > 500 milliseconds.

#### 10 141 ***Study outcomes***

12 142 The primary outcome was in-hospital mortality. The secondary outcome included  
13  
14 143 treatment outcomes and complications such as recovery/discharge, AKI, ARDS, arrhythmias, QT  
15  
16 144 prolongation, venous thromboembolism, arterial thrombosis, cerebrovascular events, heart  
17  
18 145 failure, and myocardial infarction.

#### 21 146 ***Statistical analysis***

23 147 All analyses were conducted using SPSS software version 23.0 (IBM Corp., Armonk,  
24  
25 148 NY, USA). Descriptive analyses were reported in percentage for categorical data and in mean  $\pm$   
26  
27 149 standard deviation (S.D.) or median (interquartile range; IQR) depending the data distribution.  
28  
29 150 Comparisons of outcomes for each variable were evaluated using Pearson's  $\chi^2$  tests or Fisher-  
30  
31 151 Exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher-  
32  
33 152 Exact tests were opted if the total sample in any cell count was less than five. A p-value less than  
34  
35 153 0.05 is considered statistically significant. Missing data were not included in the analysis.

#### 40 154 ***Logistic regression analysis***

42 155 Clinical risk factors that were significant from standard analyses (Pearson's  $\chi^2$  tests, Fisher-  
43  
44 156 Exact tests, t-tests) were included in univariate binary logistic regression analysis. Odds ratios  
45  
46 157 (OR) were reported along with 95% confidence interval (CI). The analysis is considered  
47  
48 158 statistically significant if the 95% CI crosses 1.0.<sup>18</sup> Variables that remained statistically significant  
49  
50 159 on univariate analysis were included in multivariate analysis using logistic regression method to  
51  
52 160 adjust for other covariates. For the analyses of overall mortality predictors, Model 1 was adjusted

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2  
3 161 for age, sex, ethnicity and obesity. Model 2 was adjusted for age, sex, ethnicity, obesity and need  
4  
5 162 for oxygen therapy. Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/chronic obstructive  
6  
7 163 pulmonary disease (COPD), the need for oxygen therapy, and ICU admission. Model 4 is adjusted  
8  
9 164 for age, sex, ethnicity, obesity, CKD, the need for oxygen therapy, and ICU admission. Model 5  
10  
11 165 is adjusted for age, sex, ethnicity, obesity, coronary artery disease, heart failure, history of  
12  
13 166 arrhythmia/conduction disorder, and ICU admission. The rationale for each Model adjustment in  
14  
15 167 multivariate analysis is available in *Supplemental Document 2*.

### 19 168 ***Sensitivity analysis***

21 169 The goodness-of-fit tests of logistic regression analyses were evaluated by Hosmer-  
22  
23 170 Lemeshow method. The validity and sustainability of the significant results from multivariate  
24  
25 171 analysis were tested using the bootstrap method to estimate the end point with imputed sample  
26  
27 172 size of 1,000.

### 31 173 ***Survival analysis***

33 174 Kaplan-Meier analysis was used to present the survival by plotting between cumulative  
34  
35 175 survival against hospital stay in all included patients and in patients requiring ICU.

## 40 177 **RESULTS**

### 42 178 ***Baseline characteristics and patient outcomes***

44 179 A total of 12,938 patients were identified during the study period. Thirty-nine patients were  
45  
46 180 outpatient and did not require hospitalization. After excluding patients with negative PCR (n =  
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48 181 7,374), duplicate medical records (n = 145), pregnant woman (n = 3), and clinical trial patients (n  
49  
50 182 = 2), 283 patients were included for further analysis. The flowchart of data selection from the  
51  
52 183 UPMC Pinnacle COVID-19 registry is depicted in *Figure 1*. *Table 1* summarizes the demographics

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2  
3 184 and baseline characteristics of included patients. All patients had confirmed SARS-Cov-2 infection  
4  
5 185 by RT-PCR. Of 283 patients, 80.6% were survivors and 19.4% were non-survivors. The mean age  
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7 186 of all patients was  $64.1 \pm 15.9$  years. 56.2% were male and 50.2% were Caucasian. Non-survivors  
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9  
10 187 were significantly older and had higher proportion of hypertension, CKD and had lower mean  
11  
12 188 eGFR. Moreover, hypoxia on presentation, rales/crackles on physical examination, leukocytosis,  
13  
14 189 lymphocytopenia, respiratory acidosis, transaminitis, and opacity/infiltrate on imaging were  
15  
16 190 common presentations in non-survivors. Higher inflammatory markers, such as D-dimer, ferritin,  
17  
18 191 lactate dehydrogenase (LDH), C-reactive protein, and procalcitonin were significantly prevalent  
19  
20 192 in deceased patients. The need for oxygen therapy regardless of the mode of oxygen delivery was  
21  
22 193 higher among those who did not survive. Furthermore, non-survivors were more likely to have  
23  
24 194 received intensive care unit (ICU) admission/transfer, extracorporeal membrane oxygenation  
25  
26 195 (ECMO), RRT, use of vasopressors, use of antibiotics, azithromycin, hydroxychloroquine,  
27  
28 196 steroids, ascorbic acid, zinc, tocilizumab and convalescent plasma. Of overall complications, the  
29  
30 197 prevalence of AKI, ARDS, arrhythmias and superimposed bacteremia was significantly higher in  
31  
32 198 non-survivors. There was no significant difference in mean hospital stay between survivors and  
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34 199 non-survivors. Up to 78.8% recovered or were discharged from the hospital. Only two patients  
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36 200 remained hospitalized as of June 18, 2020. The mean hospital stay was similar between patients  
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38 201 who received remdesivir vs. those who did not ( $9.0 \pm 4.7$  and  $7.6 \pm 7.8$  days, respectively;  $p =$   
39  
40 202  $0.359$ ). In contrast, patients who received tocilizumab had significantly longer hospital stay  
41  
42 203 compared to those who did not receive tocilizumab ( $15.3 \pm 11.7$  and  $7.4 \pm 7.2$  days, respectively;  
43  
44 204  $p < 0.001$ ).

### 205 *Univariate analysis*

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

### 212 ***Multivariate analysis***

213 Variables that were significant on univariate analysis were included in multivariate logistic  
214 regression analysis (*Table 3*). In Model 1 (adjusted for age, sex, ethnicity, and obesity), increasing  
215 patient age, hypoxia, opacity/infiltrate on imaging, leukocytosis, ferritin > 336 ng/mL, LDH (>  
216 200 U/L), procalcitonin > 0.25 ng/mL, troponin I > 0.03 ng/mL, use of high-flow oxygen nasal  
217 cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU  
218 admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for  
219 increased in-hospital mortality. In Model 2 (adjusted for all variables in Model 1 plus the need for  
220 oxygen therapy, and ICU admission), hydroxychloroquine, ascorbic acid, zinc, and convalescent  
221 plasma were not associated with increased mortality. In Model 3 (adjusted for all variables in  
222 Model 2 plus asthma/COPD), respiratory acidosis was associated with increased mortality.  
223 Moreover, AKI was an independent risk factor for in-hospital mortality from COVID-19 from  
224 Model 4. In addition, we also found that hydroxychloroquine therapy was associated with QT  
225 prolongation (OR 2.874; 95% CI 1.189-6.944; p = 0.019) after adjusted for covariates in Model 2.  
226 The association of these variables and overall mortality remained significant on bootstrap analysis  
227 when the sample size was imputed to 1,000.

### 228 ***Cohort of critically ill patients***

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3 229 A total 89 patients required intensive care during the study period. Of which, 47.2% died.  
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5 230 The demographics and clinical characteristics of critically ill patients are demonstrated in *Table*  
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7 231 4. Deceased ICU patients had significantly higher proportion of AKI and ARDS compared to  
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9 232 survived ICU patients. The treatments were similar between survivors and non-survivor patients.  
10  
11 233 In multivariate analysis, each 1-point increment of SOFA score was associated with increased  
12  
13 234 death (OR 1.544; 95% CI 1.168-2.039; p 0.002) after adjusted for age, sex, and ethnicity.  
14  
15 235 Similarly, AKI (OR 2.128, 95% CI 1.111-6.667; p = 0.034) and ARDS (OR 6.410; 95% CI  
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17 236 2.237-18.182; p = 0.023) are significantly predictive of in-hospital mortality among patients  
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19 237 admitted the ICU after adjusted for age, sex, ethnicity, and SOFA score.  
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### 24 238 *Survival analysis*

25  
26 239 Survival analyses were evaluated using Kaplan-Meier curve (*Figure 2*). In our analysis,  
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28 240 the cumulative survival declined with increasing length of hospital stay. The median survival  
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30 241 time was 25.0 days with standard error of 7.0.  
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## 33 242

### 35 243 **DISCUSSION**

36  
37 244 In this single-network, retrospective observation study, we found that the overall in-  
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39 245 hospital mortality among hospitalized COVID-19 patients was 19.4%. The reported mortality  
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41 246 among Chinese cohorts ranged from 11.7% to 28.2%.<sup>7 8 19</sup> However, our reported mortality rates  
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43 247 appeared slightly lower than what previously described from New York City.<sup>5</sup> Richardson et al  
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45 248 found that the overall mortality of 5,700 hospitalized COVID-19 patients from 12 hospitals in  
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47 249 New York City was 21%. However, one could argue that our study has significantly smaller  
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49 250 sample size which might underestimate the actual mortality of COVID-19. Our data need  
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51 251 confirmation from other studies with a larger sample size.  
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3 252 We identified several risk factors for mortality from COVID-19 using multivariate  
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5 253 logistic regression analysis. Increasing age, hypoxia and opacity/infiltrate on imaging were  
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7 254 associated with higher mortality. Moreover, we also found that patient survival diminished as the  
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9 255 disease progressed, reflected by advancement in oxygen delivery (high-flow nasal cannula,  
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11 256 NIPPV, and mechanical ventilation). Requiring a simple oxygen nasal cannula did not affect  
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13 257 mortality. Such findings are similar to previous literature. Older age is an independent risk factor  
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15 258 for severe COVID-19 and mortality.<sup>7,20</sup> In line with Zhou et al, increasing oxygen requirement  
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17 259 and need for advanced oxygen delivery were predictive of death from COVID-19.<sup>8</sup>

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19 260 Here, we showed that COVID-19 patients requiring ICU had 13.7-fold increased risk of  
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21 261 mortality. Critically ill patients generally had one or more organs in failure, and an increasing  
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23 262 number of organ failure has been linked to elevated death in sepsis patients.<sup>21</sup> For COVID-19  
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25 263 patients, we demonstrated that kidney (AKI, and RRT), pulmonary (respiratory acidosis, and  
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27 264 ARDS), cardiovascular (vasopressor requirement) failure were predictive of in-hospital  
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29 265 mortality. These findings are in line with other cohorts and each factor has been demonstrated as  
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31 266 an independent risk factor for mortality in critically ill patients.<sup>8,22-26</sup> Although the complications  
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33 267 from SARS-CoV-2 infection can be affected by multiple contributing factors, newer evidence  
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35 268 has suggested the significance of cytokine storm leading to multi-organ failure.<sup>27</sup>

36  
37 269 Here, we showed that elevated ferritin, LDH, procalcitonin, leukocytosis, troponin I and  
38  
39 270 possibly D-dimer were associated with increased death. Although, the odds ratio for D-dimer  
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41 271 cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-  
42  
43 272 dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be  
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45 273 ignored. Guan et al first demonstrated the importance of elevated inflammatory markers in  
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47 274 COVID-19 in Chinese population<sup>6</sup> which has become a standard monitoring parameter for  
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3 275 COVID-19 patients.<sup>28</sup> Elevated inflammatory markers should prompt physicians to evaluate and  
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5 276 monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated  
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7 277 procalcitonin and leukocytosis may indicate concomitant bacterial infection, which has been  
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9 278 shown to increase morbidity and mortality of viral pneumonia.<sup>29</sup> Interestingly, our study showed  
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11 279 that elevated troponin I level was associated with significantly higher death similar to a recent  
12  
13 280 meta-analysis.<sup>30</sup> Although the etiologies of elevated troponin levels were not determined in our  
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15 281 cohort, other studies proposed several mechanisms for elevated troponin level in COVID-19  
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17 282 patients. These include myocarditis, cytokine mediated myocardial injury, microangiopathy of  
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19 283 small coronary arteries, or silent coronary artery disease.<sup>26 30</sup>

24 284 The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses  
25  
26 285 or bacteria.<sup>31</sup> Cytokine storm is characterized by the overproduction of pro-inflammatory  
27  
28 286 cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1 $\beta$  resulting in an increased  
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30 287 vascular hyperpermeability, and activation of multiple coagulation pathways.<sup>27 32</sup> In light of  
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32 288 SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and  
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34 289 the protein C system were impaired during active inflammation.<sup>33</sup> These changes lead to  
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36 290 thrombin hyperactivity resulting in the development of microthrombosis, disseminated  
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38 291 intravascular coagulation (DIC) and sequential multiorgan failure.<sup>27</sup> Moreover, new studies have  
39  
40 292 revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are  
41  
42 293 beyond the scope of our article.<sup>34</sup> Such syndromes include macrophage activation syndrome,  
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44 294 adult-onset Still's disease, and catastrophic anti-phospholipid syndrome.<sup>34</sup>

49 295 Hydroxychloroquine therapy was associated with a 3-fold increased risk of QT  
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51 296 prolongation but not associated with increased risk of death. The concept of using  
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53 297 hydroxychloroquine in COVID-19 patients derived from an early *in vitro* study.<sup>35</sup> The results

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3 298 from small non-randomized clinical trials also showed promising effects on viral load  
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5 299 reduction.<sup>36 37</sup> However, the clinical benefit of hydroxychloroquine was debated by a large  
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8 300 observation study. Of 1,446 patients, Geleris et al observed that hydroxychloroquine had no  
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10 301 effect on the death, length of stay or intubation.<sup>38</sup> Later, the efficacy of hydroxychloroquine with  
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12 302 or without azithromycin has been demonstrated in a recent multicenter, randomized, open-label,  
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14 303 controlled trial in hospitalized patients with mild-to-moderate COVID-19.<sup>39</sup> In this study, the  
15  
16 304 authors found that the use of hydroxychloroquine, alone or with azithromycin did not improve  
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18 305 the clinical outcome at 15 days compared to the standard treatment. Thus, the recommendation  
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20 306 for use of hydroxychloroquine was recalled by the Infectious Diseases Society of America  
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22 307 (IDSA) due to small sample size in previous clinical trials and concern for cardiac adverse  
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24 308 effects, such as QT prolongation/torsade de pointe.<sup>40</sup>

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28 309 A meta-analysis of four randomized trials and one retrospective study showed that the  
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30 310 administration of intravenous vitamin C has vasopressor sparing effects and may reduce the need  
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32 311 for mechanical ventilation in critically ill patients while there was no effect on the mortality.<sup>41</sup>  
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34 312 However, given the lack of more supporting evidence, the standard use of ascorbic acid is not yet  
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36 313 recommended especially in COVID-19 patients. A new clinical trial investigating the treatment  
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38 314 outcome of vitamin C in severe COVID-19 is underway (NCT04264533).

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42 315 Although our study also showed that zinc supplementation was not associated with  
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44 316 increased mortality in COVID-19 patients, the routine use of zinc supplementation could not be  
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46 317 supported due to lack of randomized controlled trials. A Brazilian study revealed that plasma  
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48 318 zinc concentration in critically ill patients upon admission to the ICU was low and may make  
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50 319 these patients more susceptible to oxidative stress.<sup>42</sup> Another prospective study showed that zinc  
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52 320 supplementation in mechanically ventilated patients was related to less ventilator-associated  
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3 321 pneumonia.<sup>43</sup> However, the mean duration of intubation in this study was prolonged (29 days),  
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5 322 making it inconclusive if zinc supplementation can prevent pneumonia development in short-  
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7 323 term intubation.  
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10 324 Steroid therapy in COVID-19 patients was not associated with increased mortality. A  
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12 325 meta-analysis of 42 randomized controlled trials consisting of 10,194 patients has shown that  
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14 326 corticosteroids possibly result in a small reduction in mortality and an increased risk of  
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16 327 neuromuscular weakness among critically ill patients with sepsis.<sup>44</sup> However, the theoretical  
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18 328 concept for corticosteroid use in COVID-19 was to reduce cytokine storm caused by a reaction  
19  
20 329 to SARS-CoV-2 infection.<sup>45</sup> In early April 2020, the IDSA recommended against a routine use of  
21  
22 330 corticosteroids in the treatment of COVID-19 due to lack of evidence.<sup>40</sup> This guidelines was  
23  
24 331 updated on June 25<sup>th</sup>, 2020 after the results of the RECOVERY trial was released showing that  
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26 332 patients who received dexamethasone were more likely to be discharged from hospital at 28 days  
27  
28 333 compared to non-steroids group.<sup>46</sup> Thus, currently, the IDSA panel suggests glucocorticoids use  
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30 334 in hospitalized patients with severe COVID-19.<sup>40</sup> Here, our study is in line with the  
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32 335 recommendation from the IDSA.  
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38 336 We have observed that remdesivir and tocilizumab were not associated with mortality  
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40 337 and there was no significant improvement in hospital length of stay between patients receiving  
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42 338 these drugs. However, given the observational, non-randomized design of this study, it is  
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44 339 difficult to determine the efficacy of such treatment. Recently, the preliminary report from a  
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46 340 phase 3 randomized controlled trial revealed that remdesivir was superior to placebo in  
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48 341 shortening the time to recovery in adults hospitalized with COVID-19.<sup>47</sup> Several retrospective  
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50 342 studies reported that tocilizumab, an IL-6 inhibitor, was shown to reduce the levels of serum  
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52 343 inflammatory markers. However, the impact on clinical improvement and mortality remained  
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3 344 inconclusive.<sup>48-50</sup> Although we reported no significant clinical benefits from tocilizumab, the  
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5 345 consideration for compassionate use of tocilizumab is not discouraged but rather dependent on  
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7 346 the judgment of clinicians based on current evidence. A phase 2 (TOCIVID-19; NCT04317092)  
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10 347 and 3 randomized controlled trial (COVACTA; NCT04320615) of tocilizumab is being  
11  
12 348 investigated for the treatment of COVID-19 pneumonia. The preliminary results are expected to  
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14  
15 349 release in late 2020.

16  
17 350 Similarly, we found that convalescent plasma was not associated with in-hospital  
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19 351 mortality. The safety of convalescent plasma was demonstrated in a single-center retrospective  
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21 352 cohort of 25 patients<sup>51</sup> and in a preprint, non-peer review report.<sup>52</sup> However, the efficacy of  
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23 353 convalescent plasma remained undetermined due to lack of control group. The IDSA panel has  
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25  
26 354 recommended convalescent plasma only in the context of a clinical trials. However, at our  
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28 355 institution, convalescent plasma is considered if patients have severe symptoms and have  
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30 356 contraindications to remdesivir, such as AKI and hepatic dysfunction. Although we did not  
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32  
33 357 observe mortality adverse effect from convalescent plasma, the final recommendations on its  
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35 358 efficacy and safety are dependent on the randomized controlled trials. To date, at least one  
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37  
38 359 randomized controlled trial (NCT04342182) is being investigated to establish the clinical  
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40 360 benefits in hospitalized patients with severe COVID-19.

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42 361 From our ICU cohort, the SOFA score, AKI and ARDS were the only variables that were  
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44 362 predictive of mortality among patients admitted to the ICU. Interestingly, all treatment measures  
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46 363 had no effect on mortality once patients were critically ill and required ICU. This could imply  
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49 364 that these treatment interventions might be beneficial if given prior to clinical decompensation or  
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51 365 ICU transfer. However, interpretation is restricted due to small sample size and examining only

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3 366 critically ill patients. Our hypothesis should be substantiated by studies from other institutions  
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5 367 with larger sample sizes.  
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8 368 Our study has some limitations. The observational design made the results susceptible to  
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10 369 selection bias. Analyses could be underpowered given the small sample size. However, we  
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12 370 improved the validity of the results by performing bootstrapping analysis. Moreover, due to  
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14 371 restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir,  
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16 372 and convalescent plasma, which may limit the applicability of our findings. More importantly, the  
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18 373 mortality can be affected by confounding factors. We minimize this risk by applying multivariate  
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20 374 analysis. Most of the collected data were cross sectional, thus, making it difficult to conclude the  
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22 375 causality between the two variables. Furthermore, our binary logistic regression analyses may not  
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24 376 strictly follow the one-in-ten rule which may lead to over-fitting effect. However, our statistical  
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26 377 rationale is supported by newer simulation studies by McCulloch et al.,<sup>53</sup> and Smeden et al.<sup>54</sup>  
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28 378 Moreover, we advised the readers to consider their patient population to determine the applicability  
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30 379 of our results.  
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35 380 In conclusion, COVID-19 is a serious condition with a significant in-hospital mortality  
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37 381 rate. Multiple risk factors for in-hospital death were identified. Increasing SOFA score, AKI and  
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39 382 ARDS are significant risk factors for increased death in critically ill patients.  
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**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 ( $p = 0.504$ ).

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## DECLARATIONS

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**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.



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619 **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) <sup>†</sup>	61.9 (15.8) <sup>†</sup>	72.8 (13.5) <sup>†</sup>	< 0.001*
<b>Ethnicity</b>				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	0.705
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
<b>Co-morbidities</b>				
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	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
<b>Signs and symptoms</b>				
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 (SpO <sub>2</sub> < 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
<b>Laboratory findings</b>				
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 <sup>2</sup> )	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*
<b>Inflammatory markers</b>				
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
<b>Radiographic findings</b>				
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
<b>Oxygen therapy/delivery</b>				
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*
<b>Intervention</b>				
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*
<b>Treatment</b>				
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
<b>Complications</b>				
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
<b>Outcome</b>				
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-corporeal 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; SpO<sub>2</sub>, 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 (SpO <sub>2</sub> < 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 <sup>2</sup> 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.

Characteristics	Statistics		
	Odds ratio	95% CI	P-value
<b>Model 1</b>			
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 (SpO <sub>2</sub> < 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 <sup>2</sup> decrement) <sup>†</sup>	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



<b>Model 2</b>			
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
<b>Model 3</b>			
Respiratory acidosis	3.745	1.443-9.709	0.007*
Steroids therapy	1.107	0.459-2.667	0.821
<b>Model 4</b>			
Acute kidney injury	2.268	1.025-5.025	0.043*
<b>Model 5</b>			
Arrhythmias as complications	1.161	0.428-3.155	0.769

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631 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.

632 \*statistically significant

Model 1 is adjusted for age, sex, ethnicity and obesity

633 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

634 Model 5 is adjusted for age, sex, ethnicity, obesity, CAD, heart failure, history of arrhythmia/conduction disorder, and ICU admission

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**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) <sup>†</sup>	69.1 (12.5) <sup>†</sup>	63.3 (15.2) <sup>†</sup>	0.052
SOFA score <sup>‡</sup>	4.3 (2.0)	3.6 (1.7)	5.1 (1.9)	< 0.001*
<b>Ethnicity</b>				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	0.685
African-American	25 (28.1)	12 (25.5)	13 (31.0)	
Hispanic/Latino	12 (13.5)	8 (17.0)	4 (9.5)	
Asian	5 (5.6)	2 (4.3)	3 (7.1)	
Others	-	-	-	
<b>Treatment</b>				
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
<b>Complications</b>				
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) <sup>†</sup>	10.4 (8.1) <sup>†</sup>	15.5 (10.3) <sup>†</sup>	0.125
<b>Outcome</b>				

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

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

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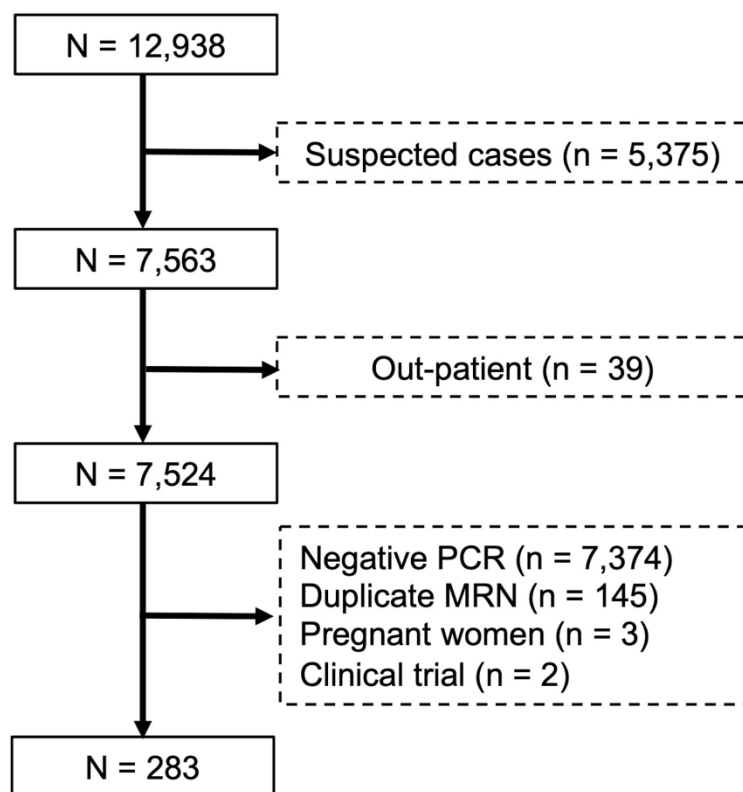


Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

203x185mm (300 x 300 DPI)

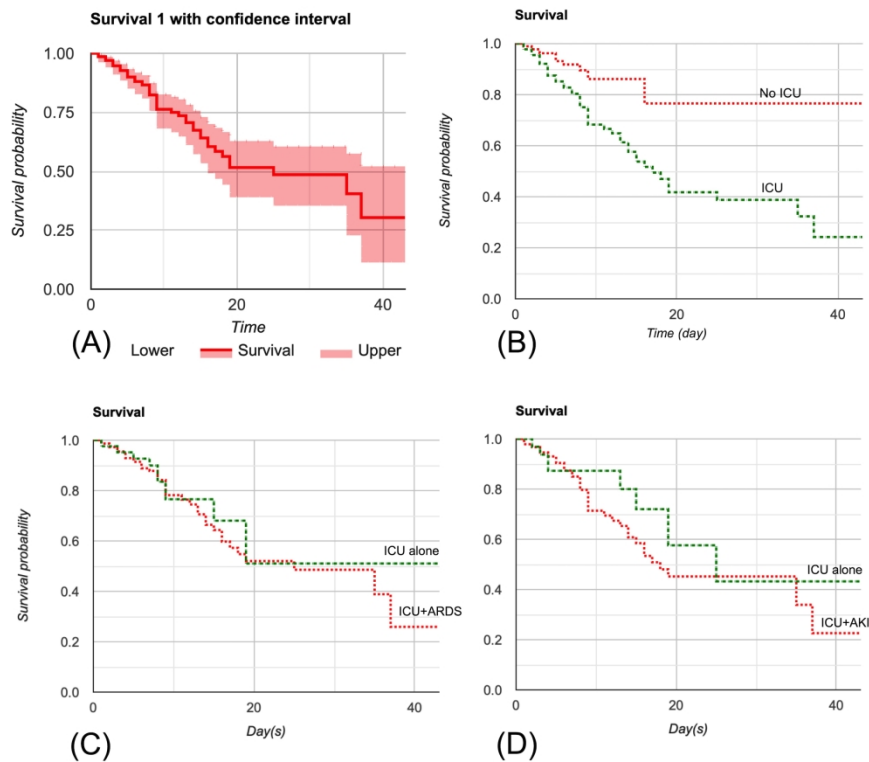


Figure 2. Survival analysis by Kaplan-Meier curves. A) The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. B) ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) 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  $\geq 30$  kg/m<sup>2</sup>), 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  $> 9,500/\mu\text{L}$ ), leukopenia (white blood cells count  $< 3,900/\mu\text{L}$ ), lymphocytopenia (absolute lymphocytes count  $< 600/\mu\text{L}$ ), thrombocytosis (platelets  $> 400,000/\mu\text{L}$ ), and thrombocytopenia (platelets  $< 140,000/\mu\text{L}$ ), respiratory acidosis (arterial pH  $< 7.35$  and arterial partial pressure of CO<sub>2</sub>  $> 45$  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-variables showed significant association with death on univariate analysis. Without these adjustments, the aforementioned co-variables 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.

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3 In Model 5, “arrhythmias” is a cardiac complication, hence we adjusted for every variable that  
4 could be the confounding factor, such as CAD, heart failure, history of arrhythmia/conduction  
5 disorder, and ICU admission.  
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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 11-16, Line 309-467
<b>Limitations</b>			
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
<b>Other information</b>			
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.

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**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](http://www.strobe-statement.org).

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# BMJ Open

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

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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTERNAL MEDICINE, MICROBIOLOGY

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3 **1 Clinical Characteristics of Hospitalized COVID-19 Patients and the Impact on Mortality:**  
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5 **2 A Single-network, Retrospective Cohort Study from Pennsylvania State**  
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8 3 Kinjal P. Gadhiya,<sup>1\*</sup> Panupong Hansrivijit,<sup>1\*</sup> Mounika Gangireddy,<sup>1\*</sup> John D. Goldman<sup>2</sup>  
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21 9 **Running title:** COVID-19 and Clinical Impact: A Retrospective Study from Pennsylvania State  
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3 24 **ABSTRACT**  
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5 25 **Objective:** Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by severe  
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8 26 acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with highest burden in the United  
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10 27 States. Data on clinical characteristics of COVID-19 patients in U.S. population are limited.  
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12 28 Thus, we aim to determine the clinical characteristics and risk factors for in-hospital mortality  
13  
14 29 from COVID-19.  
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17 30 **Design:** Retrospective observational study.  
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19 31 **Setting:** Single-network hospitals in Pennsylvania state.  
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21 32 **Participants:** Patients with confirmed SARS-CoV-2 infection who were hospitalized from  
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23 33 March 1<sup>st</sup> to May 31<sup>st</sup>, 2020.  
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26 34 **Primary and secondary outcome measures:** Primary outcome was in-hospital mortality.  
27  
28 35 Secondary outcomes were complications, such as acute kidney injury and acute respiratory  
29  
30 36 distress syndrome (ARDS).  
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33 37 **Results:** Of 283 patients, 19.4% were non-survivors. The mean age of all patients was 64.1 ±  
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35 38 15.9 years. 56.2% were male and 50.2% were white. Several factors were identified from our  
36  
37 39 adjusted multivariate analyses to be associated with in-hospital mortality: increasing age (per 1-  
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39 40 year increment; OR 1.07 [1.045-1.105]), hypoxia (SpO<sub>2</sub> < 95%; OR 4.630 [1.934-1.111]),  
40  
41 41 opacity/infiltrate on imaging (OR 3.077 [1.276-7.407]), leukocytosis (WBC > 10,000 /uL; OR  
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43 42 2.732 [1.412-5.263]), ferritin > 336 ng/mL (OR 4.016 [1.195-13.514]), lactate dehydrogenase >  
44  
45 43 200 U/L (OR 7.752 [1.639-37.037]), procalcitonin > 0.25 ng/mL (OR 2.404 [1.011-5.714]),  
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47 44 troponin I > 0.03 ng/mL (OR 2.242 [1.080-4.673]), need for advanced oxygen support other than  
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49 45 simple nasal cannula (OR 4.608-13.889 [2.053-31.250]), ICU admission/transfer (OR 13.699  
50  
51 46 [6.135-30.303]), renal replacement therapy (OR 21.277 [5.025-90.909]), need for vasopressor  
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3 47 (OR 22.222 [9.434-52.632]), acute respiratory distress syndrome (OR 23.810 [10.204-55.556]),  
4  
5 48 respiratory acidosis (OR 7.042 [2.915-16.949]), and acute kidney injury (OR 3.571 [1.715-  
6  
7 49 7.407]). When critically ill patients were analyzed independently, increasing SOFA score (OR  
8  
9 50 1.544 [1.168-2.039]), AKI (OR 2.128 [1.111-6.667]), and ARDS (OR 6.410 [2.237-18.182])  
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11 51 were predictive of in-hospital mortality.  
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14 52 **Conclusion:** We reported the characteristics of ethnically diverse, hospitalized patients with  
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16 53 COVID-19 from Pennsylvania state.  
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#### 24 56 **Strengths and Limitations of This Study**

- 25
- 26 57 - Individual patient's chart was reviewed.
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- 28 58 - Multivariate analysis (binary logistic regression model) was used to report the results.
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- 31 59 - Retrospective, observational design.
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- 33 60 - Limited sample size.
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- 35 61 - Only hospitalized patients were included in the studies.
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## 70 INTRODUCTION

71 Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused by Severe Acute  
72 Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which has become a pandemic in early  
73 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and  
74 rapidly escalated to 216 countries within five months with the highest number of infected cases  
75 in the United States.<sup>1</sup> As of August 29<sup>th</sup>, 2020, the reported cumulated number of confirmed  
76 cases in the United States was close to 6 million with a mortality rate of 3.09%.<sup>1</sup>

77 As of August 29<sup>th</sup>, 2020, the Pennsylvania Department of Health has announced more  
78 than 129,056 confirmed cases of COVID-19 leading to 7,671 deaths, making Pennsylvania the  
79 13<sup>th</sup> state with the highest confirmed cases.<sup>2</sup> To date, the characteristics of infected patients in the  
80 United States were reported in the state of Washington (n = 21), California (n = 1,299) and New  
81 York (n = 5,700) in chronological order.<sup>3-5</sup> The mortality across the U.S. studies ranged from 6.3  
82 to 24%, depending on the severity of COVID-19. Although the characteristics of hospitalized  
83 COVID-19 patients have been reported in other states, there are some limitations that preclude  
84 the generalization of the results toward our patient population. Studies from Washington and  
85 California were conducted and published during an early stage of the pandemic where treatment  
86 options, such as remdesivir, or dexamethasone were not recommended as the standard of care. In  
87 addition, multivariate analysis was not performed in the New York City cohort. The association  
88 between clinical characteristics and in-hospital mortality in the U.S. population have not been  
89 clearly established.

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

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3 93 Zhou et al demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA)  
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5 94 score, D-dimer > 1 µg/mL, cardiac troponin I ≥ 0.05 ng/mL, and pre-existing concurrent  
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8 95 cardiovascular and cerebrovascular diseases were significant predictors for increased mortality  
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10 96 from COVID-19.<sup>7 8</sup> However, these findings were primarily based on Chinese population; thus, it  
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12 97 has been unconfirmed if the results can be applicable to other patient populations.

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15 98 Clinical management of COVID-19 has been dynamic and variable based on available  
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17 99 research, which has largely been *in vitro*, such as a combination of hydroxychloroquine and  
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19 100 azithromycin,<sup>9</sup> ascorbic acid,<sup>10</sup> ivermectin,<sup>11</sup> and zinc.<sup>12</sup> These therapies have not been proven  
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21 101 beneficial in clinical studies. In the current study, we provide our experience on treatment options  
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23 102 for patients infected with SARS-CoV-2.

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26 103 In this retrospective cohort, we aimed to demonstrate the clinical characteristics of COVID-  
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28 104 19 patients, treatment outcomes and the impact on in-hospital mortality in an ethnically diverse  
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30 105 population.

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## 34 35 107 **MATERIALS AND METHODS**

### 36 37 108 ***Study design***

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40 109 This is a retrospective cohort study from seven hospitals under UPMC Pinnacle network  
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42 110 located across the state of Pennsylvania. The protocol of this study has been approved by UPMC  
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44 111 Pinnacle Institutional Review Board and UPMC Pinnacle Ethic Committee (#20E024). Written  
45  
46 112 informed consent was waived due to the retrospective, observational nature of the study. Our  
47  
48 113 current study followed the Declaration of Helsinki.

### 49 50 114 ***Patient and public involvement***

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52  
53 115 No patient involvement.

### 116 ***Data source and patient population***

117 Data were collected by extracting electronic medical records from March 1<sup>st</sup> to May 31<sup>th</sup>,  
118 2020 through UPMC Pinnacle COVID-19 registry. Adult patients with age  $\geq 18$  years who were  
119 hospitalized with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction (RT-  
120 PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalized  
121 patients, patients  $< 18$  years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-  
122 system transfer and patients enrolled in clinical trials. Transfer within the system was considered  
123 one admission. For patients with multiple admissions with study period, the first admission for  
124 COVID-19 was reviewed.

### 125 ***Data collection***

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

131 The Sequential Organ failure Assessment (SOFA) score<sup>13</sup> was calculated on the first day  
132 of ICU admission. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI  
133 equation.<sup>14</sup> Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL  
134 (27  $\mu\text{mol/L}$ ) or  $\geq 1.5$  times from the baseline value within 48 hours.<sup>15</sup> Chronic kidney disease  
135 (CKD) was defined by the Kidney Diseases Improving Global Outcomes guidelines.<sup>16</sup> Patients  
136 with history of end stage kidney disease (ESKD) on dialysis prior to admission, were not counted  
137 toward 'requirement of renal replacement therapy (RRT)/hemodialysis (HD)' during the hospital  
138 stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.<sup>17</sup>

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3 139 Arrhythmias as complications were defined either tachy- or bradyarrhythmia that were new-onset,  
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5 140 occurred during hospitalization with COVID-19. In this study, prolongation of QT segment was  
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7 141 defined as the QT duration > 500 milliseconds.

### 10 142 ***Study outcomes***

12 143 The primary outcome was in-hospital mortality. The secondary outcome included  
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14 144 treatment outcomes and complications such as recovery/discharge, AKI, ARDS, arrhythmias, QT  
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16 145 prolongation, venous thromboembolism, arterial thrombosis, cerebrovascular events, heart  
17  
18 146 failure, and myocardial infarction.

### 21 147 ***Statistical analysis***

23 148 All analyses were conducted using SPSS software version 23.0 (IBM Corp., Armonk,  
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25 149 NY, USA). Descriptive analyses were reported in percentage for categorical data and in mean  $\pm$   
26  
27 150 standard deviation (S.D.) or median (interquartile range; IQR) depending the data distribution.  
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29 151 Comparisons of outcomes for each variable were evaluated using Pearson's  $\chi^2$  tests or Fisher-  
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31 152 Exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher-  
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33 153 Exact tests were opted if the total sample in any cell count was less than five. A p-value less than  
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35 154 0.05 is considered statistically significant. Missing data were not included in the analysis.

### 40 155 ***Logistic regression analysis***

42 156 Clinical risk factors that were significant from standard analyses (Pearson's  $\chi^2$  tests, Fisher-  
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44 157 Exact tests, t-tests) were included in univariate binary logistic regression analysis. Odds ratios  
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46 158 (OR) were reported along with 95% confidence interval (CI). A 95% CI that crosses 1.0 and a p-  
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48 159 value of less than 0.05 is considered statistically significant.<sup>18</sup> Variables that remained statistically  
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50 160 significant on univariate analysis were included in multivariate analysis using logistic regression  
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52 161 method to adjust for other covariates. For the analyses of overall mortality predictors, each variable  
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3 162 was analyzed by only one model that was adjusted for several potential confounding factors for  
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5 163 that particular variable. Model 1 was adjusted for age, sex, ethnicity and obesity. Model 2 was  
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7 164 adjusted for age, sex, ethnicity, obesity and need for oxygen therapy. Model 3 is adjusted for age,  
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9 165 sex, ethnicity, obesity, asthma/chronic obstructive pulmonary disease (COPD), the need for  
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11 166 oxygen therapy, and ICU admission. Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, the  
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13 167 need for oxygen therapy, and ICU admission. Model 5 is adjusted for age, sex, ethnicity, obesity,  
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15 168 coronary artery disease, heart failure, history of arrhythmia/conduction disorder, and ICU  
16  
17 169 admission. The rationale for each Model adjustment in multivariate analysis is available in  
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19 170 *Supplemental Document 2*.

### 171 ***Survival analysis***

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

## 175 **RESULTS**

### 176 ***Baseline characteristics and patient outcomes***

177 A total of 12,938 patients were identified during the study period. Thirty-nine patients were  
178 outpatient and did not require hospitalization. After excluding patients with negative PCR (n =  
179 7,374), duplicate medical records (n = 145), pregnant woman (n = 3), and clinical trial patients (n  
180 = 2), 283 patients were included for further analysis. The flowchart of data selection from the  
181 UPMC Pinnacle COVID-19 registry is depicted in *Figure 1*. *Table 1* summarizes the demographics  
182 and baseline characteristics of included patients. All patients had confirmed SARS-Cov-2 infection  
183 by RT-PCR. Of 283 patients, 80.6% were survivors and 19.4% were non-survivors. The mean age  
184 of all patients was  $64.1 \pm 15.9$  years. 56.2% were male and 50.2% were Caucasian. Non-survivors

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3 185 were significantly older and had higher proportion of hypertension, CKD and had lower mean  
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5 186 eGFR. Moreover, hypoxia on presentation, rales/crackles on physical examination, leukocytosis,  
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7 187 lymphocytopenia, respiratory acidosis, transaminitis, and opacity/infiltrate on imaging were  
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9 188 common presentations in non-survivors. Higher inflammatory markers, such as D-dimer, ferritin,  
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11 189 lactate dehydrogenase (LDH), C-reactive protein, and procalcitonin were significantly prevalent  
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13 190 in deceased patients. The need for oxygen therapy regardless of the mode of oxygen delivery was  
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15 191 higher among those who did not survive. Furthermore, non-survivors were more likely to have  
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17 192 received intensive care unit (ICU) admission/transfer, extracorporeal membrane oxygenation  
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19 193 (ECMO), RRT, use of vasopressors, use of antibiotics, azithromycin, hydroxychloroquine,  
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21 194 steroids, ascorbic acid, zinc, tocilizumab and convalescent plasma. Of overall complications, the  
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23 195 prevalence of AKI, ARDS, arrhythmias and superimposed bacteremia was significantly higher in  
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25 196 non-survivors. There was no significant difference in mean hospital stay between survivors and  
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27 197 non-survivors. Up to 78.8% recovered or were discharged from the hospital. Only two patients  
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29 198 remained hospitalized as of June 18, 2020. The mean hospital stay was similar between patients  
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31 199 who received remdesivir vs. those who did not ( $9.0 \pm 4.7$  and  $7.6 \pm 7.8$  days, respectively;  $p =$   
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33 200  $0.359$ ). In contrast, patients who received tocilizumab had significantly longer hospital stay  
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35 201 compared to those who did not receive tocilizumab ( $15.3 \pm 11.7$  and  $7.4 \pm 7.2$  days, respectively;  
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37 202  $p < 0.001$ ).

### 203 ***Univariate analysis***

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

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

### 210 ***Multivariate analysis***

211 Variables that were significant on univariate analysis were included in multivariate logistic  
212 regression analysis (*Table 3*). In Model 1 (adjusted for age, sex, ethnicity, and obesity), increasing  
213 patient age, hypoxia, opacity/infiltrate on imaging, leukocytosis, ferritin > 336 ng/mL, LDH (>  
214 200 U/L), procalcitonin > 0.25 ng/mL, troponin I > 0.03 ng/mL, use of high-flow oxygen nasal  
215 cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU  
216 admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for  
217 increased in-hospital mortality. In Model 2 (adjusted for all variables in Model 1 plus the need for  
218 oxygen therapy, and ICU admission), hydroxychloroquine, ascorbic acid, zinc, and convalescent  
219 plasma were not associated with increased mortality. In Model 3 (adjusted for all variables in  
220 Model 2 plus asthma/COPD), respiratory acidosis was associated with increased mortality.  
221 Moreover, AKI was an independent risk factor for in-hospital mortality from COVID-19 from  
222 Model 4. In addition, we also found that hydroxychloroquine therapy was associated with QT  
223 prolongation (OR 2.874; 95% CI 1.189-6.944; p = 0.019) after adjusted for covariates in Model 2.

### 224 ***Cohort of critically ill patients***

225 A total 89 patients required intensive care during the study period. Of which, 47.2% died.  
226 The demographics and clinical characteristics of critically ill patients are demonstrated in *Table*  
227 *4*. Deceased ICU patients had significantly higher proportion of AKI and ARDS compared to  
228 survived ICU patients. The treatments were similar between survivors and non-survivor patients.  
229 In multivariate analysis, each 1-point increment of SOFA score was associated with increased  
230 death (OR 1.544; 95% CI 1.168-2.039; p 0.002) after adjusted for age, sex, and ethnicity.



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3 231 Similarly, AKI (OR 2.128, 95% CI 1.111-6.667;  $p = 0.034$ ) and ARDS (OR 6.410; 95% CI  
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5 232 2.237-18.182;  $p = 0.023$ ) are significantly predictive of in-hospital mortality among patients  
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7 233 admitted the ICU after adjusted for age, sex, ethnicity, and SOFA score.

### 10 234 *Survival analysis*

12 235 Survival analyses were evaluated using Kaplan-Meier curve of all patients were  
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14 236 presented in *Figure 2A*. The median survival time was 25.0 days with standard error of 7.0. The  
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16 237 Kaplan-Meier curves for ICU and no ICU patients were illustrated in *Figure 2B*.

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## 21 239 **DISCUSSION**

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24 240 In this single-network, retrospective observation study, we found that the overall in-  
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26 241 hospital mortality among hospitalized COVID-19 patients was 19.4%. The reported mortality  
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28 242 among Chinese cohorts ranged from 11.7% to 28.2%.<sup>7 8 19</sup> However, our reported mortality rates  
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30 243 appeared slightly lower than what previously described from New York City.<sup>5</sup> Richardson et al  
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32 244 found that the overall mortality of 5,700 hospitalized COVID-19 patients from 12 hospitals in  
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34 245 New York City was 21%. However, one could argue that our study has a significantly smaller  
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36 246 sample size. Our data need confirmation from other studies with a larger sample size.

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38 247 We identified several risk factors for mortality from COVID-19 using multivariate  
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40 248 logistic regression analysis. Increasing age, hypoxia and opacity/infiltrate on imaging were  
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42 249 associated with higher mortality. Moreover, we also found that patient survival diminished as the  
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44 250 disease progressed, reflected by advancement in oxygen delivery (high-flow nasal cannula,  
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46 251 NIPPV, and mechanical ventilation). Requiring a simple oxygen nasal cannula did not affect  
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48 252 mortality. Such findings are similar to previous literature. Older age is an independent risk factor  
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3 253 for severe COVID-19 and mortality.<sup>7 20</sup> In line with Zhou et al, increasing oxygen requirement  
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5 254 and need for advanced oxygen delivery were predictive of death from COVID-19.<sup>8</sup>  
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8 255 Here, we showed that COVID-19 patients requiring ICU had 13.7-fold increased risk of  
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10 256 mortality. Critically ill patients generally had one or more organs in failure, and an increasing  
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12 257 number of organ failure has been linked to elevated death in sepsis patients.<sup>21</sup> For COVID-19  
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14 258 patients, we demonstrated that kidney (AKI, and RRT), pulmonary (respiratory acidosis, and  
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16 259 ARDS), cardiovascular (vasopressor requirement) failure were predictive of in-hospital  
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18 260 mortality. These findings are in line with other cohorts and each factor has been demonstrated as  
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20 261 an independent risk factor for mortality in critically ill patients.<sup>8 22-26</sup> Although the complications  
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22 262 from SARS-CoV-2 infection can be affected by multiple contributing factors, newer evidence  
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24 263 has suggested the significance of cytokine storm leading to multi-organ failure.<sup>27</sup>  
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28 264 Here, we showed that elevated ferritin, LDH, procalcitonin, leukocytosis, troponin I and  
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30 265 possibly D-dimer were associated with increased death. Although, the odds ratio for D-dimer  
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32 266 cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-  
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34 267 dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be  
35  
36 268 ignored. Guan et al first demonstrated the importance of elevated inflammatory markers in  
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38 269 COVID-19 in Chinese population<sup>6</sup> which has become a standard monitoring parameter for  
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40 270 COVID-19 patients.<sup>28</sup> Elevated inflammatory markers should prompt physicians to evaluate and  
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42 271 monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated  
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44 272 procalcitonin and leukocytosis may indicate concomitant bacterial infection, which has been  
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46 273 shown to increase morbidity and mortality of viral pneumonia.<sup>29</sup> Interestingly, our study showed  
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48 274 that elevated troponin I level was associated with significantly higher death similar to a recent  
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50 275 meta-analysis.<sup>30</sup> Although the etiologies of elevated troponin levels were not determined in our  
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3 276 cohort, other studies proposed several mechanisms for elevated troponin level in COVID-19  
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5 277 patients. These include myocarditis, cytokine mediated myocardial injury, microangiopathy of  
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7 278 small coronary arteries, or silent coronary artery disease.<sup>26 30</sup>

10 279 The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses  
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12 280 or bacteria.<sup>31</sup> Cytokine storm is characterized by the overproduction of pro-inflammatory  
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14 281 cytokines, such as tumor necrosis factor (TNF), IL-6, and IL-1 $\beta$  resulting in an increased  
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16 282 vascular hyperpermeability, and activation of multiple coagulation pathways.<sup>27 32</sup> In light of  
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18 283 SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and  
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20 284 the protein C system were impaired during active inflammation.<sup>33</sup> These changes lead to  
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22 285 thrombin hyperactivity resulting in the development of microthrombosis, disseminated  
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24 286 intravascular coagulation (DIC) and sequential multiorgan failure.<sup>27</sup> Moreover, new studies have  
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26 287 revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are  
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28 288 beyond the scope of our article.<sup>34</sup> Such syndromes include macrophage activation syndrome,  
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30 289 adult-onset Still's disease, and catastrophic anti-phospholipid syndrome.<sup>34</sup>

33 290 Hydroxychloroquine therapy was associated with a 3-fold increased risk of QT  
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35 291 prolongation but not associated with increased risk of death. The concept of using  
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37 292 hydroxychloroquine in COVID-19 patients derived from an early *in vitro* study.<sup>35</sup> The results  
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39 293 from small non-randomized clinical trials also showed promising effects on viral load  
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41 294 reduction.<sup>36 37</sup> However, the clinical benefit of hydroxychloroquine was debated by a large  
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43 295 observation study. Of 1,446 patients, Geleris et al observed that hydroxychloroquine had no  
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45 296 effect on the death, length of stay or intubation.<sup>38</sup> A recent multicenter, randomized, open-label,  
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47 297 controlled trial in hospitalized patients with mild-to-moderate COVID-19 found that the use of  
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49 298 hydroxychloroquine, alone or with azithromycin did not improve the clinical outcome at 15 days  
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3 299 compared to the standard treatment.<sup>39</sup> Thus, the recommendation for use of hydroxychloroquine  
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5 300 was recalled by the Infectious Diseases Society of America (IDSA) due to small sample size in  
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7 301 previous clinical trials and concern for cardiac adverse effects, such as QT prolongation/torsade  
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10 302 de pointe.<sup>40</sup>

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12 303 A meta-analysis of four randomized trials and one retrospective study showed that the  
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14 304 administration of intravenous vitamin C has vasopressor sparing effects and may reduce the need  
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16 305 for mechanical ventilation in critically ill patients while there was no effect on the mortality.<sup>41</sup>  
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18 306 However, given the lack of more supporting evidence, the standard use of ascorbic acid is not yet  
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20 307 recommended especially in COVID-19 patients. A new clinical trial investigating the treatment  
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22 308 outcome of vitamin C in severe COVID-19 is underway (NCT04264533).

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26 309 Although our study also showed that zinc supplementation was not associated with  
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28 310 increased mortality in COVID-19 patients, the routine use of zinc supplementation could not be  
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30 311 supported due to lack of randomized controlled trials. A Brazilian study revealed that plasma  
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32 312 zinc concentration in critically ill patients upon admission to the ICU was low and may make  
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34 313 these patients more susceptible to oxidative stress.<sup>42</sup> Another prospective study showed that zinc  
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36 314 supplementation in mechanically ventilated patients was related to less ventilator-associated  
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38 315 pneumonia.<sup>43</sup> However, the mean duration of intubation in this study was prolonged (29 days),  
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40 316 making it inconclusive if zinc supplementation can prevent pneumonia development in short-  
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42 317 term intubation.

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46 318 Steroid therapy in COVID-19 patients was not associated with increased mortality. A  
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48 319 meta-analysis of 42 randomized controlled trials consisting of 10,194 patients has shown that  
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50 320 corticosteroids possibly result in a small reduction in mortality and an increased risk of  
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52 321 neuromuscular weakness among critically ill patients with sepsis.<sup>44</sup> However, the theoretical  
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3 322 concept for corticosteroid use in COVID-19 was to reduce cytokine storm caused by a reaction  
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5 323 to SARS-CoV-2 infection.<sup>45</sup> In early April 2020, the IDSA recommended against a routine use of  
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7 324 corticosteroids in the treatment of COVID-19 due to lack of evidence.<sup>40</sup> This guidelines was  
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10 325 updated on June 25<sup>th</sup>, 2020 after the results of the RECOVERY trial was released showing that  
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12 326 patients who received dexamethasone were more likely to be discharged from hospital at 28 days  
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15 327 compared to non-steroids group.<sup>46</sup> Thus, currently, the IDSA panel suggests glucocorticoids use  
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17 328 in hospitalized patients with severe COVID-19.<sup>40</sup> Here, our study is in line with the  
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19 329 recommendation from the IDSA.

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21 330 We have observed that remdesivir and tocilizumab were not associated with mortality  
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23 331 and there was no significant improvement in hospital length of stay between patients receiving  
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25 332 these drugs. However, given the observational, non-randomized design of this study, it is  
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27 333 difficult to determine the efficacy of such treatment. Recently, the preliminary report from a  
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29 334 phase III randomized controlled trial revealed that remdesivir was superior to placebo in  
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31 335 shortening the time to recovery in adults hospitalized with COVID-19.<sup>47</sup> Several retrospective  
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33 336 studies reported that tocilizumab, an IL-6 inhibitor, was shown to reduce the levels of serum  
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35 337 inflammatory markers. However, the impact on clinical improvement and mortality remained  
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37 338 inconclusive.<sup>48-50</sup> Although we reported no significant clinical benefits from tocilizumab, the  
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39 339 consideration for compassionate use of tocilizumab is not discouraged but rather dependent on  
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41 340 the judgment of clinicians based on current evidence. A phase 2 (TOCIVID-19; NCT04317092)  
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43 341 and 3 randomized controlled trial (COVACTA; NCT04320615) of tocilizumab is being  
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45 342 investigated for the treatment of COVID-19 pneumonia. The preliminary results are expected to  
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47 343 release in late 2020.

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3 344 Similarly, we found that convalescent plasma was not associated with in-hospital  
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5 345 mortality. The safety of convalescent plasma was demonstrated in a single-center retrospective  
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7 346 cohort of 25 patients<sup>51</sup> and in a preprint, non-peer review report.<sup>52</sup> However, the efficacy of  
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10 347 convalescent plasma remained undetermined due to lack of control group. The IDSA panel has  
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12 348 recommended convalescent plasma only in the context of a clinical trials. However, at our  
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14 349 institution, convalescent plasma is considered if patients have severe symptoms and have  
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16 350 contraindications to remdesivir, such as AKI and hepatic dysfunction. Although we did not  
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19 351 observe mortality adverse effect from convalescent plasma, the final recommendations on its  
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21 352 efficacy and safety are dependent on the randomized controlled trials. To date, at least one  
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23 353 randomized controlled trial (NCT04342182) is being investigated to establish the clinical  
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25 354 benefits in hospitalized patients with severe COVID-19.

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28 355 From our ICU cohort, the SOFA score, AKI and ARDS were the only variables that were  
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30 356 predictive of mortality among patients admitted to the ICU. Interestingly, all treatment measures  
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32 357 had no effect on mortality once patients were critically ill and required ICU. This could imply  
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34 358 that these treatment interventions might be beneficial if given prior to clinical decompensation or  
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36 359 ICU transfer. However, interpretation is restricted due to small sample size and examining only  
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38 360 critically ill patients. Our hypothesis should be substantiated by studies from other institutions  
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40 361 with larger sample sizes.

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42 362 Our study has some limitations. The observational design made the results susceptible to  
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44 363 selection bias. Analyses could be underpowered given the small sample size. Moreover, due to  
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46 364 restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir,  
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48 365 and convalescent plasma, which may limit the applicability of our findings. More importantly, the  
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50 366 mortality can be affected by confounding factors. We minimize this risk by applying multivariate  
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3 367 analysis with models designed to cover all possible confounding factors for each analyzed variable.  
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5 368 Most of the collected data were cross sectional, thus, making it difficult to conclude the causality  
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8 369 between the two variables. Furthermore, our binary logistic regression analyses may not strictly  
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10 370 follow the one-in-ten rule which may lead to over-fitting effect. However, our statistical rationale  
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12 371 is supported by newer simulation studies by McCulloch et al.,<sup>53</sup> and Smeden et al.<sup>54</sup> The length of  
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14 372 stay was computed in the Kaplan-Meier analysis to represent the time to death. It is worth noting  
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16 373 that the non-survivors had a curtailed length of stay. Moreover, we advised the readers to consider  
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18 374 their patient population to determine the applicability of our results.

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21 375 In conclusion, COVID-19 is a serious condition with a significant in-hospital mortality  
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23 376 rate. Multiple risk factors for in-hospital death were identified. Increasing SOFA score, AKI and  
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25 377 ARDS are significant risk factors for increased death in critically ill patients.

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12 394 **Figure 1.** Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1  
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15 395 to May 31, 2020.

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17 396 **Figure 2.** Survival analysis by Kaplan-Meier curves. **A)** The cumulative survival declined with  
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19 397 increasing length of hospital stay. The median survival time was 25 days with standard error (SE)  
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21 398 of 7.0. **B)** ICU patients significantly lower survival probability with mean survival time of 22.3  
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23 399 days (SE 1.8) and 23.0 (SE 1.3) in ICU group vs. non-ICU group, respectively ( $p = 0.002$ ). **C)** The  
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25 400 cumulative survival between ICU patients with and without acute respiratory distress syndrome ( $p$   
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27 401 = 0.302). **D)** The cumulative survival between ICU patients with and without acute kidney injury  
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29 402 ( $p = 0.504$ ).  
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**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.



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617 **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) <sup>†</sup>	61.9 (15.8) <sup>†</sup>	72.8 (13.5) <sup>†</sup>	< 0.001*
<b>Ethnicity</b>				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	0.705
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
<b>Co-morbidities</b>				
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	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
<b>Signs and symptoms</b>				
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 (SpO <sub>2</sub> < 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
<b>Laboratory findings</b>				
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) <sup>‡</sup>	1.59 (1.88) <sup>†</sup>	1.64 (1.15) <sup>†</sup>	0.808
eGFR (mL/min/1.73m <sup>2</sup> )	64.2 (51.0) <sup>†</sup>	66.7 (35.5) <sup>†</sup>	53.6 (25.3) <sup>†</sup>	0.002*
Troponin I (> 0.03 ng/mL)	91 (39.1)	61 (33.0)	30 (62.5)	< 0.001*

<b>Inflammatory markers</b>				
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
<b>Radiographic findings</b>				
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
<b>Oxygen therapy/delivery</b>				
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*
<b>Intervention</b>				
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*
<b>Treatment</b>				
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
<b>Complications</b>				
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
<b>Outcome</b>				
Recovery/discharge	223 (78.8)			
Remained hospitalized	2 (0.7)			
Death	55 (19.4)			

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ALC, absolute lymphocyte count; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extra-corporeal 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; SpO<sub>2</sub>, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.

\*statistically significant peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

†mean (standard deviation)

‡median (IQR)

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622 **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 (SpO <sub>2</sub> < 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 <sup>2</sup> 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	4.545-25.000	< 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

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

Characteristics	Statistics		
	Odds ratio	95% CI	P-value
<b>Model 1</b>			
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 (SpO <sub>2</sub> < 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 <sup>2</sup> 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
<b>Model 2</b>			
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
<b>Model 3</b>			
Respiratory acidosis	3.745	1.443-9.709	0.007*
Steroids therapy	1.107	0.459-2.667	0.821



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

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629 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.

630 \*statistically significant

Model 1 is adjusted for age, sex, ethnicity and obesity

631 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

632 Model 5 is adjusted for age, sex, ethnicity, obesity, CAD, heart failure, history of arrhythmia/conduction disorder, and ICU admission

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651 **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) <sup>†</sup>	69.1 (12.5) <sup>†</sup>	63.3 (15.2) <sup>†</sup>	0.052
SOFA score <sup>‡</sup>	4.3 (2.0)	3.6 (1.7)	5.1 (1.9)	< 0.001*
<b>Ethnicity</b>				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	0.685
African-American	25 (28.1)	12 (25.5)	13 (31.0)	
Hispanic/Latino	12 (13.5)	8 (17.0)	4 (9.5)	
Asian	5 (5.6)	2 (4.3)	3 (7.1)	
Others	-	-	-	
<b>Treatment</b>				
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
<b>Complications</b>				
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) <sup>†</sup>	10.4 (8.1) <sup>†</sup>	15.5 (10.3) <sup>†</sup>	0.125
<b>Outcome</b>				
Recovery/discharge	43 (48.3)			
Remained hospitalized	2 (2.2)			
Death	42 (47.2)			

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653 ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment

\*statistically significant

<sup>†</sup>mean (standard deviation)<sup>‡</sup>collected on the first day of ICU admission

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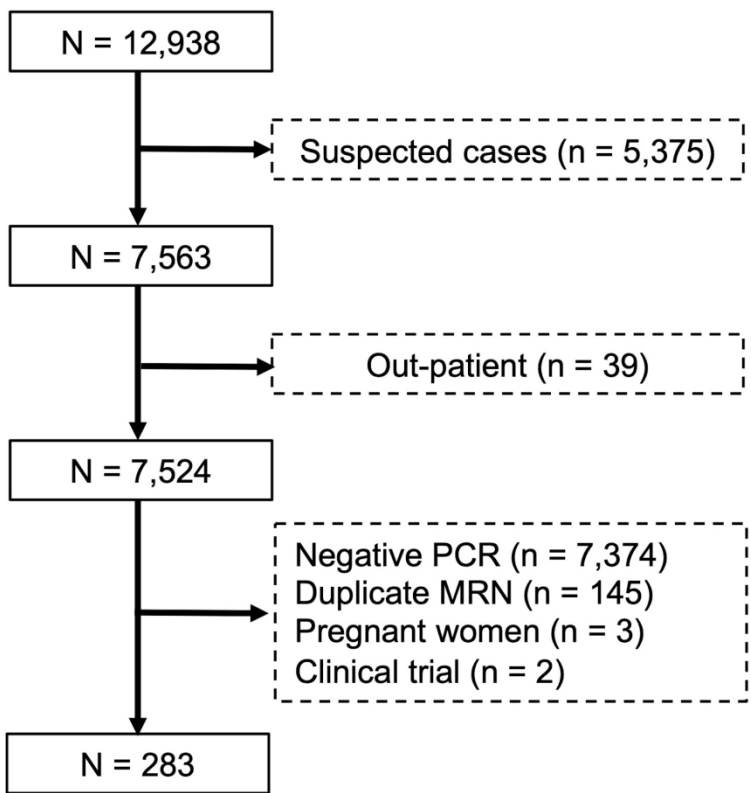


Figure 1. Flowchart of subject selection from UPMC Pinnacle COVID-19 registry from March 1 to May 31, 2020.

203x185mm (300 x 300 DPI)

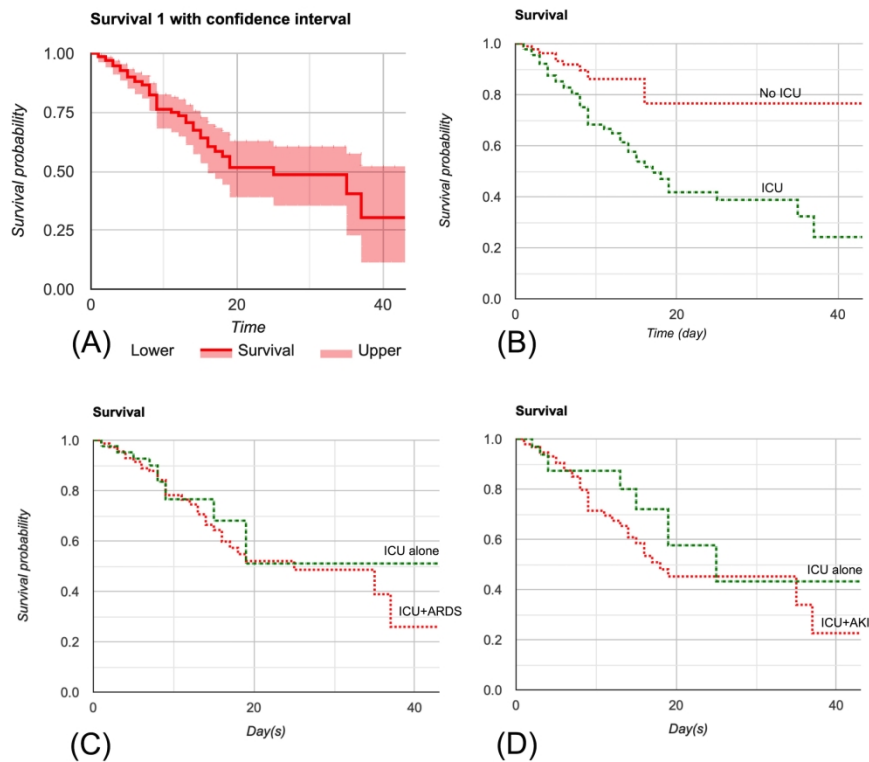


Figure 2. Survival analysis by Kaplan-Meier curves. A) The cumulative survival declined with increasing length of hospital stay. The median survival time was 25 days with standard error (SE) of 7.0. B) ICU patients significantly lower survival probability with mean survival time of 22.3 days (SE 1.8) 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  $\geq 30$  kg/m<sup>2</sup>), 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  $> 9,500/\mu\text{L}$ ), leukopenia (white blood cells count  $< 3,900/\mu\text{L}$ ), lymphocytopenia (absolute lymphocytes count  $< 600/\mu\text{L}$ ), thrombocytosis (platelets  $> 400,000/\mu\text{L}$ ), and thrombocytopenia (platelets  $< 140,000/\mu\text{L}$ ), respiratory acidosis (arterial pH  $< 7.35$  and arterial partial pressure of CO<sub>2</sub>  $> 45$  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-variables showed significant association with death on univariate analysis. Without these adjustments, the aforementioned co-variables 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.

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3 In Model 5, “arrhythmias” is a cardiac complication, hence we adjusted for every variable that  
4 could be the confounding factor, such as CAD, heart failure, history of arrhythmia/conduction  
5 disorder, and ICU admission.  
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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 11-16, Line 309-467
<b>Limitations</b>			
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
<b>Other information</b>			
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.

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3 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE  
4 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  
5 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).  
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