

# BMJ Open Clinical characteristics of hospitalised patients with COVID-19 and the impact on mortality: a single-network, retrospective cohort study from Pennsylvania state

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## ABSTRACT

**Objective** COVID-19 is a respiratory disease caused by SARS-CoV-2 with the highest burden in the USA. Data on clinical characteristics of patients with COVID-19 in US 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 hospitalised from 1 March to 31 May 2020.

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

**Results** Of 283 patients, 19.4% were non-survivors. The mean age of all patients was 64.1±15.9 years. 56.2% were male and 50.2% were white. Several factors were identified from our adjusted multivariate analyses to be associated with in-hospital mortality: increasing age (per 1-year increment; OR 1.07 (1.045 to 1.105)), hypoxia (oxygen saturation <95%; OR 4.630 (1.934 to 1.111)), opacity/infiltrate on imaging (OR 3.077 (1.276 to 7.407)), leucocytosis (white blood cell >10<sup>109</sup>/μL; OR 2.732 (1.412 to 5.263)), ferritin >336 ng/mL (OR 4.016 (1.195 to 13.514)), lactate dehydrogenase >200 U/L (OR 7.752 (1.639 to 37.037)), procalcitonin >0.25 ng/mL (OR 2.404 (1.011 to 5.714)), troponin I >0.03 ng/mL (OR 2.242 (1.080 to 4.673)), need for advanced oxygen support other than simple nasal cannula (OR 4.608–13.889 (2.053 to 31.250)), intensive care unit admission/transfer (OR 13.699 (6.135 to 30.303)), renal replacement therapy (OR 21.277 (5.025 to 90.909)), need for vasopressor (OR 22.222 (9.434 to 52.632)), ARDS (OR 23.810 (10.204 to 55.556)), respiratory acidosis (OR 7.042 (2.915 to 16.949)), and AKI (OR 3.571 (1.715 to 7.407)). When critically ill patients were analysed independently, increasing Sequential Organ Failure Assessment score (OR 1.544 (1.168 to 2.039)), AKI (OR 2.128 (1.111 to 6.667)) and ARDS (OR 6.410 (2.237 to 18.182)) were predictive of in-hospital mortality.

## Strengths and limitations of this study

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

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

## INTRODUCTION

COVID-19 is a respiratory disease caused by SARS-CoV-2 which has become a pandemic in early 2020. The spread of this virus was originally started in Wuhan, China in December 2019 and rapidly escalated to 216 countries within 5 months with the highest number of infected cases in the USA.<sup>1</sup> As of 29 August 2020, the reported cumulated number of confirmed cases in the USA was close to 6 million with a mortality rate of 3.09%.<sup>1</sup>

As of 29 August 2020, the Pennsylvania Department of Health has announced more than 129 056 confirmed cases of COVID-19 leading to 7671 deaths, making Pennsylvania the 13th state with the highest confirmed cases.<sup>2</sup> To date, the characteristics of infected patients in the USA were reported in the states of Washington (n=21), California (n=1299) and New York (n=5700) in chronological order.<sup>3–5</sup> The mortality across the US studies ranged from 6.3% to 24%, depending on the severity of COVID-19. Although the characteristics of hospitalised patients with COVID-19 have been reported in other states,

there are some limitations that preclude the generalisation of the results toward our patient population. Studies from Washington and California were conducted and published during an early stage of the pandemic where treatment options, such as remdesivir or dexamethasone, were not recommended as the standard of care. In addition, multivariate analysis was not performed in the New York City cohort. The associations between clinical characteristics and in-hospital mortality in the US population have not been clearly established.

Guan *et al*<sup>6</sup> first described the clinical characteristics of 1099 patients infected with SARS-CoV-2 across China. In this study, the overall mortality was 1.4%. However, the association between clinical risk factors and mortality was not described. Later, Du *et al* and Zhou *et al* demonstrated that older age, higher Sequential Organ Failure Assessment (SOFA) score, D-dimer >1 µg/mL, cardiac troponin I ≥0.05 ng/mL, and pre-existing concurrent cardiovascular and cerebrovascular diseases were significant predictors for increased mortality from COVID-19.<sup>7,8</sup> However, these findings were primarily based on Chinese population; thus, it has been unconfirmed if the results can be applicable to other patient populations.

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

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

## MATERIALS AND METHODS

### Study design

This is a retrospective cohort study from seven hospitals under UPMC Pinnacle network located across the state of Pennsylvania. Written informed consent was waived due to the retrospective, observational nature of the study. Our current study followed the Declaration of Helsinki.

### Patient and public involvement

No patient involvement.

### Data source and patient population

Data were collected by extracting electronic medical records from 1 March to 31 May 2020 through UPMC Pinnacle COVID-19 registry. Adult patients aged ≥18 years who were hospitalised with confirmed SARS-CoV-2 infection by real-time PCR (RT-PCR) from nasopharyngeal swab were included in this study. We excluded non-hospitalised patients, patients <18 years of age, presumed SARS-CoV-2 infection, pregnant women, out-of-system transfer and patients enrolled in clinical trials. Transfer

within the system was considered one admission. For patients with multiple admissions with study period, the first admission for COVID-19 was reviewed.

### Data collection

Individual patient charts were reviewed by three independent authors to prevent observer bias. Collected data were divided into: demographics, comorbidities, signs and symptoms, laboratory findings, radiographic findings, treatments/interventions, complications and outcomes. Online supplemental document 1 summarises the description of each variable in our cohort as well as the cut-off values for each variable.

The SOFA score<sup>13</sup> was calculated on the first day of intensive care unit (ICU) admission. Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease (CKD)-Epidemiology Collaboration equation.<sup>14</sup> Acute kidney injury (AKI) was defined by an increase in serum creatinine by 0.3 mg/dL (27 µmol/L) or ≥1.5 times from the baseline value within 48 hours.<sup>15</sup> CKD was defined by the Kidney Diseases Improving Global Outcomes guidelines.<sup>16</sup> Patients with a history of end-stage kidney disease on dialysis prior to admission were not counted toward 'requirement of renal replacement therapy (RRT)/haemodialysis' during the hospital stay. Acute respiratory distress syndrome (ARDS) was defined by the Berlin criteria.<sup>17</sup> Arrhythmias as complications were defined either tachycardia or bradycardia that were new onset, occurred during hospitalisation with COVID-19. In this study, prolongation of QT segment was defined as the QT duration >500 ms.

### Study outcomes

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

### Statistical analysis

All analyses were conducted using SPSS software V.23.0 (IBM Corp). Descriptive analyses were reported in percentage for categorical data and in mean±SD or median (IQR) depending on the data distribution. Comparisons of outcomes for each variable were evaluated using Pearson's  $\chi^2$  tests or Fisher's exact tests (for categorical data) and two-sample independent t-test (for continuous data). Fisher's exact tests were opted if the total sample in any cell count was less than five. A p value less than 0.05 is considered statistically significant. Missing data were not included in the analysis.

### Logistic regression analysis

Clinical risk factors that were significant from standard analyses (Pearson's  $\chi^2$  tests, Fisher's exact tests, t-tests) were included in univariate binary logistic regression analysis. ORs were reported along with 95% CI. A 95% CI that crosses 1.0 and a p value of less than 0.05 are considered

statistically significant.<sup>18</sup> Variables that remained statistically significant on univariate analysis were included in multivariate analysis using logistic regression method to adjust for other covariates. For the analyses of overall mortality predictors, each variable was analysed by only one model that was adjusted for several potential confounding factors for that particular variable. Model 1 was adjusted for age, sex, ethnicity and obesity. Model 2 was adjusted for age, sex, ethnicity, obesity and need for oxygen therapy. Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/chronic obstructive pulmonary disease (COPD), the need for oxygen therapy and ICU admission. Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, the need for oxygen therapy and ICU admission. Model 5 is adjusted for age, sex, ethnicity, obesity, coronary artery disease, heart failure, history of arrhythmia/conduction disorder and ICU admission. The rationale for each model adjustment in multivariate analysis is available in online supplemental document 2.

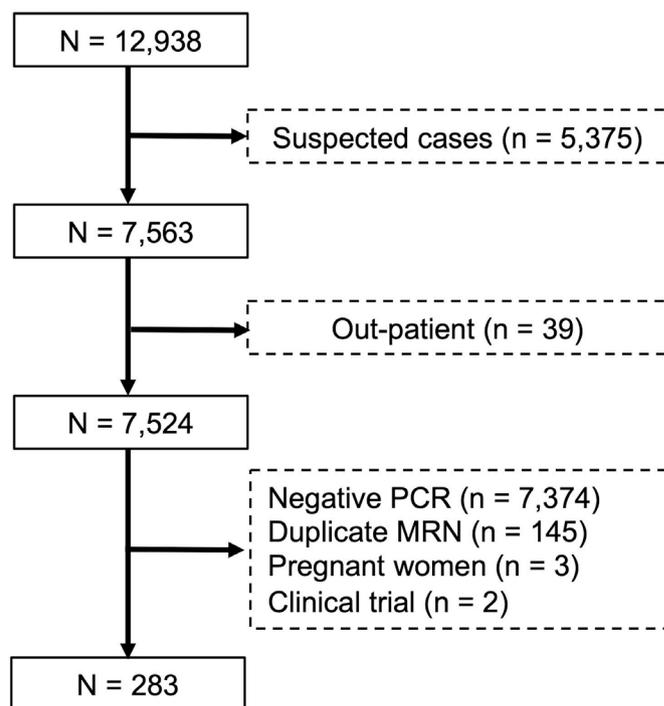
### Survival analysis

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

## RESULTS

### Baseline characteristics and patient outcomes

A total of 12 938 patients were identified during the study period. Thirty-nine patients were outpatient and did not require hospitalisation. After excluding patients with negative PCR (n=7374), duplicate medical records (n=145), pregnant woman (n=3) and clinical trial patients (n=2), 283 patients were included for further analysis. The flow chart of data selection from the UPMC Pinnacle COVID-19 registry is depicted in figure 1. Table 1 summarises the demographics and baseline characteristics of included patients. All patients had confirmed SARS-CoV-2 infection by RT-PCR. Of 283 patients, 80.6% were survivors and 19.4% were non-survivors. The mean age of all patients was 64.1±15.9 years. A total of 56.2% were male and 50.2% were Caucasian. Non-survivors were significantly older and had higher proportion of hypertension, CKD and had lower mean eGFR. Moreover, hypoxia on presentation, rales/crackles on physical examination, leucocytosis, lymphocytopenia, respiratory acidosis, transaminitis and opacity/infiltrate on imaging were common presentations in non-survivors. Higher inflammatory markers, such as D-dimer, ferritin, lactate dehydrogenase (LDH), C reactive protein and procalcitonin were significantly prevalent in deceased patients. The need for oxygen therapy regardless of the mode of oxygen delivery was higher among those who did not survive. Furthermore, non-survivors were more likely to have received ICU admission/transfer, extracorporeal membrane oxygenation (ECMO), RRT, use of vasopressors, use of antibiotics, azithromycin, hydroxychloroquine, steroids, ascorbic acid, zinc, tocilizumab and convalescent plasma.



**Figure 1** Flow chart of subject selection from UPMC Pinnacle COVID-19 registry from 1 March to 31 May 2020. MRN, medical record number.

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

### Univariate analysis

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

### Multivariate analysis

Variables that were significant on univariate analysis were included in multivariate logistic regression analysis (table 3). In model 1 (adjusted for age, sex, ethnicity and obesity), increasing patient age, hypoxia, opacity/infiltrate on imaging, leucocytosis, ferritin >336 ng/mL,

**Table 1** Demographics and baseline characteristics of included patients

Characteristics	All patients (n=283)	Survivors (n=228)	Non-survivors (n=55)	P value
Male	159 (56.2)	125 (54.8)	34 (61.8)	0.348
Age (year)	64.1 (15.9)*	61.9 (15.8)*	72.8 (13.5)*	<0.001†
Ethnicity				
Caucasian	143 (50.5)	111 (48.7)	32 (58.2)	
African-American	88 (31.1)	73 (32.0)	15 (27.3)	
Hispanic/Latino	32 (11.3)	27 (11.8)	5 (9.1)	0.705
Asian	17 (6.0)	14 (6.1)	3 (5.5)	
Others	3 (1.1)	3 (1.3)	0 (0)	
Comorbidities				
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
Hyperlipidaemia	121 (42.8)	94 (41.2)	27 (49.1)	0.290
Coronary artery disease	50 (17.7)	40 (17.5)	10 (18.2)	0.911
Heart failure/cardiomyopathy	53 (18.7)	40 (17.5)	13 (23.6)	0.299
Arrhythmia/conduction disorders	45 (15.9)	36 (15.8)	9 (16.4)	0.917
Chronic kidney disease	66 (23.3)	46 (20.2)	20 (36.4)	0.011†
End-stage kidney disease	13 (4.6)	12 (5.3)	1 (1.8)	0.474
Asthma/COPD	73 (25.8)	54 (23.7)	19 (34.5)	0.098
Cerebrovascular disease	40 (14.1)	32 (14.0)	8 (14.5)	0.922
Signs and symptoms				
Cough	185 (65.4)	149 (65.4)	36 (65.5)	0.988
Dyspnoea	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†
Rhinorrhoea	29 (10.2)	26 (11.4)	3 (5.5)	0.226
Fever/chills	179 (63.3)	143 (62.7)	36 (65.5)	0.706
Chest pain	35 (12.4)	32 (14.0)	3 (5.5)	0.109
Headache	28 (9.9)	26 (11.4)	2 (3.6)	0.128
Gastrointestinal symptoms	79 (27.9)	68 (29.8)	11 (20.0)	0.145
Asymptomatic	8 (2.8)	8 (3.5)	0 (0)	0.361
Rales/crackles	57 (20.1)	40 (17.5)	17 (30.9)	0.027†
Rhonchi	57 (20.1)	45 (19.7)	12 (21.8)	0.730
Reduced breath sound	63 (22.3)	48 (21.1)	15 (27.3)	0.320
Laboratory findings				
Leucopenia (WBC <4000/μL)	56 (19.8)	46 (20.2)	10 (18.2)	0.739
Leucocytosis (WBC >10 000/μL)	80 (28.3)	53 (23.2)	27 (49.1)	<0.001†
Lymphocytopenia (ALC <1000/μL)	109 (38.7)	78 (34.2)	31 (57.4)	0.002†
Thrombocytopenia (<140 000/μL)	57 (20.1)	41 (18.0)	16 (29.1)	0.065
Thrombocytosis (>400 000/μL)	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 >3× 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/1.73 m <sup>2</sup> )	64.2 (51.0)*	66.7 (35.5)*	53.6 (25.3)*	0.002†

Continued

Table 1 Continued

Characteristics	All patients (n=283)	Survivors (n=228)	Non-survivors (n=55)	P value
Troponin I (>0.03 ng/mL)	91 (39.1)	61 (33.0)	30 (62.5)	<0.001†
Inflammatory markers				
D-dimer (>500 ng/mL)	135 (80.4)	101 (75.4)	34 (100)	<0.001†
Ferritin (>336 ng/mL)	109 (65.3)	78 (59.1)	31 (88.6)	0.001†
Lactate dehydrogenase (>200 U/L)	108 (73.0)	77 (67.0)	31 (93.9)	0.002†
C reactive protein (>1 mg/dL)	152 (87.4)	115 (83.9)	37 (100)	0.005†
Procalcitonin (>0.25 ng/mL)	73 (47.1)	50 (41.7)	23 (65.7)	0.012†
ST-T change on ECG	84 (31.8)	63 (29.7)	21 (40.4)	0.139
Radiographic findings				
Opacity/infiltrate	209 (73.9)	162 (71.1)	47 (85.5)	0.029†
Ground-glass appearance	79 (27.9)	65 (28.5)	14 (25.5)	0.650
Pleural effusion	24 (8.5)	17 (7.5)	7 (12.7)	0.208
Pulmonary congestion	30 (10.6)	23 (10.1)	7 (12.7)	0.568
Oxygen therapy/delivery				
Nasal cannula	207 (73.1)	160 (70.2)	47 (85.5)	0.022†
High-flow nasal cannula	36 (12.7)	18 (7.9)	18 (32.7)	<0.001†
NIPPV	28 (9.9)	10 (4.4)	18 (32.7)	<0.001†
Mechanical ventilation	58 (20.5)	25 (11.0)	33 (60.0)	<0.001†
Intervention				
Intensive care unit	89 (31.4)	47 (20.6)	42 (76.4)	<0.001†
ECMO	2 (0.7)	0 (0)	2 (3.6)	0.037†
RRT	16 (5.7)	3 (1.3)	13 (23.6)	<0.001†
Vasopressor	53 (18.7)	19 (8.3)	34 (61.8)	<0.001†
Antibiotics	220 (77.7)	166 (72.8)	54 (98.2)	<0.001†
Treatment				
Azithromycin	182 (64.3)	139 (61.0)	43 (78.2)	0.017†
Hydroxychloroquine	67 (23.7)	45 (19.7)	22 (40.0)	0.002†
Steroids	46 (16.3)	26 (11.4)	20 (36.4)	<0.001†
Ascorbic acid	57 (20.1)	38 (16.7)	19 (34.5)	0.003†
Zinc	54 (19.1)	33 (14.5)	21 (38.2)	<0.001†
Tocilizumab	12 (4.2)	6 (2.6)	6 (10.9)	0.006†
Convalescent plasma	36 (12.7)	19 (8.3)	17 (30.9)	<0.001†
Remdesivir	25 (8.8)	20 (8.8)	5 (8.8)	0.940
Complications				
Acute kidney injury	115 (40.6)	75 (32.9)	40 (72.7)	<0.001†
ARDS	53 (18.7)	17 (7.5)	36 (65.5)	<0.001†
Arrhythmias	31 (11.0)	18 (7.9)	13 (23.6)	0.001†
QT prolongation	25 (8.8)	18 (7.9)	7 (12.7)	0.257
Venous thromboembolism	10 (3.5)	8 (3.5)	2 (3.6)	1.000
Arterial thrombosis	1 (0.4)	1 (0.4)	0 (0)	1.000
Cerebrovascular event	3 (1.1)	3 (1.3)	0 (0)	1.000
Myocardial infarction	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 bacteraemia	19 (6.7)	12 (5.3)	7 (12.7)	0.047†

Continued



Table 1 Continued

Characteristics	All patients (n=283)	Survivors (n=228)	Non-survivors (n=55)	P value
Hospital stay (day)	6.0 (7.0)‡	7.4 (7.53)*	9.2 (7.7)*	0.125
Outcome				
Recovery/discharge	223 (78.8)			
Remained hospitalised	2 (0.7)			
Death	55 (19.4)			

\*Mean (SD).

†Statistically significant.

‡Median (IQR).

ALC, absolute lymphocyte count; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy; SpO<sub>2</sub>, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.

LDH (>200 U/L), procalcitonin >0.25 ng/mL, troponin I >0.03 ng/mL, use of high-flow oxygen nasal cannula, non-invasive positive pressure ventilation (NIPPV), mechanical ventilation, ICU admission/transfer, RRT, vasopressor, antibiotics and ARDS were independent risk factors for increased in-hospital mortality. In model 2 (adjusted for all variables in model 1 plus the need for oxygen therapy and ICU admission), hydroxychloroquine, ascorbic acid, zinc and convalescent plasma were not associated with increased mortality. In model 3 (adjusted for all variables in model 2 plus asthma/COPD), respiratory acidosis was associated with increased mortality. Moreover, AKI was an independent risk factor for in-hospital mortality from COVID-19 from model 4. In addition, we also found that hydroxychloroquine therapy was associated with QT prolongation (OR 2.874; 95% CI 1.189 to 6.944; p=0.019) after adjusted for covariates in model 2.

### Cohort of critically ill patients

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

### Survival analysis

Survival analyses evaluated using Kaplan-Meier curve of all patients were presented in figure 2A. The median

survival time was 25.0 days with SE of 7.0. The Kaplan-Meier curves for ICU and no ICU patients were illustrated in figure 2B.

### DISCUSSION

In this single-network, retrospective observation study, we found that the overall in-hospital mortality among hospitalised patients with COVID-19 was 19.4%. The reported mortality among Chinese cohorts ranged from 11.7% to 28.2%.<sup>7 8 19</sup> However, our reported mortality rates appeared slightly lower than what previously described from New York City. Richardson *et al*<sup>5</sup> found that the overall mortality of 5700 hospitalised patients with COVID-19 from 12 hospitals in New York City was 21%. However, one could argue that our study has a significantly smaller sample size. Our data need confirmation from other studies with a larger sample size.

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

Here, we showed that patients with COVID-19 requiring ICU had 13.7-fold increased risk of mortality. Critically ill patients generally had one or more organs in failure, and an increasing number of organ failure has been linked to elevated death in patients with sepsis.<sup>21</sup> For patients with COVID-19, we demonstrated that kidney (AKI and RRT), pulmonary (respiratory acidosis and ARDS) and cardiovascular (vasopressor requirement) failure were

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

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

\*Statistically significant.

†On admission.

‡Analyses cannot be performed as at least one cell is zero.

ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy; SpO<sub>2</sub>, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.

predictive of in-hospital mortality. These findings are in line with other cohorts and each factor has been demonstrated as an independent risk factor for mortality in critically ill patients.<sup>8 22–26</sup> Although the complications

from SARS-CoV-2 infection can be affected by multiple contributing factors, newer evidence has suggested the significance of cytokine storm leading to multiorgan failure.<sup>27</sup>

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

Characteristics	Statistics		
	OR	95% CI	P value
<b>Model 1</b>			
Age (per 1-year increment)	1.075	1.045 to 1.105	<0.001*
Hypertension	1.264	0.572 to 2.793	0.562
Chronic kidney disease (CKD)	1.232	0.590 to 2.571	0.578
Hypoxia (SpO <sub>2</sub> <95%)	4.630	1.934 to 1.111	0.001*
Rales/crackles	2.016	0.955 to 4.255	0.066
Leucocytosis (WBC >10 000/ $\mu$ L)	2.732	1.412 to 5.263	0.003*
Transaminitis (ALT >3 $\times$ UNL)	2.137	0.890 to 5.128	0.089
eGFR (per 1.0 mL/min/1.73 m <sup>2</sup> decrement) <sup>†</sup>	1.002	0.990 to 1.013	0.795
Ferritin (>336 ng/mL)	4.016	1.195 to 13.514	0.025*
Lactate dehydrogenase (>200 U/L)	7.752	1.639 to 37.037	0.010*
Procalcitonin (>0.25 ng/mL)	2.404	1.011 to 5.714	0.047*
Troponin I (>0.03 ng/mL)	2.242	1.080 to 4.673	0.030*
Opacity/infiltrate on imaging	3.077	1.276 to 7.407	0.012*
Nasal cannula	1.883	0.799 to 4.444	0.148
High-flow nasal cannula	4.608	2.053 to 10.309	<0.001*
NIPPV	7.246	2.899 to 18.182	<0.001*
Mechanical ventilation	13.889	6.211 to 31.250	<0.001*
ICU admission/transfer	13.699	6.135 to 30.303	<0.001*
RRT	21.277	5.025 to 90.909	<0.001*
Vasopressor	22.222	9.434 to 52.632	<0.001*
Antibiotics	17.544	2.309 to 125.000	0.006*
ARDS	23.810	10.204 to 55.556	<0.001*
Superimposed bacteraemia	2.041	0.645 to 6.452	0.224
<b>Model 2</b>			
Azithromycin	1.916	0.788 to 4.651	0.152
Hydroxychloroquine	1.057	0.467 to 2.392	0.894
Ascorbic acid	1.008	0.440 to 2.313	0.985
Zinc	1.517	0.651 to 3.546	0.334
Tocilizumab	1.499	0.381 to 5.917	0.562
Convalescent plasma	1.513	0.600 to 3.817	0.381
<b>Model 3</b>			
Respiratory acidosis	3.745	1.443 to 9.709	0.007*
Steroids therapy	1.107	0.459 to 2.667	0.821
<b>Model 4</b>			
Acute kidney injury	2.268	1.025 to 5.025	0.043*
<b>Model 5</b>			
Arrhythmias as complications	1.161	0.428 to 3.155	0.769

Continued

Table 3 Continued

Characteristics	Statistics		
	OR	95% CI	P value

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

Model 2 is adjusted for age, sex, ethnicity, obesity, need for oxygen therapy and ICU admission.

Model 3 is adjusted for age, sex, ethnicity, obesity, asthma/COPD, need for oxygen therapy and ICU admission.

Model 4 is adjusted for age, sex, ethnicity, obesity, CKD, need for oxygen therapy and ICU admission.

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

\*Statistically significant.

ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; RRT, renal replacement therapy; SpO<sub>2</sub>, oxygen saturation; UNL, upper normal limit; WBC, white blood cell.

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

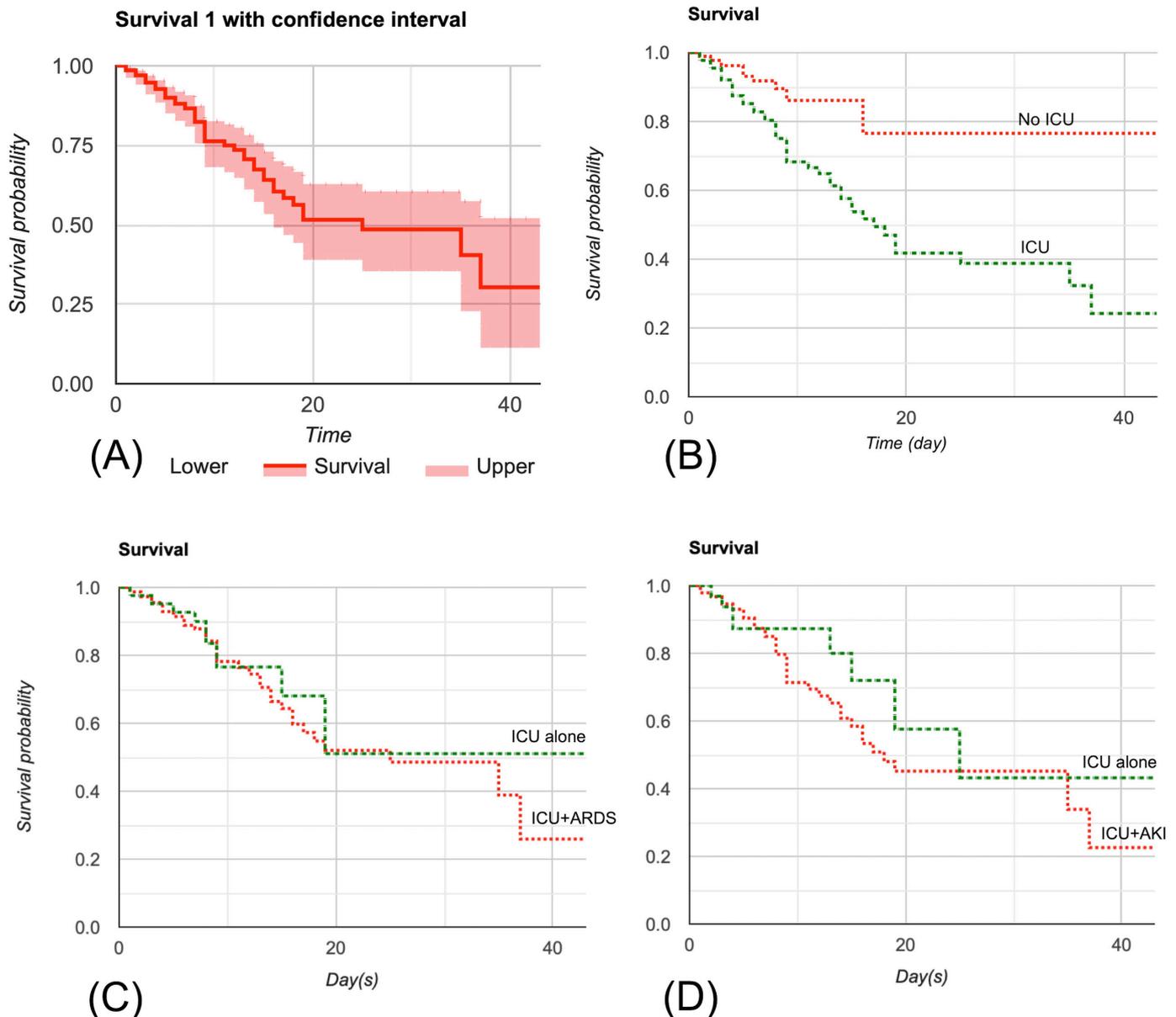
Characteristics	All patients (n=89)	Survivors (n=47)	Non-survivors (n=42)	P value
Male	61 (68.5)	30 (63.8)	31 (73.8)	0.365
Age (year)	66.0 (14.2)*	69.1 (12.5)*	63.3 (15.2)*	0.052
SOFA score*†	4.3 (2.0)	3.6 (1.7)	5.1 (1.9)	<0.001‡
Ethnicity				
Caucasian	47 (52.8)	25 (53.2)	22 (52.4)	
African-American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

\*Mean (SD).

†Collected on the first day of ICU admission.

‡Statistically significant.

.ARDS, acute respiratory distress syndrome; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.



**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 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 versus non-ICU group, respectively ( $p=0.002$ ). (C) The cumulative survival between ICU patients with and without acute respiratory distress syndrome (ARDS) ( $p=0.302$ ). (D) The cumulative survival between ICU patients with and without acute kidney injury (AKI) ( $p=0.504$ ). ICU, intensive care unit.

Here, we showed that elevated ferritin, LDH, procalcitonin, leucocytosis, troponin I and possibly D-dimer were associated with increased death. Although the OR for D-dimer cannot be calculated as one cell was zero, we observed that all deceased patients had elevated D-dimer level and the significance of elevated D-dimer toward in-hospital mortality cannot be ignored. Guan *et al* first demonstrated the importance of elevated inflammatory markers in COVID-19 in Chinese population<sup>6</sup> which has become a standard monitoring parameter for patients with COVID-19.<sup>28</sup> Elevated inflammatory markers should prompt physicians to evaluate and monitor the patients for cytokine storms and anticipated clinical deterioration. Elevated procalcitonin and leucocytosis may indicate

concomitant bacterial infection, which has been shown to increase morbidity and mortality of viral pneumonia.<sup>29</sup> Interestingly, our study showed that elevated troponin I level was associated with significantly higher death similar to a recent meta-analysis.<sup>30</sup> Although the aetiologies of elevated troponin levels were not determined in our cohort, other studies proposed several mechanisms for elevated troponin level in patients with COVID-19. These include myocarditis, cytokine-mediated myocardial injury, microangiopathy of small coronary arteries or silent coronary artery disease.<sup>26 30</sup>

The pathophysiology of cytokine storm in SARS-CoV-2 is similar to that of other viruses or bacteria.<sup>31</sup> Cytokine storm is characterised by the overproduction of

pro-inflammatory cytokines, such as tumour necrosis factor, interleukin (IL)-6 and IL-1 $\beta$ , resulting in an increased vascular hyperpermeability and activation of multiple coagulation pathways.<sup>27,32</sup> In light of SARS-CoV-2-induced hypercoagulation, antithrombin III, tissue factor pathway inhibitor and the protein C system were impaired during active inflammation.<sup>33</sup> These changes lead to thrombin hyperactivity resulting in the development of microthrombosis, disseminated intravascular coagulation and sequential multiorgan failure.<sup>27</sup> Moreover, new studies have revealed the spectrum of hyperferritinemic syndromes induced by SARS-CoV-2 but they are beyond the scope of our article.<sup>34</sup> Such syndromes include macrophage activation syndrome, adult-onset Still's disease and catastrophic antiphospholipid syndrome.<sup>34</sup>

Hydroxychloroquine therapy was associated with a threefold increased risk of QT prolongation but not associated with increased risk of death. The concept of using hydroxychloroquine in patients with COVID-19 derived from an early in vitro study.<sup>35</sup> The results from small non-randomised clinical trials also showed promising effects on viral load reduction.<sup>36,37</sup> However, the clinical benefit of hydroxychloroquine was debated by a large observation study. Of 1446 patients, Geleris *et al* observed that hydroxychloroquine had no effect on the death, length of stay or intubation.<sup>38</sup> A recent multicentre, randomised, open-label, controlled trial in hospitalised patients with mild-to-moderate COVID-19 found that the use of hydroxychloroquine, alone or with azithromycin, did not improve the clinical outcome at 15 days compared with the standard treatment.<sup>39</sup> Thus, the recommendation for use of hydroxychloroquine was recalled by the Infectious Diseases Society of America (IDSA) due to small sample size in previous clinical trials and concern for cardiac adverse effects, such as QT prolongation/torsade de pointes.<sup>40</sup>

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

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

inconclusive if zinc supplementation can prevent pneumonia development in short-term intubation.

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

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

Similarly, we found that convalescent plasma was not associated with in-hospital mortality. The safety of convalescent plasma was demonstrated in a single-centre retrospective cohort of 25 patients<sup>51</sup> and in a preprint, non-peer review report.<sup>52</sup> However, the efficacy of convalescent plasma remained undetermined due to lack of control group. The IDSA panel has recommended convalescent plasma only in the context of a clinical trial. However, at our institution, convalescent plasma is considered if patients have severe symptoms and have contraindications to remdesivir, such as AKI and hepatic dysfunction. Although we did not observe mortality adverse effect from convalescent plasma, the final recommendations on its efficacy and safety are dependent on the randomised



controlled trials. To date, at least one randomised controlled trial (NCT04342182) is being investigated to establish the clinical benefits in hospitalised patients with severe COVID-19.

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

Our study has some limitations. The observational design made the results susceptible to selection bias. Analyses could be underpowered given the small sample size. Moreover, due to restricted availability, not many cases had received compassionate use of tocilizumab, remdesivir and convalescent plasma, which may limit the applicability of our findings. More importantly, the mortality can be affected by confounding factors. We minimise this risk by applying multivariate analysis with models designed to cover all possible confounding factors for each analysed variable. Most of the collected data were cross-sectional, thus, making it difficult to conclude the causality between the two variables. Furthermore, our binary logistic regression analyses may not strictly follow the 1-in-10 rule which may lead to overfitting effect. However, our statistical rationale is supported by newer simulation studies by Vittinghoff and McCulloch<sup>53</sup> and van Smeden *et al.*<sup>54</sup> The length of stay was computed in the Kaplan-Meier analysis to represent the time to death. It is worth noting that the non-survivors had a curtailed length of stay. Moreover, we advised the readers to consider their patient population to determine the applicability of our results.

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

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**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.

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