

Hyperbaric Oxygen Therapy For Hospitalized COVID-19 Patients With Moderate To Severe Hypoxia

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Abstract

Introduction: Few treatments have demonstrated mortality benefit among hospitalized hypoxic COVID-19 patients except for steroids. We evaluated the use of hyperbaric oxygen therapy (HBOT) as a therapeutic intervention among hospitalized patients with a high oxygen requirement.

Methods: We extracted data on patients with COVID-19 hypoxia who required at least 6 L/min oxygen supplementation, and were eligible for off-label HBOT from October 2020 to February 2021. We compared patient characteristics and used Fisher's exact test and a survival analysis to assess the primary endpoint of inpatient death.

Results: We offered HBOT to 36 patients, of which 24 received treatment and 12 did not receive treatment. Patients who did not receive treatment were significantly older ($P < 0.01$) and had worse baseline hypoxia ($P = 0.06$). Three of the 24 (13%) patients who received treatment died compared to 6 of 12 (50%) patients who did not receive treatment (RR ratio: 0.25, $P = 0.04$, 95% CI: 0.08 to 0.83). In the survival analysis, there was a statistically significant reduction in inpatient mortality in the treatment group (HR: 0.19, $P = 0.02$, 95% CI: 0.05-0.74). However, after adjusting for age and baseline hypoxia, there was no difference in inpatient mortality (hazard ratio: 0.48, $P = 0.42$, 95% CI: 0.08-2.86).

Conclusions: The survival benefit of HBOT observed in our unadjusted analysis suggests the need to further study therapeutic benefits of HBOT in treating COVID-19 hypoxia through randomized clinical trials.

Introduction

The novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has overwhelmed health systems across the United States and the world, causing over 530,000 deaths in the US and over 2.6 million worldwide.¹ Symptomatic COVID-19 disease varies in its severity, ranging from mild pneumonia and mild hypoxia to critical illness involving respiratory failure and multiorgan dysfunction.² The rates of severe and critical illness are higher in hospitalized patients with COVID-19 with higher mortality in mechanically ventilated patients.²⁻⁵ The clinical syndrome of COVID-19 is atypical for a viral respiratory infection, with severe degrees of hypoxemia and a disproportionate lack of respiratory distress.^{6,7}

Treatment of hypoxic patients with COVID-19 has been evolving throughout the course of this pandemic, with ongoing investigations into antiviral and anti-inflammatory therapies. Dexamethasone, a glucocorticoid, has been shown to decrease mortality rates in hospitalized patients with hypoxia due to COVID-19 based on data from prospective randomized trials,⁸⁻¹⁰ while the mortality benefits of tocilizumab¹¹ and remdesivir¹² have been equivocal at best.

Several case series have shown that hyperbaric oxygen therapy (HBOT) may be a possible therapeutic intervention for COVID-19 respiratory failure.¹³⁻¹⁵ HBOT has been used extensively to treat conditions

with impaired gas exchange and is used in the setting of severe infections or thromboses. Through its ability to improve tissue oxygenation and its anti-inflammatory effects,^{16–18} HBOT could be a useful intervention to treat respiratory distress caused by COVID-19.

Although vaccine development and administration are in progress, the search for an efficacious treatment for COVID-19 respiratory failure remains important and there has been limited success. Despite vaccination efforts, patients may continue to acquire COVID-19, leading to death among many unvaccinated patients.^{19,20} Therefore, we sought to investigate HBOT as a therapeutic intervention for hospitalized patients with COVID-19.

Methods

Study Cohort

This was a retrospective analysis of hospitalized COVID-19 patients who were eligible to receive HBOT between October 16, 2020 and February 1, 2021 as an off-label treatment for moderate to severe hypoxia. Patients were deemed eligible for HBOT if they were age 18 years or older, had a laboratory-confirmed SARS-CoV-2 infection, and had moderate to severe hypoxemia, which was defined as having a baseline supplemental oxygen requirement of 6 L/min or higher. Patients were excluded if they were pregnant, had radiographic evidence of a pneumothorax or other chest barotrauma (e.g., pneumomediastinum, pneumopericardium, significant subcutaneous emphysema, or pulmonary blebs), required invasive or non-invasive mechanical ventilation (e.g., BiPAP, CPAP), were too critically ill to be safely transported to the hyperbaric chambers, or did not have capacity to provide informed consent. Patients were categorized into treatment and non-treatment groups based on whether they received HBOT during the hospitalization to address COVID-19 respiratory failure. All patients who were deemed eligible for HBOT were considered for treatment, however, some were unable to be treated due to limited availability of HBOT staffing and resources, patient refusal, or inability to follow instructions. Oxygen supplementation and other COVID-19 therapies such as steroids, antivirals and anti-inflammatory agents were applied per the standard-of-care guidelines at our institution during the study period. This study was deemed exempt by the Institutional Review Board at our institution.

Patient Characteristics

We reviewed the electronic medical records (EMR) of hospitalized COVID-19 patients who were candidates for HBOT and extracted patient demographics, pre-existing comorbidities (e.g., hypertension, hyperlipidemia, and diabetes), baseline vital signs and lab results, SOFA scores,^{21,22} use of other COVID-19 treatments (e.g., dexamethasone, remdesivir, convalescent plasma, tocilizumab), treatment toxicities (seizures, pneumothoraces, arrhythmias, pulmonary edema, hypoglycemia, ear/sinus barotrauma, and anxiety), and baseline oxygen requirements. Patients were categorized into treatment and non-treatment groups based on whether they were treated with HBOT to address COVID-19 hypoxia during their hospitalization.

Outcomes

The primary outcome was all-cause in-hospital mortality, which was defined as death while hospitalized due to COVID-19. Secondary outcome was progression to invasive mechanical ventilation (IMV), defined as intubation for respiratory failure due to COVID-19.

Statistical Analysis

We compared the median age and BMI in addition to the range for these values using Wilcoxon rank-sum tests and the average SOFA scores using t-tests. We analyzed the sex, ethnicity, medical comorbidities, baseline supplemental oxygen requirements, and proportion receiving other COVID-19 treatments using Fisher's exact tests. Given the small sample size of the study cohort, we used a P value of 0.10 to flag baseline characteristics that differed between the HBOT treatment and non-treatment groups.

For our primary outcome, we analyzed the relative risk ratio of inpatient mortality between the two groups using a two-sided Fisher exact test. We performed a survival analysis using competing risk regression using the dates when patients were admitted to the hospital and the dates when they were discharged or suffered inpatient mortality which analyzed the time to inpatient mortality with a competing outcome of hospital discharge. Survival curves were depicted as cumulative incidence. We also analyzed inpatient mortality by stratifying the outcome across key predictors that differed between the two groups, and adjusted the survival analysis accordingly.

For the secondary outcome we analyzed progression to intubation between the two groups using Fisher exact test. A P value of 0.05 was used to identify statistically significant results for all outcomes. All statistical analyses were performed in Stata 16.2.

Results

Patient Characteristics

Thirty-six COVID-19 positive patients were evaluated to determine whether they were eligible for and would consent to treatment with off-label HBOT. Among these 36 patients, 12 (33%) were evaluated on hospital days 0 or 1, 12 (33%) were evaluated on hospital days 2 or 3, and 12 (33%) were evaluated on hospital days 4 through 9. Of the 36 patients, 24 (67%) were appropriate for treatment, and 12 (33%) of the eligible patients were unable to be treated. The reasons for non-treatment were HBOT resource limitations (83%), and patient refusal of treatment (17%).

In comparing the demographic characteristics, medical comorbidities, baseline oxygen requirements, and SOFA scores at the time of evaluation for HBOT, we found that there was a statistically significant trend towards older patients in the non-treatment group ($P < 0.01$) as well as a trend towards worse baseline oxygen requirements among patients in the non-treatment group ($P = 0.06$). Other patient characteristics including baseline SOFA scores did not statistically differ between the two groups ($P > 0.10$). Patient and treatment characteristics are outlined in Table 1.

Table 1
 Characteristics of the Study Population (All Ages)

Patient Characteristics	Received Treatment (n = 24)	No Treatment (n = 12)	P Value
Age			
Median	56	72	< 0.01
Range	29 to 79	37 to 87	
Sex			
Male	79%	83%	1.00
Ethnicity			
Hispanic	50%	42%	1.00
BMI			
Median	28	27	0.28
Range	20 to 50	17 to 40	
Medical History			
Hypertension	38%	50%	0.50
Hyperlipidemia	29%	42%	0.48
Diabetes	29%	17%	0.69
Baseline Supplemental Oxygen			
Nasal Cannula	25%	8%	0.06
Non-Rebreather Mask	50%	25%	
High-Flow Oxygen	25%	67%	
SOFA Score			
Average	2.6	2.8	0.44
Other COVID-19 Treatments			
Dexamethasone	100%	100%	N/A
Remdesivir	96%	92%	1.00
Convalescent Plasma	33%	17%	0.44
Tocilizumab	25%	58%	0.07
ASA	92%	92%	N/A

Patient Characteristics	Received Treatment (n = 24)	No Treatment (n = 12)	P Value
Therapeutic or Intermediate Dose Anticoagulation	50%	67%	0.48

Treatment Characteristics and Tolerability

All patients in both the treatment and non-treatment groups received dexamethasone as a standard-of-care COVID-19 treatment. There was no statistically significant difference between the two groups with respect to other concurrent COVID-19 treatment (low-dose aspirin, remdesivir, convalescent plasma, therapeutic or intermediate doses of anticoagulation). There was a higher proportion of patients in the non-treatment group who also received tocilizumab ($P = 0.07$).

Of the 24 COVID-19 patients who were treated with HBOT, 15 (63%) completed all 5 planned treatment sessions and 9 (38%) prematurely discontinued treatment. The reasons for discontinuation included disease progression (4), improvement in hypoxia leading to hospital discharge (3), staffing limitations (1), and anxiety (1). Six patients experienced minor adverse events in the form of ear barotrauma (1) and anxiety (6). No patients experienced seizures, pneumothoraces, arrhythmias, pulmonary edema, or hypoglycemia.

Outcomes

Of the 24 patients who were treated with at least one session of HBOT, 3 (13%) patients died during their inpatient hospitalization. In comparison, 6 (50%) of the 12 patients in the non-treatment group died during their inpatient hospitalization. There was one additional patient who required invasive mechanical ventilation (IMV) and had a prolonged hospitalization longer than 100 days. Without adjusting for differences in characteristics such as age and baseline oxygen requirements, we found a statistically significant difference in mortality between the treatment and non-treatment groups with a relative risk ratio of 0.25 ($P = 0.04$, 95% CI: 0.08 to 0.83). However, there were substantial baseline differences between the two groups. Therefore, we stratified these results by patient age and by baseline supplemental oxygen requirements.

We noted no deaths among the youngest age group (29 to 39 years) and patients on 6 liters per minute via nasal cannula. In addition, we noted that there were 3 patients in the non-treatment group who were in the oldest age category (80 to 87 years). In all other age and baseline supplemental oxygen requirements strata, there were fewer deaths in the treatment group (3 of 24) compared to the non-treatment group (6 of 12). Inpatient mortality stratified by patient characteristics is outlined in Table 2.

Table 2
Inpatient Mortality Stratified by Patient Characteristics

Patient Characteristics	Received Treatment (n = 24)	No Treatment (n = 12)
Age Strata		
29 to 39 Years Old	0 of 5 (0%)	1 of 1 (100%)
40 to 59 Years Old	0 of 10 (0%)	1 of 2 (50%)
60 to 79 Years Old	3 of 9 (33%)	3 of 6 (50%)
80 to 87 Years Old	N/A	1 of 3 (33%)
Baseline Supplemental Oxygen		
Nasal Cannula (6 Liters)	0 of 6 (0%)	0 of 1 (0%)
Non-Rebreather Mask (15 Liters)	2 of 12 (17%)	1 of 3 (33%)
High-Flow Oxygen (30 to 60 Liters)	1 of 6 (17%)	5 of 8 (63%)

When not adjusting for other factors, patients treated with HBOT had a statistically significant reduction in inpatient mortality (sub-distribution hazard ratio [HR] of 0.19 (95% Confidence Interval [CI]: 0.05–0.74, $P=0.02$; Fig. 1).

However, after controlling for patient age and baseline supplemental oxygen requirements as continuous variables, there was no statistically significant difference in inpatient mortality those treated with and without HBOT (sub-distribution HR: 0.48, 95% CI: 0.08–2.86, $P=0.42$; Fig. 2).

We also observed that there were fewer cases of progression to IMV in the treatment group. Of the 24 patients who received HBOT, 3 patients (13%) required IMV, compared to 7 out of the 12 patients (58%) in the non-treatment group. All patients who progressed to IMV had higher baseline supplemental oxygen requirements. Notably, 100% (3 of 3) of the younger patients in the age range 29 to 59 years in the non-treatment group progressed to IMV, while none (0 of 15) of the treatment group in the same age range were intubated. Fisher exact test comparison of intubation rate between the two groups did show statistical significance with $P=0.007$. We also observed that in our cohort including both treatment and non-treatment groups, mortality in intubated patients was significantly higher than mortality in non-intubated patients who required escalation beyond nasal cannula oxygen supplementation ($P<0.001$). Intubation rate stratified by patient characteristics is listed in Table 3.

Table 3
Rate of Intubation Stratified by Patient Characteristics

Patient Characteristics	Received Treatment (n = 24)	No Treatment (n = 12)
Age Strata		
29 to 39 Years Old	0 of 5 (0%)	1 of 1 (100%)
40 to 59 Years Old	0 of 10 (0%)	2 of 2 (100%)
60 to 79 Years Old	3 of 9 (33%)	3 of 6 (50%)
80 to 87 Years Old	N/A	1 of 3 (33%)
Baseline Supplemental Oxygen		
Nasal Cannula (6 Liters)	0 of 6 (0%)	0 of 1 (0%)
Non-Rebreather Mask (15 Liters)	2 of 12 (17%)	1 of 3 (33%)
High-Flow Oxygen (30 to 60 Liters)	1 of 6 (17%)	5 of 8 (63%)

Discussion

To our knowledge, this is the first study to compare mortality outcomes in patients with COVID-19 respiratory failure treated with HBOT among a cohort of patients all of whom received dexamethasone, which to date, has been the only clearly effective treatment for COVID-19.¹⁰ Previous reports have shown preliminary efficacy of HBOT in COVID-19 but many of these studies were performed earlier when steroids were not standard-of-care and early intubation was preferred. Our results showed that among hospitalized patients with COVID-19 respiratory failure, the addition of HBOT to standard-of-care therapy was associated with a decrease in rate of intubation and mortality.

One explanation for the benefits of HBOT on the improved outcome of COVID-19 patients is its beneficial effects on the respiratory system as well as on the inflammatory cascade. The SARS-CoV-2 virus induces a dysregulated immune response in the host involving a massive release of cytokines and chemokines, inflammatory cell infiltration particularly in the lung, resulting in acute lung injury and acute respiratory distress syndrome (ARDS).^{3,23} Ventilation-perfusion mismatch due to blood perfusing lung tissue with impaired or no ventilation is thought to be a major mechanism of hypoxemia in COVID-19 respiratory failure.²⁴ Coagulopathic mechanisms leading to microemboli and hemoglobin poisoning affecting its oxygen-carrying capacity may also play a role.²⁵⁻²⁷ HBOT is thought to reduce inflammatory cytokines and tissue inflammation, as seen in the treatment of radiation injuries, soft tissue wounds, infections,¹⁶⁻¹⁸ and therefore, it may also reduce inflammatory cytokines and tissue inflammation seen in COVID-19. The ability to increase the amount of dissolved oxygen in plasma at hyperbaric pressures would allow for enhanced hemoglobin-independent tissue oxygen delivery in COVID-19 hypoxemia.²⁸ In patients requiring

high rates of supplemental oxygen or fraction of inspired oxygen (FiO₂), HBOT received at the earliest possible juncture could improve tachypnea, reduce work of breathing, and ward off the inflammatory cascade progressing into multiple organ dysfunction syndrome.²⁹

Our data showed a lower mortality in the HBOT treatment group, across all age strata. After adjusting for differences in age and baseline oxygen requirements in the survival analysis between the two groups, the difference in mortality was not statistically significant. The treatment group included younger patients with likely fewer comorbidities at the time of treatment. The baseline oxygen requirements were also lower in the treatment group. The extent of COVID-19 disease at the time of hospitalization was likely more advanced in the non-treatment group, relegating this group to higher mortality regardless of HBOT.³

We noted a higher rate of tocilizumab administration in the non-treatment group. This may have been correlated with worsening clinical course of COVID-19 hypoxia in this group requiring escalation of care with an anti-inflammatory agent that was not part of the standard-of-care treatment regimen.

Practice patterns at our institution with respect to invasive mechanical ventilation (IMV) for COVID-19 hypoxia were fairly consistent during the duration of the study, and early intubation was avoided. While our analysis showed a statistically significant correlation ($P = 0.03$) between treatment with HBOT and lower rates of progression to IMV, shifts in intubation criteria, changing attitudes in patients and families towards intubation during the pandemic may have confounded this correlation. As seen in other studies conducted during the earlier months of the pandemic,^{3,4} we did note significantly higher mortality in intubated patients, irrespective of treatment with HBOT.

It is worth noting that a number of patients with higher oxygen supplementation requirements were unable to be offered HBOT treatment due to being too unstable for transport to the HBOT suite. These patients were not included in our analysis, however, this highlights the need for early identification and evaluation of patients eligible for HBOT in addition to receiving standard-of-care therapies such as steroids and antivirals.

Our study also showed that HBOT is a safe intervention similar to other reports that have been published in this realm.^{13-15, 30} Our cohort had a small number of minor adverse events from HBOT, with a single instance of ear barotrauma, confirming the safety profile that has been established over the years for HBOT in general, as well as in the case series which specifically evaluated HBOT in COVID-19 respiratory failure.^{13-15, 31}

Our study had several limitations inherent to a retrospective analysis with a small study cohort. Due to the size and non-randomized nature of the cohort, there were differences in the baseline characteristics of the compared groups limiting the statistical significance of our results. With a larger cohort, we could potentially control for the effects of other treatments (e.g., remdesivir, tocilizumab), age, and comorbidities, all of which are potential effect modifiers. In addition, this study occurred prior to the deployment of COVID-19 vaccines, therefore, mortality may decrease in general as older and high-risk

patients are vaccinated.^{19,20,32} We acknowledge that several non-randomized studies for COVID-19 treatments (convalescent plasma, antiviral and immune-modulating agents) initially showed great potential for therapeutic benefit but failed to reveal definitive results in randomized trials.^{12,33,34} HBOT may meet with the same fate but given the effect size observed in our study, further investigation is warranted.

Conclusions

This study revealed data suggestive of reduced inpatient mortality in COVID-19 patients treated with hyperbaric oxygen therapy. This data should serve as impetus for larger, multicenter prospective randomized controlled trials to study HBOT as a safe and potentially efficacious treatment to address COVID-19 hypoxic respiratory failure. Such trials should also seek to standardize HBOT characteristics such as eligibility criteria, oxygen pressure, initiation timing and duration of treatment, number of sessions, as well as logistical concerns such as isolation, disinfection, decontamination, and personal protective equipment (PPE) protocols.

Declarations

Ethics approval and consent to participate: This study was reviewed by the Institutional Review Board at our institution in accordance with the Declaration of Helsinki and was deemed exempt from ethics approval.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the study are available from the corresponding author on reasonable request.

Competing interests: None.

Funding: Not applicable.

Authors' contributions: SKW and DCL conceived and designed the study. Data collection was performed by DJ, KE, and DRD. DCL contributed significantly to the statistical analysis with DJ and DRD contributing to interpretation of data. ES provided technical and logistical expertise pertaining to treatment equipment. DJ was the primary author of the manuscript with DRD, DCL and KE providing critical revisions to the intellectual content of the manuscript. SKW as the principal investigator, provided conceptual and technical guidance for all aspects of the project. All authors have read and approved the final version of the manuscript. All methods detailed in this manuscript were carried out in accordance with relevant publishing guidelines and regulations as stated by BMC.

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Figures

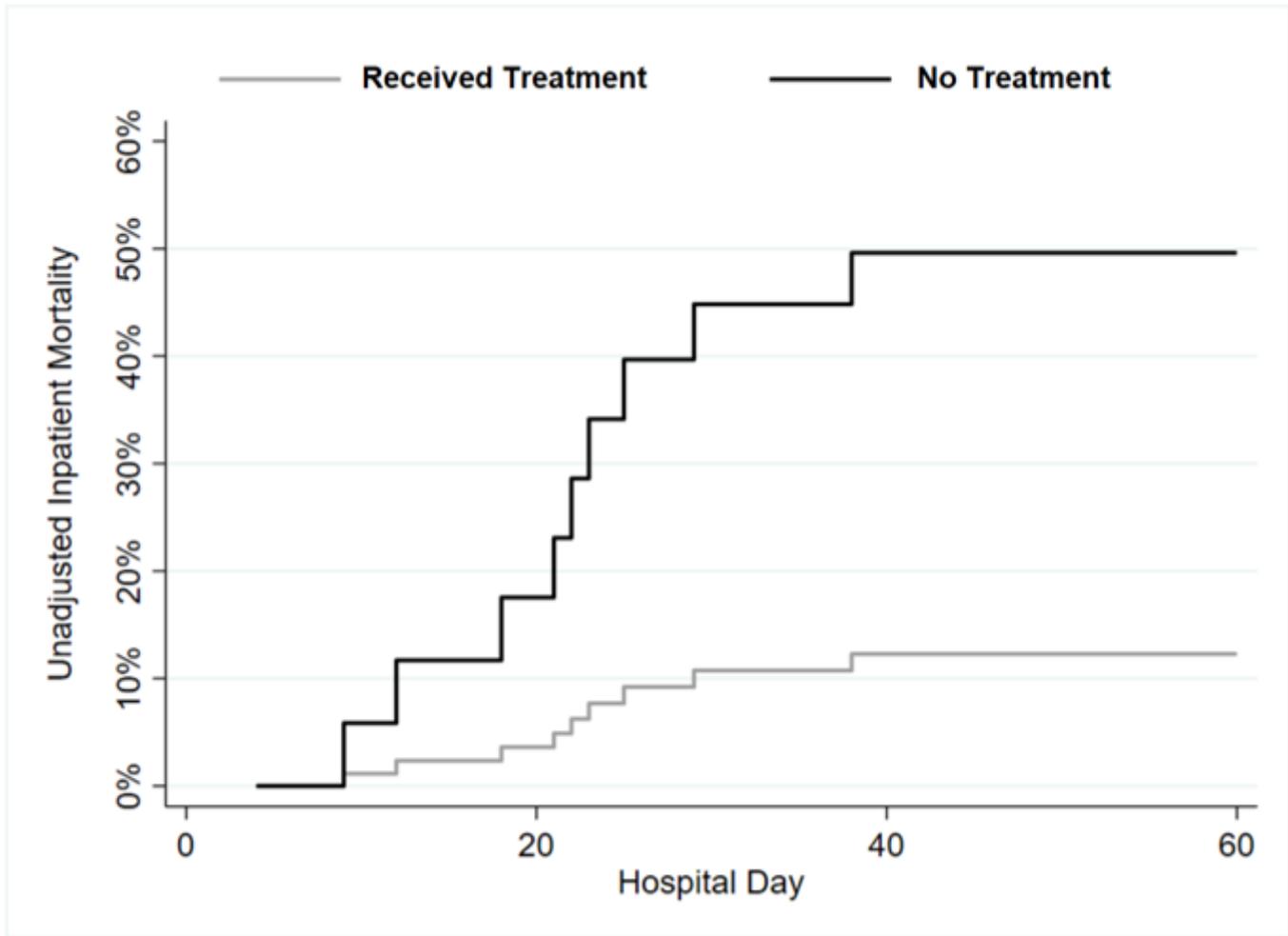


Figure 1

Unadjusted Cumulative Incidence Curves for Inpatient Mortality Among Severe COVID-19 Patients Treated versus Not Treated with Hyperbaric Oxygen Therapy

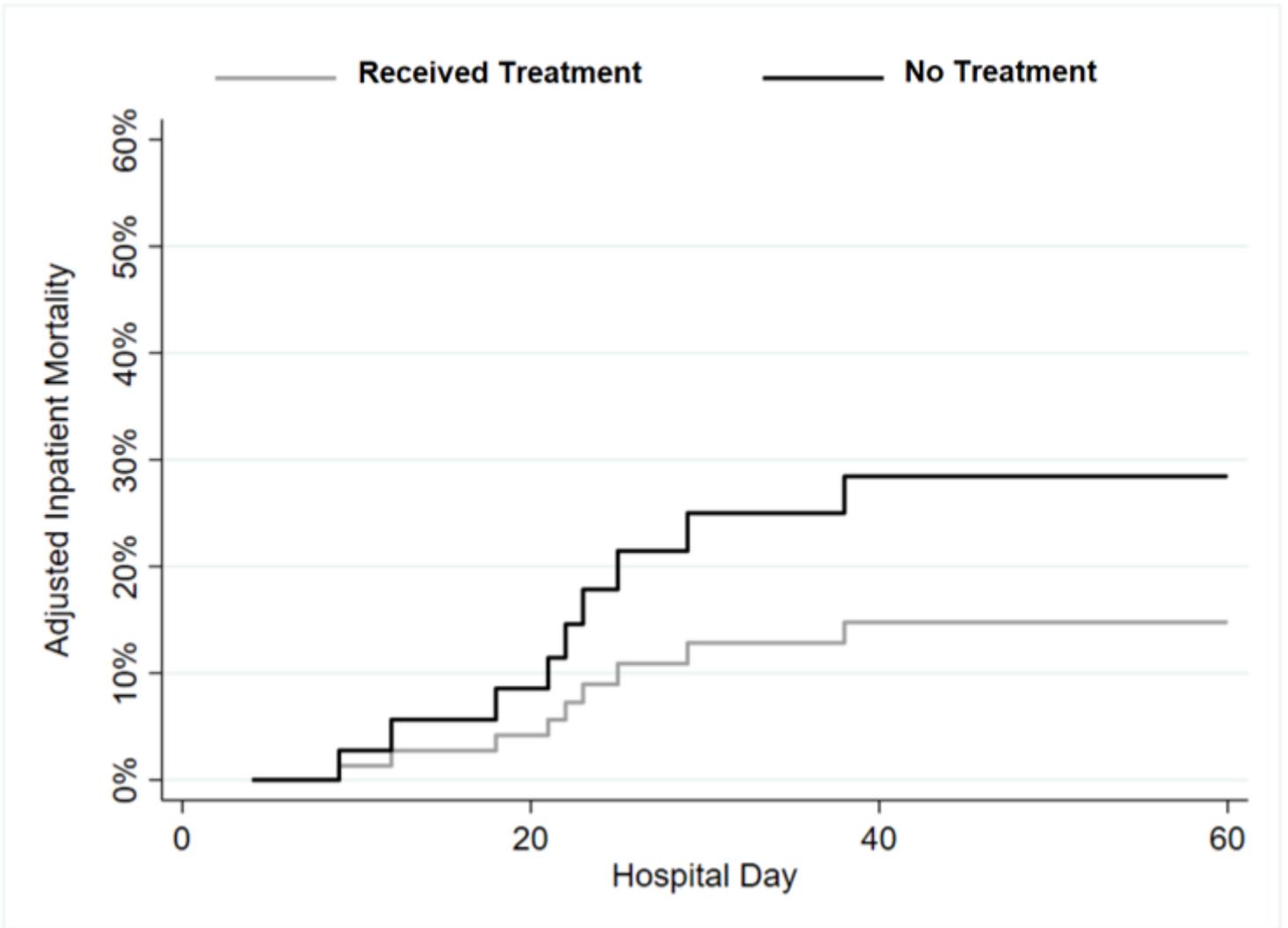


Figure 2

Adjusted Cumulative Incidence Curves for Inpatient Mortality Among Severe COVID-19 Patients Treated versus Not Treated with Hyperbaric Oxygen Therapy