



Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort

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Abstract

Coronavirus disease (COVID-19) has aggressively spread across the United States with numerous fatalities. Risk factors for mortality are poorly described. This was a multicentered cohort study identifying patient characteristics and diagnostic markers present on initial evaluation associated with mortality in hospitalized COVID-19 patients. Epidemiological, demographic, clinical, and laboratory characteristics of survivors and non-survivors were obtained from electronic medical records and a multivariable survival regression analysis was conducted to identify risk factors of in-hospital death. Of 1629 consecutive hospitalized adult patients with confirmed COVID-19 from March 1st thru March 31, 2020, 1461 patients were included in final analysis. 327 patients died during hospitalization and 1134 survived to discharge. Median age was 62 years (IQR 50.0, 74.0) with 56% of hospitalized patients under the age of 65. 47% were female and 63% identified as African American. Most patients (55%) had either no or one comorbidity. In multivariable analysis, older age, admission respiratory status including elevated respiratory rate and oxygen saturation $\leq 88\%$, and initial laboratory derangements of creatinine > 1.33 mg/dL, alanine aminotransferase > 40 U/L, procalcitonin > 0.5 ng/mL, and lactic acid ≥ 2 mmol/L increased risk of in-hospital death. This study is one of the largest analyses in an epicenter for the COVID-19 pandemic. Older age, low oxygen saturation and elevated respiratory rate on admission, and initial lab derangements including renal and hepatic dysfunction and elevated procalcitonin and lactic acid are risk factors for in-hospital death. These factors can help clinicians prognosticate and should be considered in management strategies.

Keywords COVID-19 · Mortality · Predictors · Scoring system

Introduction

In December 2019, the novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) was first detected in Wuhan, China. Since then, coronavirus disease 2019 (COVID-19) has spread rapidly to nearly every continent around the globe [1–3]. After the first case of this illness was discovered in the United States in January 2020 in Seattle, WA, it spread to every state in under 2 months [4, 5].

The United States quickly became the world leader in number of cases and deaths. As of April 30, 2020, over 3.1 million cases and 227,000 fatalities were identified worldwide, of which over 60,000 fatalities were in the United States [6].

COVID-19 patients can present with a range of symptoms, varying from asymptomatic to severe cases with acute respiratory failure requiring hospitalization [7–9]. Presently, patients with more dire illness are apparently older and have complicating comorbidities such as diabetes, hypertension, and obesity [10, 11]. There is currently no cure for COVID-19. Hospitalization results in supportive treatment with oxygen support and a myriad of medications to prevent multiple organ dysfunction and death [12]. Despite the increasing number of cases, there is limited data regarding the clinical characteristics of patients admitted to the hospital, outside of China, specifically in a diverse American population. Furthermore, while it is evident that this disease is highly contagious and virulent with local community

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and person-to-person transmission [13, 14], there is limited evidence that describes the predictors, particularly early in patients' hospital course, of poor outcomes and mortality for hospitalized patients. An improved understanding is required to guide decisions regarding admissions, hospital capacity and therapeutic and operational resources.

As COVID-19 has spread, several regions in the United States have been disproportionately impacted. It is our objective to determine early risk factors for in-hospital death for COVID-19 patients in the largest health system in south-eastern Michigan.

Methods

Study design and participants

This was an analysis of a multicentered cohort study assessing early predictors of mortality in hospitalized patients with COVID-19 comparing survivors to non-survivors. The study was conducted at Beaumont Health, an eight-hospital acute care regional health system caring for 2.2 million people across the communities within the Metro Detroit catchment area. The hospitals range from a large tertiary care academic center to intermediate-sized and smaller community hospitals. As the epidemic evolved, the health system converted one of the smaller hospitals to a complete COVID-19 center, including converting the emergency department into additional intensive care beds. As the surge in COVID-19 volume developed across the region, hospital systems collaborated to optimize the transfer process and accommodate capacity constraints. While many patients were transferred within Beaumont Health, many patients were also transferred to other hospitals.

The study was approved by the Institutional Review Board at the home institution. Written informed consent requirement was waived due to the rapid emergence of COVID-19. Data were analyzed and interpreted by the authors.

Data source

Data were obtained from the integrated electronic health record (EHR; Epic Systems, Verona, WI). Patients over 18 years of age who were admitted with COVID-19 from March 1st through March 31st 2020 were included. Data were collected until April 23, 2020. All patients had a laboratory confirmed case of COVID-19 as defined by a positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) test of nasopharyngeal swab. Exclusions consisted of patients who left the hospital against medical advice, transfers to external hospitals, or if hospital course was ongoing beyond April 23, 2020. Transfers within Beaumont Health were included as

investigators had full access to medical records. Epidemiological, demographic, radiological, therapeutic, clinical, and outcomes data were extracted. The integrity of the data was verified by two attending emergency medicine physicians.

Hospital admission was based on the clinical judgment of the treating emergency medicine provider. Laboratory and radiological testing was conducted at the discretion of the treating physicians. After initial COVID laboratory testing, patients were not routinely serially tested to evaluate for clearance of acute infection due to paucity of testing supplies. Discharge disposition post-hospitalization was based on patients' clinical condition. Patients were either discharged to home, skilled nursing facility or rehabilitation, hospice, or expired in the hospital.

Admission data included demographics such as age, race, and gender. Clinical data included symptoms prompting presentation to the ED, time of onset (days) of symptoms prior to ED visit, comorbidities, body mass index (BMI), tobacco history, vital signs including lowest oxygen level on room air within first 24 h of admission and maximum temperature, laboratory findings, and admission floor type. Radiological data included chest x-ray and chest computed tomography (CT) impressions. Common laboratory analyses included complete blood count (CBC) with absolute lymphocyte count, metabolic chemistry panel (BMP/CMP), lactate dehydrogenase, lactic acid, procalcitonin, troponin, ferritin, and D-dimer. Laboratory and radiological data depicted the first test result occurring within the first 24 h of presentation to the ED.

Hospital treatment data included use of investigational or adjunctive therapies, renal replacement therapy, extracorporeal membrane oxygenation, oxygen and ventilation therapy, and intensive care unit (ICU) admission.

Study definitions

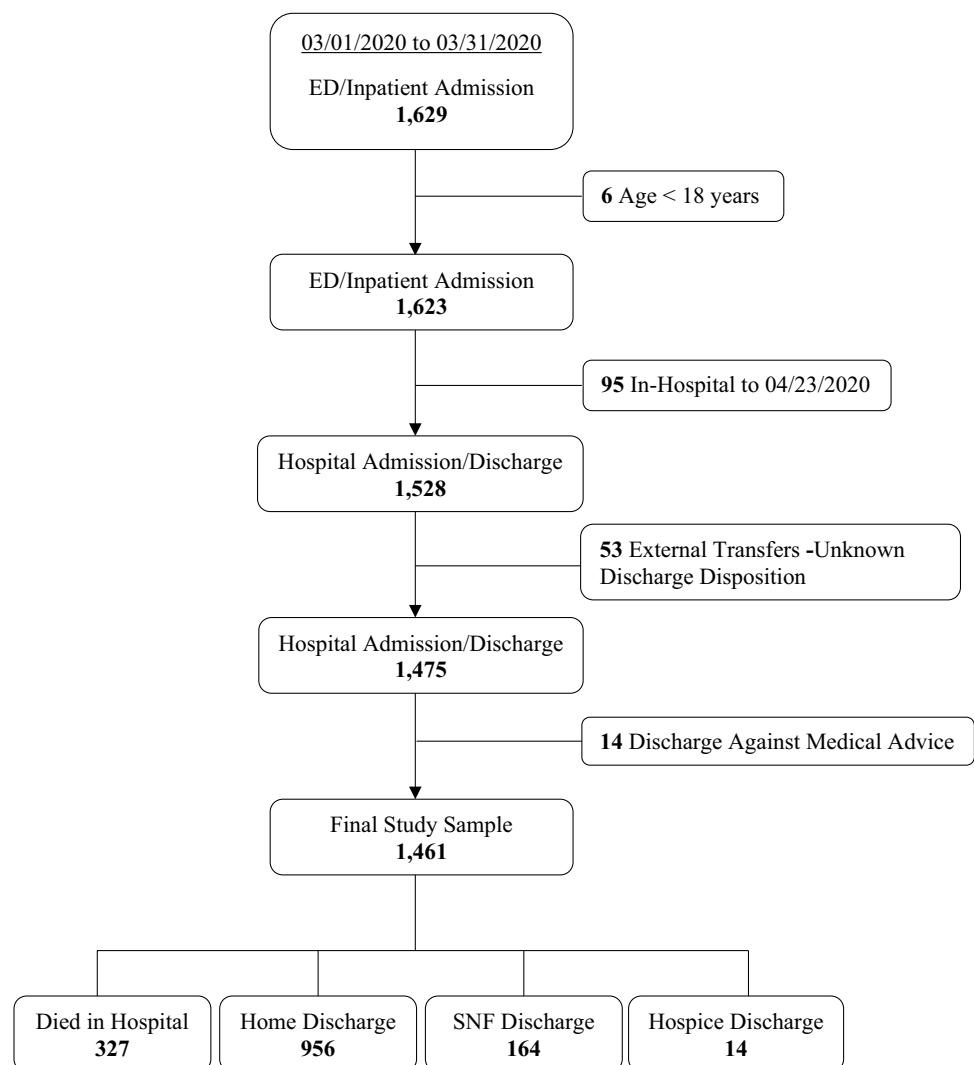
Fever was defined as an axillary temperature of ≥ 38.0 °C. Acute respiratory failure was defined as a partial pressure of oxygen (PaO_2) < 60 mm Hg on blood gas assessment. Pulse oximetry was used as a surrogate for PaO_2 , with $\leq 88\%$ on room air meeting the criteria. Acute kidney injury was defined per KDIGO clinical practice guidelines [15]. Acute cardiac injury was defined as an elevated cardiac biomarker (troponin I) $> 99\%$ of the upper reference limit [16]. Septic shock was defined as a patient with diagnosed sepsis requiring vasopressor therapy to maintain mean arterial blood pressure > 65 mmHg. Patients with a quick Sequential Organ Failure Assessment score of two or more were considered to have sepsis [17]. Extubation failure was defined as need for reintubation within 72 h [18].

Statistical analysis

Descriptive analyses were used to summarize epidemiological characteristics and clinical findings stratified by in-hospital survival status. Continuous and categorical variables were expressed as medians (interquartile ranges; IQR) and frequencies (percentages), respectively. Kruskal–Wallis test (continuous variables) and Chi-squared or Fisher’s exact test (categorical variables) were used to compare differences between non-survivors and survivors. To explore the association between risk factors and in-hospital mortality, discrete-time survival regression was employed for univariable and multivariable analyses. Missing data were imputed by the procedure of multiple imputation using PROC MI in SAS. To avoid collinearity and overfitting on multivariable model, the L1-penalized least absolute shrinkage and selection operator (LASSO) regression selection was employed to the analog with a logistic regression that fits the discrete-time survival, using a statistical package “glmnet”

in R. Variables selected via LASSO regression and clinical representative variables in terms of the basis of relevant studies were applied to multivariable analysis. The effects of risk factors were combined from 20 imputed datasets, accounting for the additional variability introduced by the multiple imputation, through PROC MIANALYZE in SAS. The corresponding c-statistics and leave-one-out validation were further used to evaluate the performance of modeling in multivariable regression. To facilitate the assessment of risk on mortality from the multivariable model, a prediction risk score using categorical variables was built. The assigned score for each risk factor was determined according to estimates of regression coefficients multiplied by 10. Patients were classified into risk groups based on their risk score and the mortality rates of each risk group was calculated. The differences in survival among risk groups over study period were also assessed using Kaplan–Meier method with the log-rank test. A bootstrap cross-validation with 1000 bootstrap samples per imputed dataset was further employed to

Fig. 1 Flow diagram of study patients. Figure shows study inclusions and exclusions leading to the final cohort, and patient disposition



validate the performance of scoring predictivity by assessing the similarity of mortality rates on risk groups. All tests of statistical significance were two-sided with p value < 0.05 indicating a significant difference. Analyses were conducted using R-3.6.2 (R Foundation for Statistical Computing) and SAS v-9.4 (SAS Institute, Inc., Cary, NC).

Results

Epidemiological characteristics

1629 patients were hospitalized at Beaumont Health with laboratory confirmed COVID-19 from March 1st thru March 31, 2020. 1461 patients were included in final analysis after exclusions (Fig. 1 shows enrollment scheme). 327 patients died during hospitalization and 1134 survived to discharge. Figure 2 illustrates admissions flow by unit type

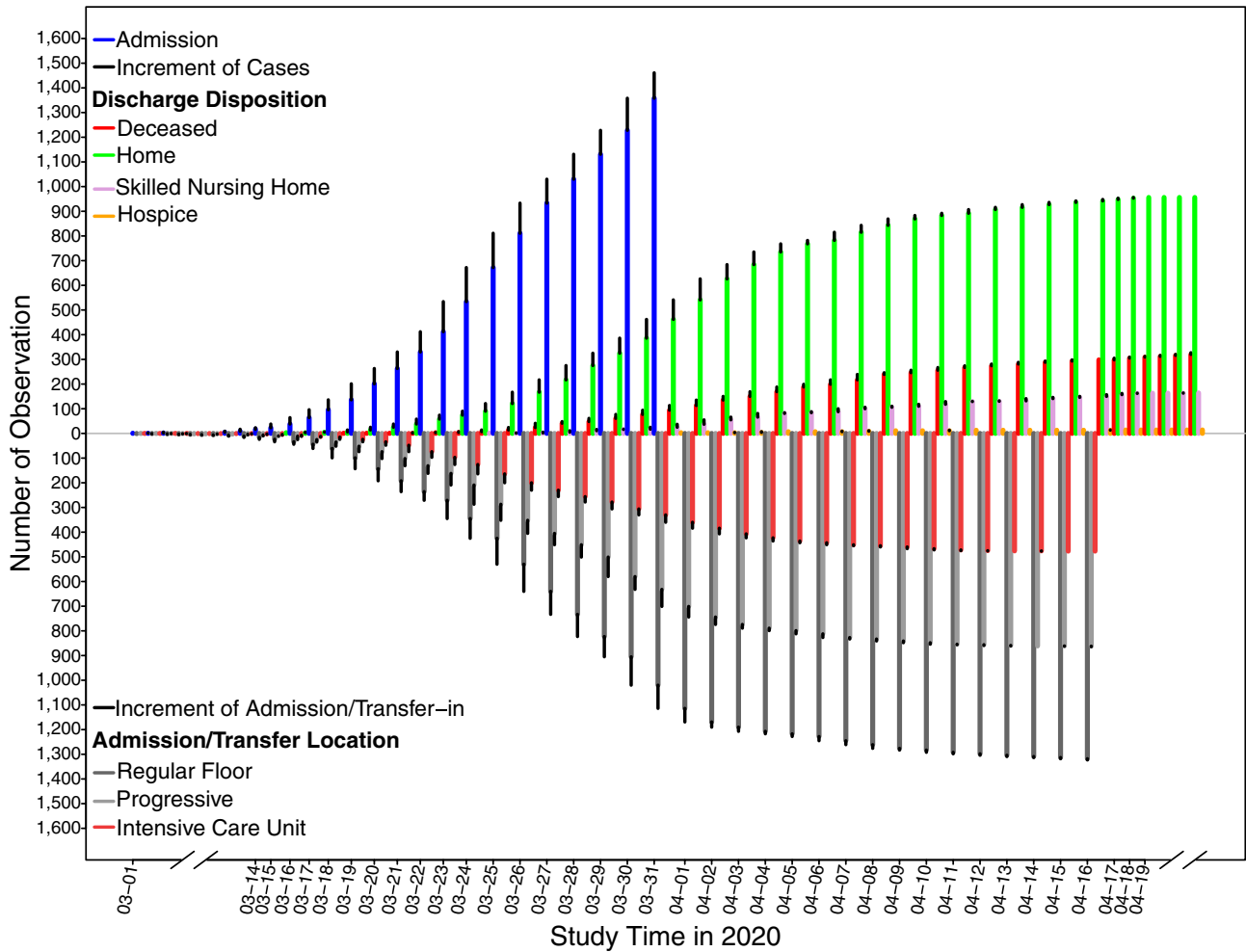


Fig. 2 Daily patient influx by unit type and discharge disposition over the course of the study period. Figure shows probing daily change on hospital admission, locations of admission and transfer-in, and hospital discharge. In the upper panel, blue vertical lines stacked with black lines indicate the cumulative number of admitted patients prior to a specific date (blue lines) and the increment of patients on a specific date (black lines) from March 1st to March 31st, 2020. Other colorful vertical lines (red; green; plum; orange) stacked with black lines indicate the cumulative number on death, home discharge, skilled nursing home (SNF) discharge, and hospice discharge, respectively, prior to a specific date (red lines; green lines; plum lines; orange lines) and the increment of new occurrence (black lines) on

a specific date until April 23rd, 2020. Similarly, in the bottom panel, colorful vertical lines (dark gray; gray; brown) stacked with black lines indicate the cumulative observations of admission/transfer-in to regular floor, progressive care, and intensive care unit (ICU), respectively, prior to a specific date (dark gray lines; gray lines; brown lines) and number of occurrence (black lines) on a specific date until April 23rd, 2020. Figure shows a daily influx of patients by unit type (Regular floor, Progressive floor, ICU) including admissions from the ED and transfers within the hospital and hospital system. Daily efflux of patients is also captured with discharge disposition including death, discharge to home, hospice, and skilled nursing facility/ rehabilitation units

Table 1 Demographic, clinical, laboratory, and radiographic findings of the study patients

Variables ^{a,b}	All	Survival status		<i>p</i> value
		Non-survivor	Survivor	
	1461	327	1134	
Demographics				
Age, years	62.0 (50.0–74.0)	73.0 (63.0–81.0)	59.0 (48.0–70.0)	<0.001
18–50–	349 (23.9)	21 (6.4)	328 (28.9)	<0.001
50–65–	462 (31.6)	75 (22.9)	387 (34.1)	
65–80–	438 (30.0)	141 (43.1)	297 (26.2)	
≥80	212 (14.5)	90 (27.5)	122 (10.8)	
Gender				
Female	691 (47.3)	147 (45.0)	544 (48.0)	0.34
Male	770 (52.7)	180 (55.0)	590 (52.0)	
Race				
White/Caucasian	431 (29.5)	124 (37.9)	307 (27.1)	0.001
Black/African American	921 (63.0)	182 (55.7)	739 (65.2)	
Asian	23 (1.6)	7 (2.1)	16 (1.4)	
Other	86 (5.9)	14 (4.3)	72 (6.3)	
Smoke				
Yes	59 (4.0)	14 (4.3)	45 (4.0)	<0.001
Ever	338 (23.1)	113 (34.6)	225 (19.8)	
Never	731 (50.0)	122 (37.3)	609 (53.7)	
Unknown	333 (22.8)	78 (23.8)	255 (22.5)	
BMI, kg/m² (<i>n</i> = 1450/325/1125)				
<25	222 (15.3)	64 (19.7)	158 (14.0)	0.01
25–30–	384 (26.5)	94 (28.9)	290 (25.8)	
30–35–	369 (25.4)	80 (24.6)	289 (25.7)	
35–40–	233 (16.1)	36 (11.1)	197 (17.5)	
≥40	242 (16.7)	51 (15.7)	191 (17.0)	
Comorbidity				
Asthma	154 (10.5)	30 (9.2)	124 (10.9)	0.36
Cancer	154 (10.5)	44 (13.5)	110 (9.7)	0.05
Coronary artery disease	163 (11.2)	59 (18.0)	104 (9.2)	<0.001
Chronic heart failure	100 (6.8)	37 (11.3)	63 (5.6)	<0.001
Chronic kidney disease	75 (5.1)	33 (10.1)	42 (3.7)	<0.001
Chronic obstructive pulmonary disease	132 (9.0)	48 (14.7)	84 (7.4)	<0.001
Cerebrovascular accident	88 (6.0)	30 (9.2)	58 (5.1)	0.01
Diabetes mellitus	430 (29.4)	127 (38.8)	303 (26.7)	<0.001
End-stage renal disease	36 (2.5)	15 (4.6)	21 (1.9)	0.01
Human immunodeficiency virus	8 (0.6)	1 (0.3)	7 (0.6)	0.69
Hypertension	751 (51.4)	200 (61.2)	551 (48.6)	<0.001
Obstructive Sleep Apnea	119 (8.2)	29 (8.9)	90 (7.9)	0.59
Pulmonary Hypertension	12 (0.8)	6 (1.8)	6 (0.5)	0.03
Venous thromboembolism	81 (5.5)	29 (8.9)	52 (4.6)	0.003
Comorbidity sum				
0	502 (34.4)	88 (26.9)	414 (36.5)	<0.001
1	302 (20.7)	45 (13.8)	257 (22.7)	
2	308 (21.1)	73 (22.3)	235 (20.7)	
3	168 (11.5)	55 (16.8)	113 (10.0)	
≥4	181 (12.4)	66 (20.1)	115 (10.1)	
Principal symptoms (<i>n</i> = 1422/313/1109)				

Table 1 (continued)

Variables ^{a,b}	All	Survival status		<i>p</i> value
		Non-survivor	Survivor	
	1461	327	1134	
Cough	684 (48.1)	122 (39.0)	562 (50.7)	<0.001
Shortness of Breath	787 (55.3)	188 (60.1)	599 (54.0)	0.06
Fever	608 (42.8)	115 (36.7)	493 (44.5)	0.01
Gastrointestinal symptoms	183 (12.9)	35 (11.2)	148 (13.4)	0.31
Altered mental status	91 (6.4)	45 (14.4)	46 (4.2)	<0.001
Chest pain	66 (4.6)	8 (2.6)	58 (5.2)	0.05
Weakness	169 (11.9)	43 (13.7)	126 (11.4)	0.25
Chills	28 (2.0)	5 (1.6)	23 (2.1)	0.59
Body aches	82 (5.8)	11 (3.5)	71 (6.4)	0.05
Syncope	61 (4.3)	6 (1.9)	55 (5.0)	0.02
Neurological symptoms	29 (2.0)	5 (1.6)	24 (2.2)	0.53
Other	104 (7.3)	26 (8.3)	78 (7.0)	0.44
Vital signs				
Systolic blood pressure, mmHg	130.0 (118.0–142.0)	131.0 (117.0–147.0)	129.5 (118.0–141.0)	0.11
Diastolic blood pressure, mmHg	73.0 (65.0–81.0)	71.0 (63.0–79.0)	73.0 (65.0–82.0)	0.02
Pulse, beats per minute	90.0 (80.0–101.0)	90.0 (79.0–103.0)	91.0 (80.0–100.0)	0.89
Respiratory rate, breaths per minute	22.0 (19.0–25.0)	24.0 (21.0–28.0)	21.0 (19.0–24.0)	<0.001
Temperature, °F	100.2 (99.0–101.7)	100.1 (98.8–101.5)	100.2 (99.0–101.7)	0.39
Blood oxygen saturation, %	92.0 (88.0–95.0)	88.0 (77.0–93.0)	92.0 (89.0–95.0)	<0.001
≤ 88	433 (29.6)	165 (50.5)	268 (23.6)	<0.001
88 + to 94–	523 (35.8)	95 (29.0)	428 (37.7)	
≥ 94	505 (34.6)	67 (20.5)	438 (38.6)	
Laboratory findings				
White blood cell count, 10 ⁹ /L (<i>n</i> = 1459/326/1133)	6.3 (4.8–8.3)	6.8 (5.1–9.7)	6.1 (4.7–8.0)	<0.001
< 4	182 (12.5)	31 (9.5)	151 (13.3)	<0.001
4–10	1,067 (73.1)	220 (67.5)	847 (74.8)	
> 10	210 (14.4)	75 (23.0)	135 (11.9)	
Lymphocyte count, 10 ⁹ /L (<i>n</i> = 1437/326/1111)	0.9 (0.7–1.3)	0.9 (0.6–1.2)	1.0 (0.7–1.3)	<0.001
< 0.8	465 (32.4)	134 (41.1)	331 (29.8)	<0.001
≥ 0.8	972 (67.6)	192 (58.9)	780 (70.2)	
Hemoglobin, g/dL (<i>n</i> = 1459/326/1133)	13.2 (11.8–14.4)	12.7 (11.3–14.3)	13.3 (11.9–14.5)	0.001
Platelet count, 10 ⁹ /L (<i>n</i> = 1458/326/1132)	196.0 (158.0–248.0)	182.5 (149.0–234.0)	199.0 (160.0–253.5)	<0.001
< 100	54 (3.7)	22 (6.8)	32 (2.8)	0.001
≥ 100	1,404 (96.3)	304 (93.2)	1100 (97.2)	
ALT, U/L (<i>n</i> = 1335/319/1016)	28.0 (19.0–48.0)	30.0 (18.0–55.0)	28.0 (19.0–46.5)	0.18
≤ 40	901 (67.5)	200 (62.7)	701 (69.0)	0.04
> 40	434 (32.5)	119 (37.3)	315 (31.0)	
AST, U/L (<i>n</i> = 1335/319/1016)	43.0 (29.0–66.0)	53.0 (33.0–85.0)	40.0 (27.0–60.0)	<0.001
≤ 40	624 (46.7)	110 (34.5)	514 (50.6)	<0.001
> 40	711 (53.3)	209 (65.5)	502 (49.4)	
Creatinine, mg/dL (<i>n</i> = 1458/326/1132)	1.18 (0.92–1.66)	1.57 (1.11–2.37)	1.12 (0.89–1.47)	<0.001
≤ 1.33	901 (61.8)	131 (40.2)	770 (68.0)	<0.001
> 1.33	557 (38.2)	195 (59.8)	362 (32.0)	
Lactate dehydrogenase, U/L (<i>n</i> = 884/241/643)	421.5 (312.5–584.5)	511.0 (353.0–717.0)	396.0 (304.0–531.0)	<0.001

Table 1 (continued)

Variables ^{a,b}	All	Survival status		p value
		Non-survivor	Survivor	
	1461	327	1134	
≤ 245	90 (10.2)	18 (7.5)	72 (11.2)	0.10
> 245	794 (89.8)	223 (92.5)	571 (88.8)	
Troponin, ng/mL (<i>n</i> = 1,115/297/818)	0.02 (0.01–0.05)	0.04 (0.02–0.12)	0.01 (0.01–0.03)	< 0.001
≤ 0.3	1,052 (93.3)	260 (87.5)	792 (96.8)	< 0.001
> 0.3	63 (5.7)	37 (12.5)	26 (3.2)	
D-dimer, ng/mL FEU (<i>n</i> = 803/254/549)	1,064.0 (637.0–2,181.0)	1441.5 (903.0–5041.0)	885.0 (568.0–1,691.0)	< 0.001
≤ 500	125 (15.6)	18 (7.1)	107 (19.5)	< 0.001
500–1000	263 (32.7)	61 (24.0)	202 (36.8)	
> 1000	415 (51.7)	175 (68.9)	240 (43.7)	
Procalcitonin, ng/mL (<i>n</i> = 974/251/723)	0.17 (0.08–0.48)	0.47 (0.18–1.40)	0.12 (0.07–0.31)	< 0.001
< 0.1	324 (33.3)	31 (12.3)	293 (40.5)	< 0.001
0.1–0.25	272 (27.9)	55 (21.9)	217 (30.0)	
0.25–0.5	143 (14.7)	44 (17.5)	99 (13.7)	
> 0.5	235 (24.1)	121 (48.2)	114 (15.8)	
C reactive protein, mg/L (<i>n</i> = 1,002/269/733)	106.4 (59.1–177.1)	155.9 (89.5–218.8)	94.8 (51.7–153.0)	< 0.001
< 50	201 (20.1)	23 (8.5)	178 (24.3)	< 0.001
50–100	258 (25.7)	51 (19.0)	207 (28.2)	
> 100	543 (54.2)	195 (72.5)	348 (47.5)	
Lactic acid, mmol/L (<i>n</i> = 806/262/544)	1.4 (1.0–1.9)	1.7 (1.2–2.4)	1.3 (1.0–1.7)	< 0.001
< 2	612 (75.9)	160 (61.1)	452 (83.1)	< 0.001
≥ 2	194 (24.1)	102 (38.9)	92 (16.9)	
CT/Chest x-ray (<i>n</i> = 1,442/326/1,116)				
Patchy ground-glass opacities	1,048 (72.7)	236 (72.4)	812 (72.8)	0.90
Pleural effusion	17 (1.2)	3 (0.9)	14 (1.3)	0.78
Pulmonary embolism	118 (8.2)	50 (15.3)	68 (6.1)	< 0.001

BMI body mass index, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CT* computerized tomography

^aFor continuous variables, medians (Interquartile Ranges) were presented. For categorical variables, frequencies (percentages) were presented

^bFor any missing on variables, the corresponding number of observations was presented as *n* = the number of observations for all/the number of observations for non-survivors/the number of observations for survivors within parentheses

and discharge dispositions during the study period. The median age was 62 years (IQR 50.0–74.0) and 47.3% were female (Table 1). Almost two-thirds (63.0%) identified as Black or African American compared to 29.5% as White or Caucasian. Most patients (55.1%) had either no comorbidities (34.4%) or one comorbidity (20.7%). The most common pre-existing medical condition was hypertension (51.4%). The median BMI was 31.3 (IQR 27.1–37.1) with 41.8% of patients having a BMI of < 30. See Table 1 for full demographic and epidemiological data.

Clinical features

Shortness of breath was the most common presenting complaint present in 55.3% of patients followed closely

by cough and fever. The median admission oxygen saturation and respiratory rate were 92.0% (IQR 88.0–95.0) and 21.0 (IQR 19.0–24.0) for survivors and 88.0% (77.0–93.0) and 24.0 (21.0–28.0) for non-survivors, respectively ($p < 0.001$). Renal impairment was more common in non-survivors (Cr = 1.57 mg/dL; IQR 1.11–2.37) compared to survivors (Cr = 1.12 mg/dL; IQR 0.89–1.47; $p < 0.001$). Procalcitonin level was higher in non-survivors (0.47 ng/mL; IQR 0.18–1.40) compared to survivors (0.12 ng/mL; IQR 0.07–0.31); $p < 0.001$). Lactic acid was elevated in non-survivors (1.7 mmol/L; IQR 1.2–2.4) compared to survivors (1.2 mmol/L; IQR 1.0–1.7; $p < 0.001$). Patchy ground glass opacities on imaging were commonly seen in patients (72.7%) (Table 1).

Table 2 Treatments, complications, and clinical outcomes

Variables ^{a,b}	All	Survival status		p value
		Non-survivor	Survivor	
	1461	327	1134	
Treatments				
Hydroxychloroquine	1073 (73.4)	290 (88.7)	783 (69.1)	<0.001
Corticosteroids	617 (42.2)	211 (64.5)	406 (35.8)	<0.001
NSAIDs	103 (7.1)	12 (3.7)	91 (8.0)	0.01
Vitamin C	407 (27.9)	116 (35.5)	291 (25.7)	<0.001
Zinc	372 (25.4)	111 (33.9)	261 (23.0)	<0.001
ACE inhibitors	209 (14.3)	28 (8.6)	181 (16.0)	0.001
ARBs or Sartanics	104 (7.1)	23 (7.0)	81 (7.1)	0.95
Renal replacement therapy	82 (5.6)	50 (15.3)	32 (2.8)	<0.001
Non-invasive ventilation	106 (7.3)	53 (16.2)	53 (4.7)	<0.001
High flow oxygen therapy	419 (28.7)	206 (63.0)	213 (18.8)	<0.001
Inv. Mechanical ventilation	308 (21.1)	219 (67.0)	89 (7.9)	<0.001
Extubation (n = 308/219/89)				
No extubation trial	175 (56.8)	146 (66.7)	29 (32.6)	<0.001
Unsuccessful wean	63 (20.5)	62 (28.3)	1 (1.1)	
Success	70 (22.7)	11 (5.0)	59 (66.3)	
Outcomes				
Respiratory failure	767 (52.5)	307 (93.9)	460 (40.6)	<0.001
Septic shock	237 (16.2)	196 (59.9)	41 (3.6)	<0.001
Acute cardiac injury	133 (9.1)	85 (26.0)	48 (4.2)	<0.001
Acute kidney injury	382 (26.2)	233 (71.3)	149 (13.1)	<0.001
ICU admission	374 (25.6)	211 (64.5)	163 (14.4)	<0.001
ICU length of stay, days	7.0 (4.0–12.0)	7.0 (4.0–11.0)	8.0 (4.0–14.0)	0.32
Hospital length of stay, days	7.0 (4.0–11.0)	10.0 (6.0–15.0)	6.0 (3.0–10.0)	<0.001
Time from illness onset to ICU admission, days	8.0 (5.0–10.0)	8.0 (5.0–11.0)	8.0 (4.0–10.0)	0.31
Time from illness onset to hydroxychloroquine therapy, days	7.0 (5.0–9.0)	6.0 (4.0–9.0)	8.0 (5.0–10.0)	<0.001
Time from illness onset to corticosteroids therapy, days	9.0 (6.0–13.0)	8.0 (5.0–12.0)	9.0 (6.0–13.0)	0.11
Time from illness onset to high flow oxygen therapy, days	8.0 (6.0–11.0)	8.0 (5.0–10.0)	9.0 (6.0–12.0)	<0.001
Time from illness onset to mechanical ventilation, days	8.0 (6.0–12.0)	8.0 (6.0–11.0)	9.0 (7.0–13.0)	0.11
Time from illness onset to death or discharge, days	13.0 (9.0–18.0)	15.0 (10.0–21.0)	12.0 (8.0–17.0)	<0.001

NSAIDs nonsteroidal anti-inflammatory drugs, ACE angiotensin-converting enzyme, ARB angiotensin II receptor blocker, ICU intensive unit care

^aFor continuous variables, medians (Interquartile Ranges) were presented. For categorical variables, frequencies (percentages) were presented

^bFor results of extubation, only 308 patients who received mechanical ventilation, including 219 non-survivors and 89 survivors, were assessed

Respiratory failure was the most common patient outcome complicating 52.5% of admissions and present in 93.9% of non-survivors. High-flow oxygen therapy via nasal cannula was used in 28.7% of patients, more commonly employed in non-survivors (63.0%) compared to survivors (18.8%). Invasive mechanical ventilation was employed in 308 patients (21.1%). It was used in 67.0% of non-survivors compared to 7.9% of survivors ($p < 0.001$). Overall, 71.1% of patients did not survive to hospital discharge when invasive mechanical ventilation was utilized. Acute kidney injury was noted in 382 patients and developed in 71.3% of non-survivors compared to 13.1% of survivors ($p < 0.001$). Of

these patients, 20.9% required hemodialysis. Acute cardiac injury was a less frequent complication occurring in 9.1% of cases but was a more common complication in non-survivors (26.0%). Septic shock requiring vasopressors occurred in 16.2% of patients, occurring in 59.9% of non-survivors compared to 3.6% of survivors ($p < 0.001$). Of the 237 patients classified as septic shock, only 30 patients (12.65%) had positive blood cultures. 25 patients had blood cultures that identified a bacterial source and six patients had blood cultures that grew *Candida albicans*, treated with an antifungal. 7 patients had more than one bacteria isolated, and one patient had bacteria and *Candida* isolated. 207 patients had

Table 3 Risk factors associated with study patients deceased in-hospital

Variables	Univariable model		Multivariable model 1 ^a		Multivariable model 2 ^a	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Demographics						
Age, years	1.06 (1.04–1.06)	<0.001	1.05 (1.04–1.06)	<0.001		
Age, years						
18–50-	1 [Reference]				1 [Reference]	
50–65-	1.93 (1.18–3.14)	0.01			1.89 (1.14–3.15)	0.01
65–80-	3.40 (2.14–5.41)	<0.001			3.29 (1.99–5.44)	<0.001
≥80	6.62 (4.09–10.74)	<0.001			7.13 (4.14–12.27)	<0.001
Gender						
Male	1 [Reference]		1 [Reference]		1 [Reference]	
Female	1.11 (0.89–1.39)	0.36	1.11 (0.86–1.45)	0.42	1.14 (0.88–1.48)	0.31
Race						
Black/African American	0.67 (0.53–0.85)	0.001	0.72 (0.55–0.94)	0.01	0.69 (0.53–0.89)	0.006
White/Caucasian	1 [Reference]		1 [Reference]		1 [Reference]	
Other	0.57 (0.36–0.91)	0.02	0.57 (0.35–0.93)	0.03	0.54 (0.33–0.89)	0.01
BMI, kg/m ²	0.98 (0.96–0.99)	0.002	1.01 (0.99–1.02)	0.30	1.00 (0.99–1.02)	0.68
Comorbidity						
Asthma	0.97 (0.66–1.43)	0.89				
Cancer	1.05 (0.76–1.46)	0.77				
Coronary artery disease	1.69 (1.26–2.27)	<0.001	1.23 (0.89–1.70)	0.21	1.32 (0.95–1.83)	0.10
Chronic heart failure	1.49 (1.05–2.13)	0.02				
Chronic kidney disease	1.62 (1.10–2.36)	0.01				
Chronic obstructive Pulmonary disease	1.77 (1.29–2.43)	<0.001				
Cerebrovascular accident	1.38 (0.94–2.04)	0.10				
Diabetes mellitus	1.33 (1.06–1.67)	0.01	1.08 (0.83–1.41)	0.56	1.08 (0.83–1.41)	0.55
End-stage renal disease	1.23 (0.71–2.14)	0.46				
Human immunodeficiency virus	0.55 (0.08–4.00)	0.55				
Hypertension	1.20 (0.96–1.51)	0.11	0.84 (0.64–1.10)	0.20	0.89 (0.68–1.17)	0.41
Obstructive sleep apnea	0.99 (0.67–1.46)	0.95				
Pulmonary hypertension	1.12 (0.49–2.56)	0.79				
Venous thromboembolism	1.18 (0.80–1.75)	0.40				
Vital sign						
Systolic blood pressure, mmHg	1.00 (1.00–1.01)	0.34				
Diastolic blood pressure, mmHg	0.99 (0.98–1.00)	0.21				
Pulse, beats per minute	1.00 (0.99–1.01)	0.82				
Respiratory rate, breaths per minute	1.06 (1.03–1.08)	<0.001	1.06 (1.04–1.09)	<0.001	1.06 (1.04–1.09)	<0.001
Temperature, °F	0.95 (0.89–1.02)	0.14				
Blood oxygen saturation, %						
≤88	2.01 (1.50–2.69)	<0.001	1.82 (1.33–2.50)	<0.001	1.81 (1.32–2.49)	<0.001
88+ to 94–	1.25 (0.90–1.72)	0.18	1.27 (0.90–1.78)	0.17	1.28 (0.92–1.80)	0.14
≥94	1 [Reference]		1 [Reference]		1 [Reference]	
Principal symptoms						
Cough	0.65 (0.51–0.82)	<0.001				
Shortness of Breath	1.27 (1.01–1.61)	0.04				
Fever	0.80 (0.63–1.01)	0.07				
Gastrointestinal symptoms	0.87 (0.61–1.26)	0.47				
Altered mental status	2.09 (1.50–2.92)	<0.001				
Chest pain	0.83 (0.41–1.68)	0.60				
Weakness	1.22 (0.88–1.70)	0.24				

Table 3 (continued)

Variables	Univariable model		Multivariable model 1 ^a		Multivariable model 2 ^a	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Chills	0.65 (0.27–1.59)	0.35				
Body aches	0.61 (0.33–1.12)	0.11				
Syncope	0.66 (0.29–1.50)	0.32				
Neurological symptoms	0.78 (0.32–1.89)	0.58				
Other	1.07 (0.70–1.63)	0.75				
Laboratory findings						
White blood cell count × 10 ⁹ /L						
< 4	0.86 (0.58–1.27)	0.45	1.05 (0.70–1.58)	0.80	1.01 (0.68–1.52)	0.94
4–10	1 [Reference]		1 [Reference]		1 [Reference]	
> 10	1.35 (1.03–1.77)	0.03	0.72 (0.53–0.97)	0.03	0.74 (0.54–1.01)	0.06
Lymphocyte count × 10 ⁹ /L						
< 0.8	1.30 (1.04–1.63)	0.02				
≥ 0.8	1 [Reference]					
Hemoglobin, g/dL	0.94 (0.90–0.99)	0.02	0.94 (0.89–1.00)	0.05	0.94 (0.89–0.99)	0.04
Platelet count × 10 ⁹ /L						
< 100	1.76 (1.13–2.75)	0.01				
≥ 100	1 [Reference]					
ALT, U/L						
≤ 40	1 [Reference]		1 [Reference]		1 [Reference]	
> 40	1.27 (1.01–1.60)	0.04	1.36 (1.05–1.77)	0.02	1.41 (1.09–1.83)	0.01
AST, U/L						
≤ 40	1 [Reference]					
> 40	1.28 (1.01–1.62)	0.04				
Creatinine, mg/dL						
≤ 1.33	1 [Reference]		1 [Reference]		1 [Reference]	
> 1.33	1.79 (1.43–2.25)	< 0.001	1.41 (1.08–1.85)	0.01	1.38 (1.05–1.82)	0.02
Lactate dehydrogenase, U/L						
≤ 245	1 [Reference]					
> 245	0.93 (0.60–1.45)	0.75				
Troponin, ng/mL						
≤ 0.3	1 [Reference]					
> 0.3	1.88 (0.76–4.67)	0.16				
D-dimer, ng/mL FEU						
≤ 500	1 [Reference]		1 [Reference]		1 [Reference]	
500–1000	1.24 (0.73–2.08)	0.43	1.00 (0.59–1.68)	0.99	1.06 (0.63–1.79)	0.81
> 1000	1.97 (1.20–3.22)	0.007	1.08 (0.64–1.81)	0.78	1.14 (0.68–1.93)	0.61
Procalcitonin, ng/mL						
< 0.1	1 [Reference]		1 [Reference]		1 [Reference]	
0.1–0.25	1.45 (0.94–2.21)	0.09	1.23 (0.78–1.95)	0.36	1.23 (0.78–1.94)	0.37
0.25–0.5	1.88 (1.21–2.92)	0.005	1.38 (0.84–2.25)	0.20	1.37 (0.84–2.23)	0.20
> 0.5	3.17 (2.18–4.60)	< 0.001	2.14 (1.37–3.36)	0.001	2.11 (1.34–3.31)	0.001
C reactive protein, mg/L						
< 50	1 [Reference]					
50–100	1.28 (0.81–2.02)	0.30				
> 100	1.60 (1.06–2.41)	0.03				
Lactic acid, mmol/L						
< 2	1 [Reference]		1 [Reference]		1 [Reference]	
≥ 2	2.15 (1.65–2.80)	< 0.001	1.57 (1.17–2.12)	0.003	1.59 (1.19–2.14)	0.002

Table 3 (continued)

Variables	Univariable model		Multivariable model 1 ^a		Multivariable model 2 ^a	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
CT/Chest x-ray						
Pulmonary embolism	1.76 (1.29–2.40)	< 0.001				

ALT alanine aminotransferase, AST aspartate aminotransferase, HR hazard ratio, CI confidence interval

^aThe model assessment indicated the predictive ability (*c* statistics) on in-hospital survival status was as high as 0.78 and the leave-one-out cross-validated results showed that there was no overfitting in the multivariable model

blood cultures without any growth. The most common isolates were gram positive bacteria, such as several different species of *Staphylococcus*, including methicillin resistant *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus viridans*. There were less gram negative isolates but included *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*.

The median length of illness (symptom onset) for survivors was 12.0 days compared to 15.0 days for non-survivors. The median hospital stay was 7 days. Intensive care admission was required in 25.6% of patients with a median ICU length of stay of 7.0 days (Table 2).

The most commonly employed investigational treatment was hydroxychloroquine, used in 73.4% of patients with the average time from illness onset to therapy start of 7.0 days (IQR 5.0–9.0). Systemic glucocorticoids were utilized in 42.2% of patients with median time from illness onset to therapy start of 9.0 days (IQR 6.0–13.0).

In univariable analysis, epidemiological and clinical characteristics listed on Table 1 were utilized to illustrate the unadjusted effects on the hazard of in-hospital patient death. In multivariable survival model 1, older age (HR 1.05, 95% CI 1.04 to 1.06), admission elevated respiratory rate (HR 1.06, 95% CI 1.04–1.09), pulse oximetry oxygen saturation less than or equal to 88% (HR 1.82, 95% CI 1.33–2.50) and initial laboratories: creatinine > 1.33 mg/dL (HR 1.41, 95% CI 1.08–1.85), ALT > 40 U/L (HR 1.36, 95% CI 1.05–1.77), procalcitonin > 0.5 ng/mL (HR 2.14, 95% CI 1.37–3.36), and lactic acid \geq 2.0 mmol/L (HR 1.57, 95% CI 1.17 to 2.12) were predictors of in-hospital death. Similar results were found when using age groups as a risk factor in multivariable survival model 2 (Table 3).

To facilitate the assessment of risk on mortality, a multivariable survival model using categorical variables for predicting mortality is shown in Table 4 with a scoring system depicted in Table 5. According to our model, a score of \leq 12, 13–26, and \geq 27 carries a mortality risk of 3.91%, 17.98%, and 51.50%, respectively, with the significant differences among risk-scoring groups ($p < 0.001$, Fig. 3).

Discussion

In this study, we described the characteristics of 1461 patients requiring hospitalization for laboratory-confirmed COVID-19 in Metro Detroit.

We also delineated the average clinical course and identified risk factors for mortality that were present early in the hospitalization course. Overall, mortality exceeded 22% for hospitalized patients and is consistent with other published reports, ranging between 14 and 28% [14, 19–21]. Specifically older age, abnormal respiratory parameters on presentation, and initial laboratory results demonstrating renal insufficiency, liver injury, and elevated procalcitonin and lactic acid levels were risk factors for in-hospital death. These factors can help clinicians prognosticate so a scoring system was developed based on these variables among others to help predict inpatient mortality. It was found that a score of less than 12 was low risk of mortality, while a score \geq 27 represented greater than 50% likelihood of death. This scoring system is based on the clinical features in our cohort and could help physicians estimate mortality and possibly aid in resource allocation, although has not been validated outside of this cohort.

In this analysis, we identified a strong association of demographic and epidemiologic characteristics with hospitalization and mortality. Age was a significant predictor of death as median age of fatalities was 73 compared to 59 years for survivors. This is consistent with other reports citing that the geriatric population is at the highest risk in this pandemic [14]. Interestingly, though, while mortality predominantly occurs in the elderly population, younger adults remain at high risk for hospitalization as nearly 56% of patients in our study were between 18 and 64 years. Gender vulnerability of males has also been a commonly reported descriptive within investigations, with male gender comprising 73% of deaths and 82% of ICU admissions in Chinese and Italian publications, respectively [20, 21]. It is postulated that women may be partially protected due to genetic, biological, and hormonal factors [22–24]. We, however, did not find a male predominance to the COVID-19 illness within our large sample size. While males made

up slightly more hospital admissions (53%) than females, there was no mortality difference between genders. Race was another relevant variable. In our study, we found that African Americans were over twice as likely to be hospitalized due to COVID-19 compared to Caucasians. In a quality analysis of demographics at Beaumont Health, African Americans accounted for only 22% of hospitalizations in 2019, yet they accounted for 63% of COVID-19 hospitalizations. The African American community had a higher prevalence of hospitalizations but not mortality, leading us to speculate that other factors such as inability to socially distance due to multi-generational households, the need to work outside the home, and other similar characteristics, put this population at greater risk to be exposed to the illness.

Pre-existing conditions are described as significant predictors of COVID-19 disease outcomes in the literature [14, 19, 20, 25, 26]. Specifically, coronary artery disease and hypertension have been identified as risk factors for mortality. In our study, 34% of hospitalized patients had no comorbidities and 55% had one or no pre-existing medical conditions. This prevalence demonstrates the virulence of COVID-19 in a seemingly healthier population. Unlike other publications, our multivariable analysis did not provide supportive evidence for an association between specific comorbidities and mortality. Additionally, obesity has reportedly been associated with poor outcomes in COVID-19. In a large recent analysis based in New York, BMI greater than 30 was associated with critical illness and a threshold over 40 was implicated as a variable associated with hospitalization [14]. Our cohort had a median BMI of 31; however, while obesity is considered a pro-inflammatory state, in a multivariable analysis, this did not present a significant positive association with mortality.

There are several clinical variables that increase the risk of in-hospital death. Laboratory analysis revealed that elevated lactic acid and procalcitonin levels were risk factors for death. These tests have been described in other investigations as predictors of mortality in COVID-19 patients likely due to relationship of these markers to severe sepsis and secondary bacterial infections [27–29].

Our study also identified renal insufficiency on initial laboratories as a prognosticator for severe illness and mortality. This has also been documented in Wuhan, where the presence of kidney disease was associated with in-hospital mortality. It has been postulated this is multifactorial but could be due to the novel coronavirus using angiotensin converting enzyme 2 (ACE2) receptor for renal cell entry [30, 31]. It is also thought that virus-induced cytokines could cause indirect effects on renal cells via shock or hypoxia [30, 32].

Not surprisingly, there was a strong association between hypoxia with both hospitalization and death. The hospitalized

patient was hypoxic at baseline, with median admission pulse oximetry of 92%. Additionally, admission pulse oximetry $\leq 88\%$ was predictive of demise. The use of high flow oxygenation and mechanical ventilation were common

Table 4 Multivariable survival model using categorical variables for predicting mortality

Variables ^b	Log-HR (β)	SE	<i>p</i> value	Assigned points ^a
Age				
50 to 65 years	0.58	0.26	0.02	6
65 to 80 years	1.15	0.25	<0.001	12
≥ 80 years	1.96	0.27	<0.001	20
Female	0.14	0.13	0.27	1
Race				
Black/African American	-0.36	0.13	0.01	-4
Other	-0.52	0.25	0.04	-5
BMI ≥ 30 kg/m ²	0.14	0.13	0.26	1
Comorbidity				
Coronary artery disease	0.27	0.17	0.10	3
Diabetes Mellitus	0.09	0.13	0.49	1
Hypertension	-0.12	0.14	0.38	-1
Respiratory rate ≥ 24 breaths per minute	0.50	0.12	<0.001	5
Blood oxygen saturation				
$\leq 88\%$	0.62	0.16	<0.001	6
88+ to 94- %	0.29	0.17	0.09	3
White blood cell count				
$< 4 \times 10^9/L$	0.07	0.21	0.74	1
$> 10 \times 10^9/L$	-0.24	0.16	0.13	-2
Hemoglobin ≤ 11 g/dL	0.34	0.15	0.03	3
ALT > 40 U/L	0.36	0.13	0.01	4
Creatinine > 1.33 mg/dL	0.30	0.14	0.03	3
D-dimer				
500–1000 ng/mL FEU	0.07	0.26	0.78	1
> 1000 ng/mL FEU	0.10	0.27	0.71	1
Procalcitonin				
0.1–0.25 ng/mL	0.22	0.23	0.33	2
0.25–0.5 ng/mL	0.35	0.25	0.16	4
> 0.5 ng/mL	0.79	0.23	<0.001	8
Lactic acid ≥ 2 mmol/L	0.46	0.15	0.002	5

ALT alanine aminotransferase, HR hazard ratio, SE standard error

^aEstimates of regression coefficient (β) were pooled from survival models fitted on 20 imputed datasets. Points associated with the presence of a given level of a risk factor (variable) were assigned by multiplying β by 10 and rounding to the nearest integer. The reference level was assigned zero point. The theoretical ranges of total score were -8 and 62

^bUsing bootstrap cross-validation with 1000 bootstrap samples per imputed dataset, the estimate of the concordance index (c-statistics) was 0.78 (95% CI 0.75–0.81)

Table 5 Mortality assessment using the predictor scoring system

Scoring group ^{a,b}	Mortality rate (95% confidence interval)	Hazard ratio (95% confidence interval)	p value
≤ 12 (Low Risk)	3.91% (1.88–5.94%)	1 [Reference]	
13–26	17.98% (15.01–20.95%)	2.82 (15.59–5.00)	< 0.001
≥ 27 (High Risk)	51.50% (46.16%–56.83%)	9.15 (5.19–16.14)	< 0.001

^aThe observed ranges of total score were – 4 and 58 on 20 imputed datasets. The median score was 19 and the 25th and 75th percentiles (IQR) were 12 and 26, respectively. The 10th and 90th percentiles were 7 and 33, respectively. Mortality rates and the corresponding estimates of hazard ratios were pooled from 20 imputed datasets

^bUsing bootstrap cross-validation with 1000 bootstrap samples per imputed dataset, estimates of mortality rates from low risk to high risk were 3.92% (95% CI 2.03–6.05%), 17.98% (95% CI 15.04–21.01%) and 51.48% (95% CI 46.15–56.80%), respectively

interventions employed in 29% and 21% of patients, respectively. Patients receiving invasive mechanical ventilation had

poor outcomes with a 71% case fatality rate in this cohort. In other smaller case series, reported mortality associated with invasive ventilation was also dismal with 97% mortality in one cohort of 32 patients and 100% in a 17-patient series [19, 20]. The utilization of invasive mechanical ventilation represents a complicated provider decision based on oxygen saturation, dyspnea, respiratory rate, chest x-ray, and other factors [33]. In our cohort this decision was also likely influenced by factors including guidelines supporting early intubation and cautioning the use of noninvasive mechanical ventilation strategies [34]. Noninvasive strategies such as bilevel positive airway pressure were used in less than 10% of cases due to the potential risk of viral aerosolization [35]. Other countries used non-invasive ventilation treatments more liberally and some research suggests a possible benefit [36]. In a Chinese study of 113 fatalities, only 6% of patients received invasive treatment compared to 37% receiving noninvasive ventilation [20]. It is unclear whether this strategy was employed purposefully or due to limited resources, and the impact of this choice on mortality is unclear. Given the high mortality rates associated with invasive mechanical ventilation, the overall

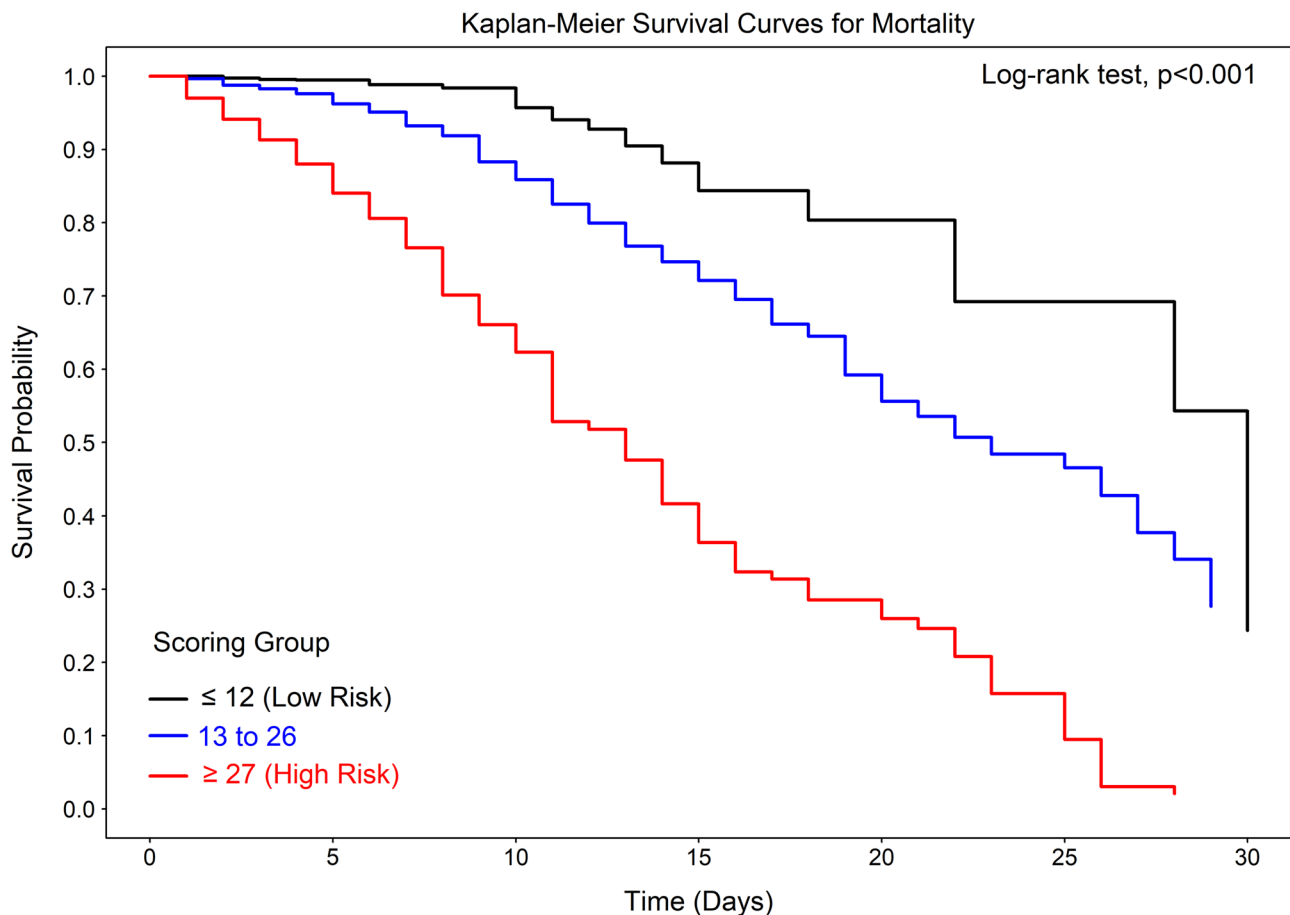


Fig. 3 Kaplan–Meier survival curve for mortality for three risk groups. Figure shows overall survival of study patients associated with three risk groups (score: ≤ 12, 13 to 26, ≥ 27) during study period. The estimated survival curves were pooled from 20 imputed datasets

strategy for oxygenation and ventilation deserves additional investigation with full consideration of all modes of oxygen delivery, both invasive and noninvasive ventilation, delayed intubation with permissive hypoxia, positioning maneuvers, among other therapies.

The study has several limitations. Patients are from a single geographic region, treated within a single health system and factors that are associated with hospitalization and oxygen requirements could differ in other regions, although the region is relatively diverse. While the health system services a range of urban to suburban populations, the rural community is relatively absent from this cohort. Second, ED provider discretion regarding need for admission created potential variability in admission characteristics of patients. Third, data from the EHR were occasionally incomplete. Finally, the case fatality rate likely underrepresents true mortality as transfers out of the health system often needed intensive care resources and ICU admission [19, 37]. Further, we quantified in-hospital mortality through the designated follow-up date of April 23rd. We recently queried clinical status for all patients and found that an additional 17 patients who were discharged home or to a skilled nursing facility had also expired.

This study represents one of the largest cohort analyses in a region considered an epicenter for the COVID-19 pandemic. Older age, low admission saturation $\leq 88\%$, elevated respiratory rate, and initial laboratory derangements including renal and hepatic injury, and elevated procalcitonin and lactic acid levels were the most significant risk factors for in-hospital death. These factors, in addition to our scoring system, can help clinicians prognosticate and should be considered in management strategies.

Compliance with ethical standards

Conflict of interest This manuscript in part or in full has not been submitted or published anywhere. No authors have any relevant conflict of interest disclosures.

Statement of human and animal rights The study was approved by the Institutional Review Board at the home institution.

Informed consent Written informed consent requirement was waived due to the rapid emergence of COVID-19.

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