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Outcomes in Patients With COVID-19 Disease and High Oxygen Requirements

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Abstract

Background: Approximately 19% of people infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) progress to severe or critical stages of the coronavirus disease 2019 (COVID-19) with a mortality rate exceeding 50%. We aimed to examine the characteristics, mortality rates, intubation rate, and length of stay (LOS) of patients hospitalized with COVID-19 disease with high oxygen requirements (critically ill).

Methods: We conducted a retrospective analysis in a single center in Brooklyn, New York. Adult hospitalized patients with confirmed COVID-19 disease and high oxygen requirements were included. We performed multivariate logistic regression analyses for statistically significant variables to reduce any confounding.

Results: A total of 398 patients were identified between March 19th and April 25th, 2020 who met the inclusion criteria, of which 247 (62.1%) required intubation. The overall mortality rate in our study was 57.3% (n = 228). The mean hospital LOS was 19.1 ± 17.4 days. Patients who survived to hospital discharge had a longer mean LOS compared to those who died during hospitalization (25.4 ± 22.03 days versus10.7 ± 1.74 days). In the multivariate analysis, increased age, intubation and increased lactate dehydrogenase (LDH) were each independently associated with increased odds of mortality. Diarrhea was associated with decreased mortality (OR 0.4; CI 0.16, 0.99). Obesity and use of vasopressors were each independently associated with increased intubation.

Conclusions: In patients with COVID-19 disease and high oxygen requirements, advanced age, intubation, and higher LDH levels were associated with increased mortality, while diarrhea was associated with decreased mortality. Gender, diabetes, and hypertension did not have any association with mortality or length of hospital stay.

Keywords: COVID-19 disease; SARS-CoV-2; High oxygen requirement; Critically ill

Introduction

The coronavirus disease 2019 (COVID-19) is the most devastating pandemic of the 21st century. The first case was detected in Wuhan, China in December 2019 [1]. Since then, the virus has spread globally with an exponential increase in the number of cases. The causative organism, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a single-stranded ribonucleic acid (RNA) virus that belongs to the Coronaviridae family, and is transmitted mainly by respiratory droplets [1, 2]. As of December 28th 2020, over 80 million cases have been diagnosed worldwide with more than 13 million cases in the USA [3]. Infection with SARS-CoV-2 ranges from an asymptomatic carrier state to critical illness characterized by acute respiratory distress syndrome (ARDS) with multi-organ failure and death in the most severe cases [4].

Approximately 19% of people infected with the SARS-CoV-2 virus progress to severe or critical COVID-19 disease [4]. Critical illness is characterized by high oxygen requirements that ranges from oxygen supplementation via face mask to intubation and mechanical ventilation. Risk factors associated with development of critical disease include older age, hypertension, diabetes, and obesity [5]. Oxygen levels upon admission and inflammatory markers, including C-reactive protein (CRP) and lactate dehydrogenase (LDH) have been proposed as predictors of poor prognosis in these patients [6].

Mortality in critically ill patients with COVID-19 is extremely high and exceeds 50% [4, 7]. Studies from the USA have been limited by the inclusion of a large number of patients who remain hospitalized at the time of the analysis [5, 8]. We conducted a retrospective analysis to describe the characteristics, mortality, intubation rate, and length of stay (LOS) of patients hospitalized with COVID-19 disease and high oxygen requirement (critically ill) in a single center in Brooklyn, New York.

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Materials and Methods

Study setting

We conducted a single center, retrospective, observational analysis at Maimonides Medical Center, a 711-bed tertiary care teaching hospital in Brooklyn, New York. The Maimonides Medical Center Institutional Review Board approved the study as minimal risk research and waived the need for informed consent. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

We identified patients 18 years of age and older who were admitted between March 19th and April 25th, 2020 with COVID-19 disease and high oxygen requirements. We considered patients to have a high oxygen requirement if they developed acute hypoxemic respiratory failure and required intubation with mechanical ventilation or needed high-level oxygen supplementation (face mask at more than 10 L per minute, high-flow nasal cannula (HFNC), or non-rebreather (NRB) oxygen face mask) at the time of admission or during hospitalization. The accepted method for diagnosing SARS-CoV-2 infection was real-time reverse transcription-polymerase chain reaction (RT-PCR) of a nasopharyngeal sample. All patients included in this study presented to our emergency department with either symptoms suggestive of COVID-19 infection or had a history of exposure to a person with known COVID-19 infection. For patients who presented with symptoms and had a positive result after being tested as outpatient, they were re-tested in our emergency department to confirm COVID-19 infection. We excluded patients not requiring high concentrations of oxygen, patients who died within 1 day of being admitted, and those who died during their emergency room stay.

Data collection

Data were manually collected from the hospital's electronic medical record (Sunrise Clinical Manager). The information collected included patients' demographics, presenting symptoms, comorbidities, initial vital signs on admission, pertinent laboratory tests, treatment received for COVID-19 disease, need for vasopressor support, anticoagulation, use of antibiotics for suspected bacterial superinfection, and outcomes, including length of hospital stay, complications, and mortality.

Outcomes

The primary outcome was in-hospital mortality. Mortality was described as death in hospital following the diagnosis of COVID-19 disease. The secondary outcome was length of hospital stay.

Prediction models

Based on the clinical demographics, pertinent laboratory results upon admission and the highest values recorded during hospitalization (CRP, ferritin, D-dimer, LDH, troponin, and procalcitonin), and complications including hemodialysis, need for extracorporeal membrane oxygenation (ECMO), bacteremia, and/or fungemia, we developed prediction models for intubation, length of hospital stay, and mortality.

Statistical analysis

Descriptive statistics of mean and standard deviation were used to express continuous variables. Frequencies and percentages were used to describe categorical variables. Skewed variables were logarithmic-transformed. Troponin had values of 0, so 0.01 was added to all values and then the values underwent logarithmic transformation. For intubation, analysis of variance was used to compare the continuous variables and the Pearson's Chi-square test compared the categorical variables except for when expected cell size was < 5 in which case Fisher's exact test was performed. Any variable that was statistically significant in the univariate analysis was included in the multivariate logistic regression analysis. Univariate logistic regression was conducted for the outcome variable of mortality. Any variable statistically significant in the univariate analysis for mortality was included in the multivariate analysis. Univariate linear regression was conducted for the outcome variable of LOS. Any variable statistically significant in the univariate analysis for LOS was included in the multivariate analysis. All P values were two tailed. Alpha level for significance was at $P < 0.05$. IBM SPSS Statistics Version 26 was used for all analyses (IBM, 2019).

Results

Baseline characteristics

A total of 398 critically ill patients with COVID-19 disease were included in this study. Two-hundred forty-seven (62.1%) patients required intubation, and 151 (37.9%) needed oxygen supplementation via HFNC or NRB oxygen mask. The mean age was 65.8 years ± 16.26, and 52.8% of patients were 65 years or older. Two thirds of the patients (66.6%) were males, while 19.1% Hispanic. Hypertension was the most common comorbidity, (n = 237; 59.5%) followed by obesity (n = 167; 42.0%), and diabetes mellitus (n = 141; 35.4%). Other comorbidities included coronary artery disease (CAD) at 14.1%, heart failure at 11.3%, atrial fibrillation at 9.8%, and chronic obstructive pulmonary disease (COPD) at 6.8%. The most common presenting symptoms included shortness of breath (83.2%), fever (73.4%), and cough (70.9%). Patients' demographics, comorbidities, presenting symptoms, and laboratory values are given in Table 1. Additional baseline characteristics are shown here (Supplementary Material 1, www.jocmr.org).

Management

Most patients received hydroxychloroquine (93.7%) and

Table 1. Baseline Characteristics for the Study Population

Variable	M (SD) or frequency (%) Whole sample (n = 398)	M (SD) or frequency (%) Non-intubated (n = 151)	M (SD) or frequency (%) Intubated (n = 247)	P value
Demographics				
Age (years) (mean)	65.8 (16.26)	67.5 (17.32)	64.8 (15.51)	0.11
Age (> 65 years)	210 (52.8)	78 (51.7)	132 (53.4)	0.73
Female sex	133 (33.4)	55 (36.4)	78 (31.6)	0.32
Race				0.66
White	229 (57.5)	82 (54.3)	147 (59.5)	
Black	35 (8.8)	14 (9.3)	21 (8.5)	
Asian	44 (11.1)	20 (13.2)	24 (9.7)	
Other	90 (22.6)	35 (23.2)	55 (22.3)	
Ethnicity				0.16
Non-Hispanic	315 (79.1)	120 (79.5)	195 (78.9)	
Hispanic	76 (19.1)	26 (17.2)	50 (20.2)	
Unknown	7 (1.8)	5 (3.3)	2 (0.8)	
Comorbidities				
Obesity	167 (42.0)	48 (34.0)	119 (48.6)	0.01
Smoking				0.42
Never	153 (38.4)	57 (37.7)	96 (38.9)	
Active	7 (1.8)	2 (1.3)	5 (2.0)	
Former	37 (9.3)	10 (6.6)	27 (10.9)	
Unknown	201 (50.5)	82 (54.3)	119 (48.2)	
Hypertension	237 (59.5)	88 (58.3)	149 (60.3)	0.69
Diabetes mellitus	141 (35.4)	47 (31.1)	94 (38.1)	0.16
Cerebrovascular accident	17 (4.3)	8 (5.3)	9 (3.6)	0.43
Atrial fibrillation	39 (9.8)	15 (9.9)	24 (9.8)	0.95
Heart failure	45 (11.3)	15 (9.9)	30 (12.2)	0.49
Chronic obstructive pulmonary disease	27 (6.8)	15 (9.9)	12 (4.9)	0.052
Chronic kidney disease	22 (5.5)	10 (6.6)	12 (4.9)	0.46
Coronary artery disease	56 (14.1)	21 (13.9)	35 (14.2)	0.94
Dementia	36 (9.0)	21 (13.9)	15 (6.1)	0.01
Presenting symptoms				
Fever	292 (73.4)	104 (68.9)	188 (76.1)	0.11
Cough	282 (70.9)	105 (69.5)	177 (71.7)	0.65
Myalgia	74 (18.6)	24 (15.9)	50 (20.2)	0.28

Table 1. Baseline Characteristics for the Study Population - *(continued)*

Variable	M (SD) or frequency (%) Whole sample (n = 398)	M (SD) or frequency (%) Non-intubated (n = 151)	M (SD) or frequency (%) Intubated (n = 247)	P value
Nausea	39 (9.8)	16 (10.7)	23 (9.3)	0.66
Diarrhea	58 (14.6)	25 (16.6)	33 (13.4)	0.38
Shortness of breath	331 (83.2)	124 (82.1)	207 (83.8)	0.66
Chest pain	37 (9.3)	15 (10.0)	22 (8.9)	0.72
Vital signs				
Heart rate (per minute)	101.5 (20.78)	98.0 (19.31)	103.6 (21.40)	0.01
Oxygen saturation	86.9 (10.86)	88.1 (9.53)	86.2 (11.54)	0.09
Respiratory rate (per minute)	27.1 (7.76)	24.6 (5.66)	28.6 (8.46)	< 0.001
Laboratory values[a]				
White blood cell ($\times 10^3/\mu L$)	8.8 (4.31)	8.8 (4.74)	8.8 (4.03)	0.88
Lymphocyte count ($\times 10^3/\mu L$)	12.2 (9.52)	12.9 (11.24)	11.8 (8.29)	0.81
Platelet	211.2 (90.93)	227.5 (107.78)	202.8 (77.72)	0.01
Serum sodium (mmol/L)	135.7 (7.79)	137.3 (8.06)	134.8 (7.48)	0.002
Creatinine (mg/dL)	1.5 (1.55)	1.5 (1.47)	1.4 (1.60)	0.92
C-reactive protein (mg/dL) (highest)	24.7 (11.44)	18.6 (9.23)	28.5 (11.04)	< 0.001
Ferritin ng/mL (highest)	1,594.5 (1,734.71)	1,239.2 (1,413.14)	1,815.5 (1,876.75)	0.001
D-dimer (ng/mL) (highest)	7,564.7 (11,514.70)	3,368.2 (6,482.24)	9,692.1 (12,867.37)	< 0.001
Lactate dehydrogenase (IU/L) (highest)	748.6 (824.14)	575.7 (419.27)	848.9 (972.58)	< 0.001
Glomerular filtration rate	51.1 (15.40)	48.7 (17.08)	52.5 (14.14)	0.02
Troponin (ng/mL) (highest)	1.3 (6.43)	1.4 (8.49)	1.2 (4.84)	< 0.001
Procalcitonin (ng/mL) (highest)	6.5 (12.25)	1.9 (4.50)	9.2 (14.35)	< 0.001
Aspartate transaminase (IU/L) (days 6 - 10) (> 120)	48 (12.1)	4 (5.0)	44 (21.6)	0.001

[a]Laboratory values are on admission unless otherwise specified. One patient was still hospitalized. Those with sample size for continuous variables less than 398 are: white blood cell (n = 397), lymphocyte (n = 397), platelet (n = 397), creatinine (n = 396), C-reactive protein (n = 390), ferritin (n = 373), D-dimer (n = 217), lactate dehydrogenase (n = 373), glomerular filtration rate (n = 391), troponin (n = 387), and procalcitonin (n = 350). Sample size for continuous variables less than 398 are: oxygen saturation (n = 396), respiratory rate (n = 391); sample size for categorical variables missing are: obesity (n = 12), atrial fibrillation (n = 1), heart failure (n = 1), chronic obstructive pulmonary disease (n = 1), chronic kidney disease (n = 1), nausea (n = 1), and chest pain (n = 1). M: mean; SD: standard deviation.

azithromycin (93.2%). Tocilizumab was given to 29.6% of the patients while 9.8% received remdesivir. Convalescent plasma was given to 7.5% of patients, while 39.2% received full dose anticoagulation. Table 2 summarizes the treatments received during admission.

Complications

More than half of the patients (57.8%) needed vasopressor support. Hemodialysis was used in one-fifth of patients while blood transfusion was administered to 20.9%. Bacteremia and/or fungemia were documented in one-fifth of the cases. The majority of patients (91.5%) received antibiotics (Table 2). Figure 1 shows the percentage of some of the complications observed in the study population.

Predictors of intubation

Tables 1 and 2 show univariate comparisons for those patients who were either intubated or nonintubated. In the multivariate analysis, only obesity and use of vasopressor were each independently associated with increased odds for intubation (Table 3).

Predictors of mortality

Overall mortality in our study was 57.3% (n = 228). In an analysis comparing intubation and mortality, the mortality rate was significantly higher in intubated patients (78.1%) as compared to those not intubated (23.2%). Table 4 shows logistic regression analyses for mortality. In the multivariate analysis, increased age, intubation, and increased LDH were each independently associated with increased odds of mortality. Diarrhea was independently associated with decreased mortality. None of the comorbidities (including diabetes and hypertension), vital signs, treatment management, or complications was significantly associated with mortality.

Predictors of LOS

The mean hospital LOS for the entire cohort was 19.1 ± 17.4 days. In the subset of patients who were discharged alive, mean LOS was 25.4 ± 22.03 days. Patients who died during hospitalization had a mean LOS of 10.7 ± 1.74 days. In an analysis comparing intubation and LOS, intubated patients had significantly greater mean LOS (21.7 ± 19.08 days) as compared to those not intubated (14.8 ± 12.67 days) as shown in Table 2.

Table 5 shows the linear regression analyses for LOS. In the multivariate analysis, Asian race, hemodialysis, ECMO support, blood transfusion, treatment with steroids, remdesivir, or vitamin C, and diagnosis of bacteremia and/or fungemia were each independently associated with increased LOS. CAD was significantly associated with decreased LOS. In a multivariate analysis in the subset of patients who survived to discharge for variables significant in the whole sample multivariate analysis, hemodialysis, blood transfusion, use of vitamin C, and diagnosis of bacteremia/fungemia were each significantly associated with increased LOS. In the subset of patients with mortality for those variables significant in the whole sample multivariate analysis, blood transfusion, treatment with steroids, remdesivir, or vitamin C were each significantly associated with increased LOS. CAD was significantly associated with decreased LOS.

Discussion

Our study represents one of the largest analyses of patients with COVID-19 disease with high oxygen requirements and complete outcomes. We included 398 critically ill patients, of which 247 (62.1%) were intubated. The reported percentage of intubation in COVID-19 patients with critical disease ranges from 57% to 88% [7, 9-12]. We found obesity and use of vasopressors were each independently associated with higher odds of intubation. These findings are consistent with a study that reported higher rates of intubation in obese COVID-19 patients [10].

The mean LOS in our study population was 19.1 days. Other studies on critically patients with COVID-19 have reported a LOS of 15 - 22 days [5, 10]. We found that patients who died had a 2.5-time shorter LOS as compared to those who lived. This finding is consistent with other studies that have reported LOS for patients who died between 4 and 21 days and 4 to 53 days for those who were discharged alive [13].

The overall mortality in our cohort was 57.3%. This finding was mainly driven by a significantly higher mortality in intubated patients than non-intubated patients (78.1% versus 23.2%). In a previous study addressing patients with COVID-19, we reported a mortality of 50%; however, that study included patients with less severe disease [14]. Our current findings are consistent with reports from China concerning critically ill patients with COVID-19 disease. A study that examined 239 critically ill patients, of which 69% were intubated, showed a 61.5% mortality [7]. Similarly, another group reported a mortality rate of 56% in which more than half of the studied patients were intubated [9]. In a study from Italy that included 1,300 patients with COVID-19 treated in the intensive care unit (ICU), mortality was 26% despite 88% of the patients being intubated. However, more than 50% of patients remained hospitalized at the time of the analysis [15].

Studies from the New York City area have included cohorts of similar illness severity as our sample. The mortality rate reported in these studies ranged from 39% to 68%. However, they included a high percentage of patients (ranging from 23% to 37%) who remained hospitalized at the time of the analysis, which makes their results on mortality and LOS inconclusive [8, 11, 16]. In our study, only one patient remained hospitalized under hospice care.

Various authors examined predictors of mortality and many reported older age to be independently associated with increased mortality [7, 11]. Other factors associated with higher mortality in critically ill patients with COVID-19 include chronic cardiac

Table 2. Management and Outcomes

Variable	M (SD) or frequency (%) Whole sample (n = 398)	M (SD) or frequency (%) Non-intubated (n = 151)	M (SD) or frequency (%) Intubated (n = 247)	P value
Oxygen requirement				
Face mask[a]	1 (0.25)	1 (0.25)		
HFNC/NRB mask[b]	150 (37.7)	150 (37.7)		
Intubation	247 (62.1)	0 (0.0)	247 (100.0)	-
Treatment management				
Vasopressor	230 (57.8)	11 (7.3)	219 (88.7)	< 0.001
Hemodialysis	80 (20.1)	5 (3.3)	75 (30.4)	< 0.001
ECMO support	4 (1.0)	0 (0.0)	4 (1.6)	0.30
Blood transfusion	83 (20.9)	8 (5.3)	75 (30.6)	< 0.001
Hydroxychloroquine	373 (93.7)	137 (91.3)	236 (95.9)	0.06
Azithromycin	371 (93.2)	138 (92.0)	233 (94.3)	0.36
Steroids	153 (38.4)	31 (20.7)	122 (49.4)	< 0.001
Prophylactic anticoagulation	309 (77.6)	124 (84.4)	185 (75.8)	0.045
Therapeutic anticoagulation	156 (39.2)	47 (31.3)	109 (44.3)	0.01
Convalescent plasma	30 (7.5)	10 (6.8)	20 (8.2)	0.62
Remdesivir	39 (9.8)	0 (0.0)	39 (15.8)	< 0.001
Vitamin C	252 (63.3)	85 (58.2)	167 (67.6)	0.06
Zinc	213 (53.5)	63 (43.2)	150 (60.7)	0.001
Tocilizumab	118 (29.6)	41 (27.2)	77 (31.2)	0.39
Antibiotics for suspected bacterial infection	364 (91.5)	120 (80.0)	244 (98.8)	< 0.001
Complications				
Bacteremia/fungemia	83 (20.9)	8 (5.3)	75 (30.5)	< 0.001
Deep vein thrombosis/pulmonary embolism	18 (4.5)	6 (4.0)	12 (4.9)	0.68
Cerebrovascular accident	11 (2.8)	4 (2.8)	7 (2.9)	1.00
Outcomes				
Mortality	228 (57.3)	35 (23.2)	193 (78.1)	< 0.001
Overall length of stay (days) (mean)	19.1 (17.40)	14.8 (12.67)	21.7 (19.08)	< 0.001
Length of stay (days) for patients who died	10.7 (1.74)	-	-	-
Length of stay for patients who did not die	25.4 (22.03)	-	-	-

[a]Face mask higher than 10 L/min. [b]High-flow nasal cannula (HFNC)/non-rebreather oxygen mask (NRB mask). One patient was still hospitalized. Those with sample size for categorical variables missing are: vasopressor (n = 1), need for hemodialysis (n = 1), need for ECMO support (n = 1), need for blood transfusion (n = 3), hydroxychloroquine (n = 2), azithromycin (n = 1), steroids (n = 1), prophylactic anticoagulation (n = 7), therapeutic anticoagulation (n = 2), convalescent plasma (n = 6), remdesivir (n = 1), vitamin C (n = 5), zinc (n = 5), antibiotics for suspected bacterial infection (n = 1), diagnosis of deep vein thrombosis/pulmonary embolism (n = 3), diagnosis of cerebrovascular accident (n = 8), and diagnosis of bacteremia/fungemia (n = 1). Comparison between non-intubation and intubation groups reports percentages only for cases analyzed and does not include missing cases. Prophylactic anticoagulation included enoxaparin 40 mg (n = 58, 14.6%) enoxaparin 60 mg (n = 123, 30.9%), heparin (n = 74, 18.6%), and low-dose apixaban (n = 54, 13.6%). Therapeutic anticoagulation included enoxaparin (n = 64, 16.1%), heparin drip (n = 18, 4.5%), DOAC (n = 71, 17.8%), and coumadin (n = 3, 0.8%). M: mean; SD: standard deviation; DOAC: direct oral anticoagulants; ECMO: extracorporeal membrane oxygenation.

Table 3. Logistic Regression for Intubation

Variable	Multivariate, OR (95% CI)
Comorbidities	
Obesity	6.33 (1.45, 27.61)*
Dementia	2.01 (0.20, 20.54)
Vital signs	
Heart rate (per minute)	1.01 (0.98, 1.04)
Respiratory rate (per minute)	1.03 (0.92, 1.15)
Laboratory values[a]	
Platelet ($\times 10^3/\mu L$)	1.09 (0.98, 1.21)
Serum sodium (mmol/L)	0.99 (0.91, 1.07)
C-reactive protein (mg/dL) (highest)	1.06 (0.99, 1.13)
Ferritin (ng/mL) (highest)	0.21 (0.03, 1.27)
Lactate dehydrogenase (IU/L) (highest)	15.40 (0.56, 427.25)
Glomerular filtration rate	1.05 (0.99, 1.11)
Troponin (ng/mL) (highest)	1.70 (0.72, 4.03)
Treatment management	
Vasopressor	92.25 (19.51, 436.28)***
Hemodialysis	3.30 (0.34, 32.28)
Blood transfusion	3.99 (0.37, 42.51)
Steroids	2.31 (0.60, 8.94)
Prophylactic anticoagulation	0.40 (0.05, 3.03)
Therapeutic anticoagulation	0.26 (0.04, 1.53)
Remdesivir	2.60 E8 (< 0.001, -)
Zinc	0.93 (0.25, 3.44)
Antibiotics for suspected bacterial infection	0.61 (0.08, 5.02)
Complications	
Diagnosis of bacteremia/fungemia	2.13 (0.31, 14.89)

*P < 0.05, ***P < 0.001. Analysis included one patient still hospitalized. Analysis includes 238 patients due to missing data. D-dimer, procalcitonin, and aspartate transaminase were not included in the multivariate analysis due to a lot of missing data. Nagelkerke R Square = 0.82. [a]Laboratory values are on admission unless otherwise indicated. OR: odds ratio; CI: confidence interval.

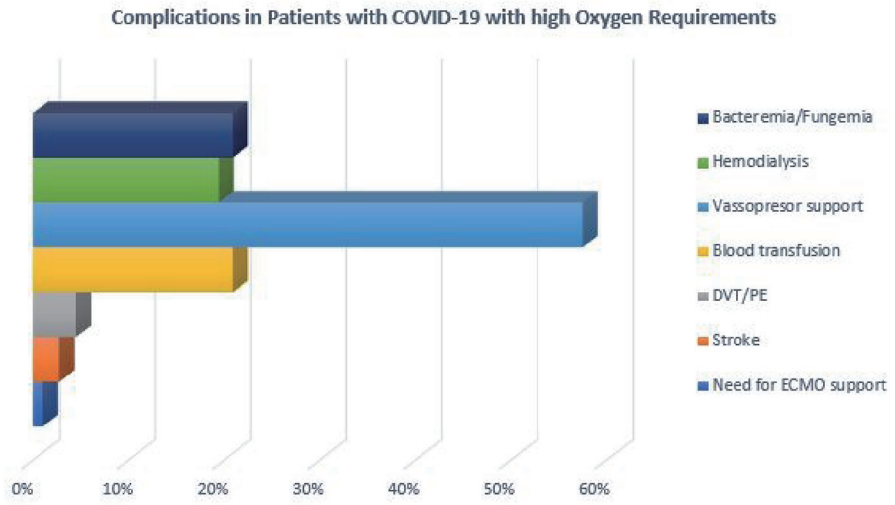

Figure 1. Complications in patients with COVID-19 disease and high oxygen requirements.

Table 4. Mortality Analysis

Variable	Univariate	Multivariate
	OR (95% CI)	OR (95% CI)
Demographics		
Age (years)	1.04 (1.03, 1.06)***	1.07 (1.05, 1.10)***
Female sex	0.90 (0.59, 1.38)	-
Race		
White	1.00	1.00
Black	1.20 (0.57, 2.53)	1.23 (0.39, 3.87)
Asian	0.68 (0.36, 1.31)	1.06 (0.40, 2.83)
Other	0.52 (0.32, 0.86)*	0.71 (0.32, 1.56)
Comorbidities		
Hypertension	2.28 (1.51, 3.43)***	1.26 (0.65, 2.47)
Heart failure	1.98 (1.01, 3.90)*	0.85 (0.31, 2.34)
Presenting symptoms		
Diarrhea	0.56 (0.32, 0.97)*	0.40 (0.16, 0.99)*
Vital signs		
Respiratory rate (per minute)	1.05 (1.02, 1.08)**	1.03 (0.99, 1.07)
Laboratory values[a]		
Creatinine (mg/dL)	2.59 (1.14, 5.88)*	2.62 (0.65, 10.58)
C-reactive protein (mg/dL) (highest)	1.05 (1.03, 1.07)***	1.02 (0.98, 1.05)
Ferritin (ng/mL) (highest)	1.58 (1.003, 2.49)*	0.65 (0.28, 1.52)
D-dimer (ng/mL) (highest)	1.98 (1.24, 3.15)**	-
Lactate dehydrogenase (IU/L) (highest)	5.11 (1.98, 13.19)**	4.92 (0.999, 24.23)[b]
Glomerular filtration rate	0.99 (0.98, 1.01)	-
Troponin (ng/mL) (highest)	2.23 (1.61, 3.09)***	0.92 (0.58, 1.44)
Procalcitonin (ng/mL) (highest)	1.72 (1.24, 2.40)**	-
Aspartate transaminase (IU/L) (days 6 - 10) (> 120)	2.89 (1.41, 5.93)**	-
Disease severity		
Intubation	11.85 (7.30, 19.21)***	15.71 (5.48, 45.02)***
Treatment management		
Vasopressor	7.60 (4.84, 11.92)***	2.09 (0.76, 5.78)
Hemodialysis	2.46 (1.43, 4.24)**	0.78 (0.35, 1.72)
Antibiotics for suspected bacterial infection	4.03 (1.82, 8.91)**	0.80 (0.23, 2.84)
Complications		
Diagnosis of deep vein thrombosis/pulmonary embolism	0.58 (0.22, 1.50)	-
Diagnosis of cerebrovascular accident	0.89 (0.27, 2.96)	-
Diagnosis of bacteremia/fungemia	1.83 (1.10, 3.07)*	0.55 (0.26, 1.17)

[a]Laboratory values are on admission unless otherwise indicated. [b]P = 0.05, *P < 0.05, **P < 0.01, ***P < 0.001. Analysis included one patient still hospitalized. Multivariate analysis includes 333 patients due to missing data. D-dimer, procalcitonin, and aspartate transaminase were not included in the multivariate analysis due to missing data. Nagelkerke R Square = 0.54. OR: odds ratio; CI: confidence interval. For brevity purposes, many variables not statistically significant in the univariate analyses are not shown in the table.

disease (CAD and heart failure combined), high concentration of interleukin-6, elevated D-dimer, thrombocytopenia, acute kidney injury, and ARDS [7, 11, 17]. We found increased age, LDH levels and intubation were each independently associated with increased mortality. In a pooled analysis including 1,532 patients, LDH levels were found to be associated with a 16-fold increase in mortality [18]. That analysis was based on the LDH value upon admission, whereas in our study we used the highest

Table 5. Linear Regression for Length of Hospital Stay

Variable	Univariate	Multivariate	Multivariate	Multivariate
	B (SE)	B (SE)	No mortality, B (SE)	Yes mortality, B (SE)
Demographics				
Age (years) (mean)	-0.01 (0.001)***	-0.002 (0.01)	-	-
Race				
White	Reference	Reference	Reference	Reference
Black	< 0.001 (0.07)	0.02 (0.07)	0.09 (0.10)	0.02 (0.07)
Asian	0.07 (0.06)	0.13 (0.06)*	0.10 (0.07)	0.11 (0.07)
Other	0.12 (0.05)**	0.01 (0.05)	0.06 (0.06)	0.03 (0.05)
Ethnicity			-	-
Non-Hispanic	Reference	Reference		
Hispanic	0.13 (0.05)*	0.05 (0.05)		
Unknown	-0.05 (0.14)	-0.11 (0.13)		
Comorbidities				
Hypertension	-0.12 (0.04)**	-0.03 (0.04)	-	-
Atrial fibrillation	-0.14 (0.06)*	-0.09 (0.06)	-	-
Heart failure	-0.12 (0.06)*	0.03 (0.06)	-	-
Coronary artery disease	-0.17 (0.05)**	-0.13 (0.05)*	-0.12 (0.08)	-0.19 (0.05)**
Laboratory values[a]				
Serum sodium (mmol/L)	-0.01 (0.002)**	-0.001 (0.002)	-	-
Creatinine (mg/dL)	-0.28 (0.07)***	-0.14 (0.14)	-	-
C-reactive protein (mg/dL) (highest)	0.01 (0.002)***	0.001 (0.002)	-	-
Ferritin (ng/mL) (highest)	0.10 (0.04)*	-0.02 (0.04)	-	-
D-dimer (highest)	0.12 (0.04)**	-	-	-
Glomerular filtration rate	0.01 (0.001)***	-5.63 E-5 (0.002)	-	-
Procalcitonin (ng/mL) (highest)	0.08 (0.03)**	-	-	-
Alanine transaminase (IU/L) (days 6 - 10) (> 180)	-0.13 (0.06)*	-	-	-
Disease severity				
Intubation	0.12 (0.04)**	-0.03 (0.06)	-	-
Treatment management				
Vasopressor	0.11 (0.04)**	-0.09 (0.06)	-	-
Hemodialysis	0.19 (0.05)***	0.11 (0.05)*	0.17 (0.08)*	0.09 (0.05)
ECMO support	0.85 (0.18)***	0.36 (0.16)*	0.21 (0.18)	0.48 (0.29)
Blood transfusion	0.44 (0.04)***	0.28 (0.05)***	0.25 (0.08)**	0.23 (0.05)***
Ritonavir/lopinavir	0.29 (0.14)*	0.24 (0.16)	-	-

Table 5. Linear Regression for Length of Hospital Stay - *(continued)*

Variable	Univariate	Multivariate	Multivariate	Multivariate
	B (SE)	B (SE)	No mortality, B (SE)	Yes mortality, B (SE)
Steroids	0.21 (0.04)***	0.11 (0.04)**	0.07 (0.05)	0.12 (0.04)**
Therapeutic anticoagulation	0.12 (0.04)**	0.03 (0.04)	-	-
Convalescent plasma	0.18 (0.07)*	0.05 (0.07)	-	-
Remdesivir	0.24 (0.04)***	0.16 (0.06)*	0.13 (0.09)	0.20 (0.06)**
Vitamin C	0.23 (0.04)***	0.08 (0.04)*	0.11 (0.05)*	0.12 (0.04)**
Zinc	0.24 (0.04)***	0.04 (0.04)	-	-
Tocilizumab	0.10 (0.04)*	0.01 (0.04)	-	-
Diagnosis of cerebrovascular accident	0.25 (0.11)*	0.19 (0.11)	-	-
Diagnosis of bacteremia/fungemia	0.28 (0.04)***	0.12 (0.04)**	0.30 (0.08)***	0.09 (0.05)

[a]Laboratory values are on admission unless otherwise indicated. *P < 0.05, **P < 0.01, ***P < 0.001. Analysis included one patient still hospitalized. Multivariate whole sample analysis includes 338 patients due to missing data. Multivariate no mortality subsample includes 165 patients. Multivariate mortality subsample includes 225 patients. D-dimer, procalcitonin, and alanine transaminase were not included in the multivariate analysis due to a lot of missing data. Multivariate whole sample adjusted R Square = 0.39. Multivariate no mortality subsample adjusted R Square = 0.44. Multivariate mortality subsample adjusted R Square = 0.34. B: unstandardized beta; SE: standard error. For brevity purposes, many variables not statistically significant in the univariate analyses are not shown in the table.

LDH value during hospitalization.

Even though diabetes mellitus and hypertension are recognized risk factors for developing severe COVID-19 disease, they have failed to consistently show any association with higher mortality in critically ill patients [17, 19, 20]. One study found no difference in the rate of hypertension or diabetes between survivors and non-survivors of critical COVID-19 disease [7]. In contrast, another study reported a significant difference in mortality in patients with severe COVID-19 disease with diabetes versus non-diabetic patients (81% versus 47%). However, this difference in outcome could also be explained by the 10-year difference in age between the groups in that study [9]. Nonetheless, despite having a lower rate of hypertension and diabetes as compared to our cohort, both studies reported similar number of intubated patients and mortality rate similar to our findings [7, 9].

A study from Detroit, Michigan in the USA reported a mortality rate of 39% in 141 patients with COVID-19 who were treated in the ICU, including 114 (80%) intubated patients. Their cohort included 51.8% with diabetes and 78.7% with hypertension and yet the reported mortality was significantly lower than other reports with COVID-19 patients of similar severity [10]. These studies, including ours, suggest that diabetes and hypertension might not affect mortality in patients with COVID-19 disease once they progress to critical illness. Similarly, we did not find any association between gender and mortality. This finding is consistent with previously published data [7].

Previous studies examined gastrointestinal involvement in COVID-19 and reported diarrhea to be associated with prolonged symptoms, viral carriage, development of cytokine storm, and multi-organ damage [21, 22]. Other researchers have failed to establish an association between gastrointestinal symptoms, including diarrhea, with increased mortality, LOS, or mechanical ventilation [23]. Our analysis showed diarrhea to be independently associated with decreased mortality.

Limitations

Our study has some limitations. First, our analysis is subject to data entry errors given that the information was manually collected. To minimize this, we performed multiple checks during the process of data collection. Prior to data analysis, we double checked very abnormal laboratory values. Second, we did not include mechanical ventilation settings, which could be important information for management of these patients. However, our objective was to focus on mortality and LOS outcome. Third, smoking information was self-reported and was not provided in over 50% of patients. This information could be an important risk factor in patients with COVID-19 disease.

Conclusions

Our study shows a high mortality rate in COVID-19 patients with high oxygen requirements. This finding is driven mainly

by higher mortality in intubated patients. We found a significant difference in LOS between patients who died during hospitalization as compared to those who survived to discharge. Older age, intubation, and higher LDH levels were associated with increased mortality, while diarrhea was associated with decreased mortality. Gender, diabetes, and hypertension did not have any association with mortality or length of hospital stay.

Supplementary Material

Suppl 1. Complete list of baseline characteristics.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent was not needed due to the retrospective nature of the study and data anonymization.

Author Contributions

All the authors reviewed the manuscript and agreed with the findings and interpretation. Geurys Rojas-Marte: conception and design, supervision, drafting of the manuscript, critical review, review of data integrity and final approval. Arsalan Talib Hashmi: supervision, review of data integrity, critical review. Mazin Khalid, Nnamdi Chukwuka: drafting the manuscript, scientific writing, critical review, and content approval. Joshua Fogel: review of data and statistical analysis. Alejandro Munoz-Martinez, Samantha Ehrlich, Maham Akbar Waheed, Dikshya Sharma, Shaurya Sharma, Awais Aslam, Sabah Siddiqui, Chirag Agarwal, Yuri Malyshev, Carlos Henriquez-Felipe: data acquisition. Jacob Shani: final approval of publication, critical review.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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