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Effect of Hyperbaric Oxygen Therapy on Patients with SARS-CoV-2 Infection: A Retrospective Cohort Study

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Objective: The aim of this study was to evaluate the impact of hyperbaric oxygen therapy (HBOT) on patients with SARS-CoV-2 infection and determine its efficacy and safety in reducing treatment failure events.

Methods: A retrospective cohort study involving patients with COVID-19 was conducted. Inverse probability of treatment weighting (IPTW) was used to balance covariates between the HBOT and non-HBOT groups. The primary endpoint was the occurrence of a clinical treatment failure event, defined as all-cause mortality, abandonment of treatment, or transfer to the Intensive Care Unit due to worsening condition.

Results: A total of 720 patients with COVID-19 were enrolled in the study, with 27 patients receiving HBOT and 693 patients not receiving HBOT. The occurrence of treatment failure was significantly lower in the HBOT group compared to the non-HBOT group, with no treatment failure events in the HBOT group versus 36 events in the non-HBOT group. The IPTW database analysis results showed that in comparison to the non-HBOT group, the hazard ratio (HR) for treatment failure in the HBOT group was less than 0.001 (95% CI: <0.001 ~ <0.001, p<0.001). Lymphocyte count >0.8×10^9/L and HBOT was associated with a significantly lower risk of treatment failure. Glucocorticoid use was associated with a higher risk of treatment failure. The incidence of venous thrombosis events was significantly higher in the HBOT group compared to the non-HBOT group.

Conclusion: This study revealed that adjunctive HBOT significantly reduces the risk of treatment failure in patients with COVID-19 and is associated with satisfactory safety. HBOT shows promise as a beneficial therapy for improving outcomes in COVID-19-infected patients.

Keywords: hyperbaric oxygen therapy, COVID-19, retrospective cohort, inverse probability of treatment weighting, SARS-CoV-2 infection

Introduction

The medical treatment brought about by the novel coronavirus (SARS-CoV-2) infection is an important task. Clinical treatment is imminent to reduce the incidence of mortality from COVID-19.

At present, non-invasive oxygen inhalation methods such as nasal catheters and face masks were widely used to improve hypoxia in patients with SARS-CoV-2 infection.[1] However, hyperbaric oxygen therapy (HBOT) has advantages in improving the oxygenation of tissues. Compared with standard pressure oxygen therapy methods, HBOT increases the diffusion distance, diffusion rate, and physical dissolved amount of oxygen in the body.[2] At the same time, HBOT can

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reduce the permeability of pulmonary capillaries, thereby reducing alveolar exudation and pulmonary edema, further improving lung ventilation and ventilation function, and correcting hypoxemia.[3]

In previously published studies, HBOT has been confirmed to reduce the level of inflammatory response and cytokines,[4,5] alleviate tissue damage by reducing oxidative stress and reactive oxygen species levels,[6] enhance the immune system function, and form a superimposed and synergistic effect with antibacterial drugs to jointly exert anti-infective effects,[7] reduce the activation and aggregation of platelets in the lung and improve the microcirculation of lung tissue.[8] Previously published randomized controlled studies elaborated the therapeutic effect of hyperbaric oxygen therapy on post COVID-19 status, which refers to a range of persisting physical, neurocognitive, and neuropsychological symptoms after SARS-CoV-2 infection, for example, neurocognitive function,[9] myocardial function,[10] and brain function and structural connectivity.[11]

Published studies were supporting the use of HBOT in patients infected with SARS-CoV-2. Trials showed most of the patients recovered after receiving HBOT, and blood oxygen saturation increased after several sessions of HBOT. Of the studies, three clinical trials were trying to show the efficacy of the HBOT on patients infected with COVID-19.[12–14] The results indicated a significant effect of HBOT on patients, and it was safe and beneficial for them to breathe 100% oxygen. Although the guidelines and indication lists published by the Undersea and Hyperbaric Medicine Society (UHMS) reference several studies involving COVID-19 patients treated with HBOT,[15] none of these studies explored the effectiveness and safety of HBOT through large sample data. Meanwhile, the available literature thus far has not yielded definitive findings regarding the efficiency and safety of HBOT in treating COVID-19. The purpose of this study was to analyze the safety and efficacy of HBOT in the treatment of patients with COVID-19.

Method

Trial Design

This was a single-center retrospective cohort study. The enrolled subjects were divided into the HBOT and non-HBOT groups based on their treatment regimens.

Data Retrieve

This retrospective cohort study enrolled SARS-CoV-2 infected patients who visited Shanxi Bethune Hospital from December 2022 to February 2023. Data were collected from our hospital's Medicine Information Database. This study was conducted according to the guidelines of the Declaration of Helsinki. As retrospective research, informed consents was not obtained from patients before this study. The Research Ethics Committee of Shanxi Bethune Hospital (No. YXLL-2023-254) approved the study protocol and granted a waiver of informed consent from the participants.

Inclusion Criteria

Age 18–85;

Following the American Guidelines for COVID-19,[1] patients diagnosed with moderate, severe and critical infection. Critical illness was defined as patients on mechanical ventilation and extracorporeal mechanical oxygenation (ECMO). Critical illness included end organ dysfunction as was seen in sepsis/septic shock. Severe illness was defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen. Moderate illness was defined as a patient with a SpO_2 >94% not requiring supplemental oxygen.

Exclusion Criteria

1) Patients with incomplete data for relevant variables;
2) Suffering from severe systemic disease(s), such as hematological disorders, malignant tumor, mechanical ventilation at admission, classified as mild disease severity, chronic obstructive pulmonary disease, interstitial lung disease, occurrences of events on the same day as hospitalization and acute respiratory distress syndrome (ARDS);
3) Patients recurred in other clinical trials.

Treatment Regimens

Patients who received HBO therapy (once per day for 85 minutes at 1.6ATA, lasting for seven days) after their diagnosis of COVID-19 were selected as the study group. The control groups were comprised of patients with COVID-19 who did not undergo HBO therapy. Of the 720 patients diagnosed with COVID-19, 27 and 693 were treated with and without HBO, respectively.

The HBO Therapy Regimen for COVID-19 Includes the Following

The physician determines whether hyperbaric oxygen therapy was necessary based on the patient's condition and formulated a comprehensive treatment plan. Patients undergoing hyperbaric oxygen therapy must signed, or have their family members signed, the informed consent form for this treatment. If the patient has untreated tension pneumothorax, external ventricular drainage, skull base fracture with cerebrospinal fluid leakage, severe upper respiratory tract infection, hypertension (systolic pressure >140 mmHg, diastolic pressure >90 mmHg), or chronic obstructive pulmonary disease with CO2 retention; after weighing the potential risks and benefits, the physician would proceed with treatment while minimizing adverse factors. During compression and decompression, should any special situation arise in the chamber, the operator must immediately stabilized the pressure and await the physician's discretion to determine whether to continue or ceased compression and decompression.

The medical air compression oxygen chamber (GY2800 model, Yantai Hongyuan Oxygen Industry Co., Ltd) was employed, utilizing a face mask for oxygen inhalation. The sequence involved a 10-minute pressurization, followed by 30 minutes of oxygen inhalation, a 5-minute rest, an additional 30-minute oxygen inhalation, and a 10-minute decompression, totaling 85 minutes. The pressure parameter was set at 0.16 MPa (1.6 ATA)[16] with a 7-day treatment period.

Prior to commencing hyperbaric oxygen therapy, a thorough blood pressure and chest CT scan were required. Patients with normal blood pressure and no signs of emphysema or pulmonary bulla were eligible for hyperbaric oxygen therapy. During the therapy, groups of 10 individuals were to sit and inhale oxygen through a face mask. If a patient had hypertension (systolic pressure >140 mmHg, diastolic pressure >90 mmHg) prior to entering the chamber, hyperbaric oxygen therapy must be halted. After a rest period, therapy can resumed once the blood pressure returns to the normal range. Professional nursing staff were present during the entire hyperbaric oxygen therapy session. In the event of an emergency within the chamber, prompt symptomatic measures will be taken. If necessary, the chamber may be urgently opened for further treatment. Once the patient's condition stabilizes, hyperbaric oxygen therapy can be resumed. If treatment was interrupted due to an emergency chamber opening, the patient's treatment sessions must be increased to ensure a total of seven treatments are delivered.

The Standard Treatment Regimen for COVID-19 Includes the Following

According to the Diagnosis and Treatment Plan for COVID-19 (Trial Version 10),[17] the hospitalized patients with COVID-19 were given routine treatment depending on their individual status, including oxygen therapy, oral administration of azivudine (5mg/day) or Nirmatrelvir-Ritonavir (300mg-100mg/12h) for anti-virus therapy, and glucocorticoid therapy (dexamethasone 5–7.5 mg/day or methylprednisolone injection 40–80 mg/day) so on until hospital discharge or death.

Primary Endpoint

The primary endpoint of this study was the treatment failure defined as one of the following while in hospital:

1) All-cause of mortality;
2) Abandonment treatment: Patients or their family members perceived the treatment as ineffective, leading them to decide to discontinue hospital treatment.
3) Transferred to the Intensive Care Unit (ICU) due to a worsening of their condition.

The study endpoint was determined by the occurrence of one of the above events or the study's end date (February 28, 2023).

Statistical Analysis

Continuous variables with a normal distribution were presented using the mean and standard deviation. On the other hand, the abnormal distribution of continuous variables was introduced using the median and the interquartile range (from the first quartile, Q1, to the third quartile, Q3).

To analyze the baseline data, the Student's *t*-test and Wilcoxon rank-sum test were used for normally and abnormally distributed quantitative data, respectively. Categorical variables at baseline were analyzed using either the chi-squared test or Fisher's exact test. The propensity score was calculated based on various variables, including sex, age, smoking status, neutrophil count, lymphocyte count, oxygen saturation, D-Dimer, Interleukin-6, disease severity, hypertension, coronary heart disease, stroke, diabetes mellitus, renal dysfunction, liver dysfunction, the usage of glucocorticoids, the usage of antiviral medication, standard oxygen therapy, and the use of baricitinib. Subsequently, a propensity score analysis was conducted to generate an inverse probability of treatment weighting (IPTW) dataset. Each patient was then weighted by the inverse probability of being in the HBOT group compared to the non-HBOT group to balance the observable characteristics between the two groups.

A multivariate Cox regression was performed as the primary analysis to assess the association between treatment failure and the two treatment groups. Sensitivity analysis was conducted using the IPTW dataset.

The result of the primary endpoint was reported as adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) to quantify the associations. All hypothesis tests were two-sided, and statistical significance was considered at p-values less than 0.05. All p-values besides tested on primary endpoint were nominal p-values and should not be used on statistical inference. Stata SE 13 (Serial number 401306302851), R software version 4.2.0 (http://cran.r-project.org), and easy-R (www.empowerstats.com) were used for statistical analysis.

Result

Between December 2022 and February 2023, a total of 1,765 SARS-CoV-2 infected patients were hospitalized. After excluding 1,045 patients, 720 participants were enrolled (Figure 1). Analyses were performed on the non-HBOT group (n= 693) and HBOT group (n= 27).

General Characteristics of All Participants at Baseline

Table 1 presented the general characteristics of all participants, comparing the non-HBOT and HBOT groups. Significant differences were observed in oxygen saturation, D-dimer levels, stroke, glucocorticoid use, and antiviral therapy. The mean oxygen saturation was significantly lower in the HBOT group (0.90, SD 0.08) compared to the non-HBOT group (0.93, SD 0.05), with a p-value of 0.007. The median D-dimer level was significantly higher in the HBOT group (482, IQR 285–811) compared to the non-HBOT group (280, IQR 156–525), with a p-value of 0.017. The prevalence of stroke was significantly higher in the HBOT group (37.0%) compared to the non-HBOT group (18.0%), with a p-value of 0.013. Glucocorticoid use was significantly higher in the non-HBOT group (88.9%) compared to the HBOT group (70.4%), with a p-value of 0.021. Antiviral therapy use was significantly higher in the non-HBOT group (63.2%) compared to the HBOT group (25.9%), with a p-value of less than 0.001.

Other variables such as sex, age, smoking status, neutrophil count, lymphocyte count, interleukin-6 levels, disease severity, hypertension, CHD, diabetes mellitus, renal dysfunction, liver dysfunction, and standard oxygen therapy did not show significant differences between the groups.

Analysis on the Primary Endpoint

Table 2 presented the failure events among the subjects, comparing the non-HBOT and HBOT groups. There were no treatment failure in the HBOT group, while there were 36 events (5.19%) in the non-HBOT group. This difference was not statistically significant (p=0.391). Specifically, the non-HBOT group experienced 8 deaths (1.15%) and 28 cases of abandonment treatment (4.04%), with no such events in the HBOT group.

Table 3 presented the results of univariate and multivariate Cox regression analyses on the primary endpoint.

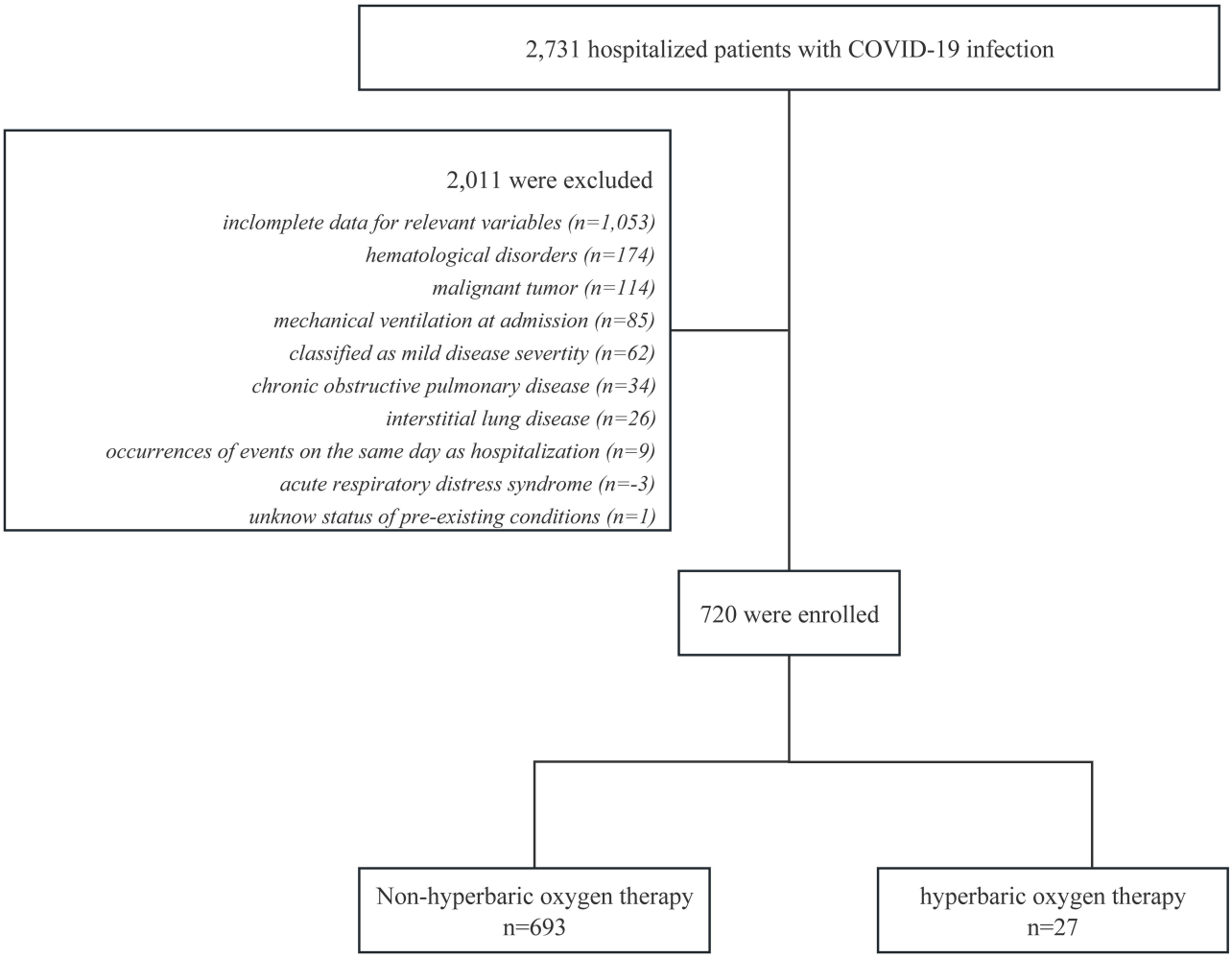

Figure 1 Flowchart of the study design, matching criteria, and allocation of the study subjects.
Abbreviation: HBOT, hyperbaric oxygen therapy.

Univariate and Multivariate Analysis

In the univariate analysis, significant associations were found for age above 80, neutrophil count >7×10^9/L, lymphocyte count >0.8×10^9/L, oxygen saturation >93%, D-dimer >1500 ng/mL, interleukin-6 >8 pg/mL, disease severity, renal dysfunction, and liver dysfunction. Age above 80 (HR 5.07, 95% CI 2.21–11.62, p<0.001), neutrophil count >7×10^9/L (HR 4.59, 95% CI 2.36–8.93, p<0.001), D-dimer >1500 ng/mL (HR 2.34, 95% CI 1.06–5.16, p=0.036), interleukin-6 >8 pg/mL (HR 9.68, 95% CI 2.97–31.62, p<0.001), severe disease (HR 4.70, 95% CI 1.10–20.10, p=0.037), critical disease (HR 37.14, 95% CI 8.33–165.65, p<0.001), renal dysfunction (HR 3.20, 95% CI 1.44–7.12, p=0.004), and liver dysfunction (HR 2.47, 95% CI 1.12–5.44, p=0.025) were associated with a higher risk of treatment failure. Lymphocyte count >0.8×10^9/L (HR 0.44, 95% CI 0.22–0.89, p=0.023) and oxygen saturation >93% (HR 0.49, 95% CI 0.25–0.95, p=0.034) were associated with a lower risk of treatment failure.

Multivariate Analysis

In the multivariate analysis, age above 80 remained significantly associated with a higher risk of treatment failure (HR 2.55, 95% CI 1.01–6.40, p=0.046). Interleukin-6 >8 pg/mL remained significantly associated with a higher risk of treatment failure (HR 6.09, 95% CI 1.80–20.66, p=0.004). Critical disease severity remained significantly associated with a higher risk of treatment failure (HR 8.91, 95% CI 1.77–44.93, p=0.008). In comparison to the non-HBOT group, the HBOT group was related to a lower HR (3.77 e $^{(-20)}$, p<0.001).

Table 1 General Characteristics of All Participants at Baseline

		Non-HBOT (n=693)	HBOT (n=27)	Statistics	p-value
Sex, n (%)	Male	399 (57.6)	16 (59.3)	χ^2= 0.03	0.862
Age	Mean (SD)	73.2 (13.4)	68.3 (12.6)	t= 1.85	0.065
Smoking, n (%)	No	542 (78.2)	21 (77.8)		0.857*
	Yes	144 (20.8)	6 (22.2)		
	Unreported	7 (1.0)	0 (0.0)		
Neutrophil (10^9/L)	Median (IQR)	4.6 (3.2–6.7)	4.8 (4.1–7.4)	z= −1.13	0.259
Lymphocyte (10^9/L)	Median (IQR)	0.8 (0.5–1.3)	0.8 (0.5–1.4)	z= −0.16	0.875
Oxygen saturation	Mean (SD)	0.93 (0.05)	0.90 (0.08)	t= 2.70	0.007
D-Dimer (ng/mL)	Median (IQR)	280 (156–525)	482 (285–811)	z= −2.40	0.017
Interleukin-6 (pg/mL)	Median (IQR)	8.7 (3.2–36.5)	6.4 (1.6–42.6)	z=0.62	0.535
Diseases Severity, n (%)	Moderate	234 (33.8)	9 (33.3)		1.000*
	Severe	430 (62.0)	17 (63.0)		
	Critical	29 (4.2)	1 (3.7)		
Hypertension, n (%)		257 (37.1)	11 (40.7)	χ^2=0.15	0.700
CHD, n (%)		58 (8.4)	1 (3.7)		0.717*
Stroke, n (%)		125 (18.0)	10 (37.0)	χ^2=6.16	0.013
Diabetes Mellitus, n (%)	No	483 (69.7)	22 (81.5)		0.309*
	Yes	209 (30.2)	5 (18.5)		
	Unreported	1 (0.1)	0 (0.0)		
Renal dysfunction, n (%)	No	648 (93.5)	26 (96.3)		1.000*
	Yes	44 (6.3)	1 (3.7)		
	Unreported	1 (0.1)	0 (0.0)		
Liver dysfunction, n (%)	No	611 (88.2)	25 (92.6)		0.768*
	Yes	81 (11.7)	2 (7.4)		
	Unreported	1 (0.1)	0 (0.0)		
Glucocorticoids, n (%)	No	76 (11.0)	8 (29.6)		0.021*
	Yes	616 (88.9)	19 (70.4)		
	Unreported	1 (0.1)	0 (0.0)		
Antiviral therapy, n (%)		438 (63.2)	7 (25.9)	χ^2=15.30	<0.001
Standard Oxygen therapy, n (%)		637 (91.9)	24 (88.9)		0.479*
Baricitinib, n (%)		128 (18.5)	2 (7.4)		0.201*

Abbreviations: CHD, coronary heart disease; DM, diabetes mellitus; HBOT, hyperbaric oxygen therapy; *Fisher exact test.

Table 2 Failure Events Among Subjects

	Non-HBOT (n=693)	HBOT (n=27)	p-value
Primary Endpoint	36 (5.19%)	0 (0.00%)	0.391*
Death	8 (1.15%)	0 (0.00%)	
Abandonment treatment	28 (4.04%)	0 (0.00%)	
Transferred to the intensive care unit (ICU)	0 (0.00%)	0 (0.00%)	

Abbreviation: HBO, hyperbaric oxygen therapy; * Fisher exact test.

Table 3 Univariate and Multivariate Cox Regression on the Primary Endpoint

		Univariate Analysis			Multivariate Analysis	
		Number	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (female)		305 (42.36%)	0.52 (0.25, 1.08)	0.082	0.98 (0.45, 2.15)	0.970
Age (above 80)		282 (39.17%)	5.07 (2.21, 11.62)	0.000	2.55 (1.01, 6.40)	0.046
Smoking (no as ref.)	Yes	150 (20.83%)	1.76 (0.87, 3.59)	0.118		
	Unreported	7 (0.97%)	0.00 (0.00, Inf) 0	0.997		
Neutrophil > 7×10^9/L		164 (22.78%)	4.59 (2.36, 8.93)	<0.001	2.01 (0.93, 4.36)	0.077
Lymphocyte > 0.8×10^9/L		373 (51.81%)	0.44 (0.22, 0.89)	0.023	1.30 (0.56, 2.98)	0.540
Oxygen saturation > 93%		459 (63.75%)	0.49 (0.25, 0.95)	0.034	1.02 (0.50, 2.07)	0.960
D-dimer >1500 (ng/mL)		73 (10.14%)	2.34 (1.06, 5.16)	0.036	1.81 (0.78, 4.22)	0.168
Interleukin-6 >8 (pg/mL)		375 (52.08%)	9.68 (2.97, 31.62)	0.000	6.09 (1.80,20.66)	0.004
Diseases severity (moderate as ref.)	Severe	447 (62.08%)	4.70 (1.10, 20.10)	0.037	2.22 (0.49,10.14)	0.303
	Critical	30 (4.17%)	37.14 (8.33, 165.65)	<0.001	8.91 (1.77,44.93)	0.008
Hypertension		268 (37.22%)	1.73 (0.90, 3.33)	0.1		
CHD		59 (8.19%)	0.40 (0.05, 2.90)	0.361		
Stroke		135 (18.75%)	1.16 (0.53, 2.54)	0.715		
DM (no as ref.)	Yes	214 (29.72%)	0.92 (0.44, 1.90)	0.815		
	Unreported	1 (0.14%)	0.00 (0.00, Inf) 0	0.998		
Renal dysfunction (no as ref.)	Yes	45 (6.25%)	3.20 (1.44, 7.12)	0.004	1.40 (0.58, 3.37)	0.454
	Unreported	1 (0.14%)	0.00 (0.00, Inf 0)	0.997	4.88 e $^{(-20)}$	
Liver dysfunction (no as ref.)	Yes	83 (11.53%)	2.47 (1.12, 5.44)	0.025	1.62 (0.68, 3.87)	0.273
	Unreported	1 (0.14%)	0.00 (0.00, Inf 0)	0.997	1.57 e $^{(-18)}$	
Glucocorticoids (no as ref.)	Yes	635 (88.19%)	inf. (0.00, Inf 0)	0.997	5.14 e $^{(15)}$	0.002
	Unreported	1 (0.14%)	1.00 (0.00, Inf 1)	0.000		
Anti-virus therapy		445 (61.81%)	0.89 (0.46, 1.74)	0.738		

(*Continued*)

Table 3 (Continued).

		Univariate Analysis			Multivariate Analysis	
		Number	HR (95% CI)	P-value	HR (95% CI)	P-value
Oxygen therapy		661 (91.81%)	inf. (0.00, Inf 0)	0.997		
Baricitinib		130 (18.06%)	1.77 (0.88, 3.54)	0.109		
HBOT		27 (3.75%)	0.00 (0.00, Inf 0)	0.996	3.77 e $^{(-20)}$	<0.001

Abbreviations: CHD, coronary heart disease; DM, diabetes mellitus; HBOT, hyperbaric oxygen therapy; ref.: reference; HR: hazard ratio; CI: confidence interval; e: Euler's number.

Sensitivity Analysis on the IPTW Dataset

Analysis based on the IPTW dataset showed that HBOT was associated with a significantly lower risk (HR <0.001, 95% CI 0.000–0.000, p<0.001). For further information, please check sTables 1 and 2.

Adverse Events

The incidence of venous thrombosis events was significantly higher in the HBOT group (22.22%) compared to the non-HBOT group (6.98%), with a p-value of 0.003. The incidence of lower limb thrombosis was significantly higher in the HBOT group (18.52%) compared to the non-HBOT group (5.56%), with a p-value of 0.006. The incidence of bacterial infections was significantly higher in the HBOT group (18.52%) compared to the non-HBOT group (3.02%), with a p-value of less than 0.001. Other adverse events, including cardiovascular events, cardiovascular death, myocardial infarction, stroke, pulmonary embolism, thrombosis in other locations, secondary infections, fungal infections, influenza virus infections, and mycoplasma or chlamydia infections, did not show significant differences between the groups (sTable 3).

Discussion

Drawing from the insights of pathological anatomy, COVID-19 manifested primary pathological abnormalities through alveolar inflammation and excessive mucilaginous secretion.[18] Respiratory impairment in individuals affected by COVID-19-infected patients was predominantly typified by alveolar ventilation dysfunction, culminating in pronounced hypoxemia.[19–21] It was widely believed that the underlying mechanism of tissue damage subsequent to COVID-19 potentially involved exaggerated inflammatory immune responses,[22,23] oxidative stress-induced damage,[24,25] and consequential injury stemming from hypoxemia.[26] Rapidly attending to the subsequent multiple organ injuries and dysfunctions triggered by hypoxia was a pivotal step toward enhancing patient prognosis.

According to the guidelines for COVID-19, cases classified as moderate to severe were recommended to undergo standardized prone position trans nasal high-flow oxygen therapy to enhance oxygenation.[27] Citing published research,[13,28,29] HBOT had demonstrated its promising potential in alleviating hypoxia among patients afflicted with COVID-19-related oxygen deficiency and forestalling the progression of hypoxia-induced deterioration. HBOT constituted a medical intervention wherein the patient inhales pure oxygen under increased pressure, effectively transitioning them from a hypoxic to an oxygen-rich condition. Administering oxygen at 3ATA (atmospheres absolute) can escalated the concentration of physically dissolved oxygen in bodily fluids by a factor of twenty.[3] Up to now, the existing literature had not reached a clear conclusion about the efficiency of HBOT in the treatment of COVID-19. There was limited knowledge and evidence regarding the effects of HBOT in the settings of COVID-19.

The multivariate COX regression analysis showed that HBOT was related to reduce the incidence of treatment failure. This study highlighted the significant impact of HBOT in reducing treatment failure events, which independently influenced the treatment outcomes for COVID-19-infected patients. Our study revealed that none of the twenty-seven subjects who underwent HBOT experienced death or abandonment treatment. This result suggests that HBOT treatment may reduce mortality risk in COVID-19 patients, aligning with findings reported by Gorenstein SA et al.[13] Our study posited that HBOT held the capacity to curtail the occurrence of treatment failures in notably COVID-19-infected patients. Previous publications[8,29,30] had proposed the HBOT hypothesis as a secure and efficacious treatment option and postulating potential underlying mechanisms.

Concurrently, case series from China and the United States had been published, suggesting that HBOT could represented a safe and advantageous modality for individuals afflicted by COVID-19.[13,28,31] We posited that HBOT rapidly augmented the partial pressure of alveolar oxygen within a concise timeframe, significantly amplifying the rate of oxygen diffusion. This, in turn, promptly diminished or rectified severe hypoxia. Moreover, HBOT can ameliorate the permeability of pulmonary capillaries, curtail exudation, and minimize the extent of pulmonary edema. Consequently, it mitigated the emergence of respiratory-related complications and reduced the incidence of treatment failure.[32] HBOT benefited patients by intensifying the oxygen pressure in the alveoli. Consequently, the diffusion rate and the diffusion instance of oxygen would increase compared to standard oxygen therapy (eg, face mask, invasive ventilation, non-invasive ventilation, nasal cannula, and ECMO).[33] HBOT provided tissue perfusion exchange capacity due to the increased diffusion instance of oxygen, distinguishing HBOT from all other oxygen therapy methods. Patients treated with HBOT showed improvements in their clinical factors and indexes as follows: arterial blood gas analysis, liver function tests, complete blood count and improvement of lung structure clearance based on computed tomography (CT-scan).[33]

The COX regression analysis results for the primary endpoint events also showed that after adjusting for confounding factors, age above 80, interleukin-6 >8 pg/mL and critical disease severity were risk factors for treatment failure. Existing research has identified that advanced age was a significant independent predictor of mortality in patients infected with SARS-CoV-2,[34] and that advanced age was associated with mortality in COVID-19 patients.[35] Our study also found that older patients were prone to treatment failure. A plethora of inflammatory mediators (interleukin-6) caused damage to alveolar epithelial and vascular endothelial cells, alterations in vascular permeability, and copious protein effusion within the alveoli, leading to alveolar edema and disruption of the alveolar architecture. Concurrently, damage to the pulmonary capillary mucosal epithelial cells resulted in diminished pulmonary surfactant, reduced lung compliance, decreased vital capacity, and impaired pulmonary ventilation.[36,37] This led to the emergence of treatment failure. Patients diagnosed with critical infection have underlying chronic illnesses, often developed multi-organ complications, and faced a high risk of mortality,[21] making them more likely to lead the primary endpoint events.

Our investigation also revealed that the lower lymphocyte count at baseline was an independent factor significantly contributing to good outcomes among individuals with COVID-19. Meanwhile, the administration of glucocorticoids was associated with a higher risk of treatment failure. Numerous clinical studies indicated that commencing treatment either excessively early, in the absence of severe symptoms, or excessively late, in patients with multi-organ failure, yields no benefit and may lead to unfavorable outcomes.[38] A comprehensive meta-analysis involving over 20,000 COVID-19-infected patients demonstrated that the overall mortality rate was higher among glucocorticoids administered than those not.[39] Current guidelines recommend glucocorticoids as a treatment for patients with COVID-19.[27,40] However, our study had challenged this treatment option, as we believed that glucocorticoids could be a double-edged sword in the context of COVID-19 treatment. Prior to their use, it was crucial to weigh the potential benefits and drawbacks carefully. Moreover, active evaluation of the patient's imaging manifestations and oxygenation status after glucocorticoid administration, continuous monitoring of adverse reactions, and the provision of timely and targeted treatment were essential components of a comprehensive approach.

We analyzed adverse event rates in the overall population. In line with these previous studies, our investigation unearthed no severe complications among patients subjected to HBOT, thus affirming its safety in managing COVID-19 cases. Meanwhile, our findings indicated that, compared to the non-HBOT group, the HBOT group had a higher incidence of lower limb thrombosis and secondary infections. We speculated that HBOT required patients to maintain position (sitting or lying) for 1 hour per day during the treatment period, which may increase the risk of lower limb thrombosis. This clinical finding may imply that monitoring of lower limb extremity vascular ultrasound and coagulation function was necessary during the period of HBOT. Besides, the sample size should be expanded for further exploration.

As a retrospective cohort analysis, our study did acknowledge certain limitations. Firstly, all the data were sourced exclusively from our hospital's HIS database. This approach led to the absence of certain variables, necessitating their imputation as unreported, potentially introducing a selection bias despite the fact that employing the IPTW analysis to address this concern, it was essential to note that balancing such unreported variables might not be entirely achievable. Secondly, the small sample size in the HBOT group was a constraint that could curtail the generalizability of the study's results. While our research effectively addressed the primary endpoint pertaining to validating HBOT's role in COVID-19-infected patients, it was prudent to acknowledged that establishing the clinical efficacy of HBOT across a wider

spectrum of patients with COVID-19 might demand more than just statistical power. In order to fortify the conclusions regarding the effectiveness of HBOT in treating COVID-19 in a broader context, future investigations should encompassed more extensive sample sizes and a more diverse range of patient groups.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement and Consent to Participate

This study was performed according to the Helsinki Declaration. The Research Ethics Committee of Shanxi Bethune Hospital (No. YXLL-2023-254) approved the study protocol and granted a waiver of informed consent from the participants. Confidentiality and anonymity were guaranteed.

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Disclosure

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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