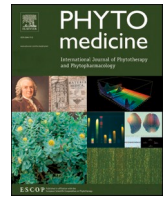




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Original Article

The effect of *Huashibaidu* formula on the blood oxygen saturation status of severe COVID-19: A retrospective cohort study

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ABSTRACT

Background: *Huashibaidu* Formula (HSBD) for the COVID-19 treatment has been supported by the China's *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*. However, it is not clear whether HSBD can improve blood oxygen saturation and when it should be used with conventional therapies.

Purpose: To access the effect of HSBD combined with conventional treatment on blood oxygen saturation of COVID-19 patients.

Methods: A single-center retrospective cohort study was conducted to collect the confirmed severe COVID-19 patients' information, treated by the National Traditional Chinese Medicine Medical Team at the Jinyintan hospital between January 24 and March 31, 2020. According to whether HSBD was used during hospitalization, participants were separated into the conventional treatment group and the HSBD group (HSBD and conventional treatment). The primary observation indicators included the time for relieving blood oxygen saturation and the improvement ratio of blood oxygen saturation in each group.

Results: Of 111 patients with severe COVID-19, 53.2% (59/111) received HSBD, and 46.8% (52/111) only received conventional treatment, respectively. No statistically significant difference was found in image, clinical symptoms, and past medical history between the two groups ($p > 0.05$). Notably, the median time for relieving blood oxygen saturation in the conventional treatment group was 11 days (IQR, 8–14.25), while that in the HSBD group was only 6 days (IQR, 3.25–10.75), which was significantly shortened by 4.09 days (95%CI, 2.07–6.13; $p = 0.0001$), compared with the conventional treatment group. After repeated measurement design analysis, the main effect within times ($p < 0.001$) and the main effect were significantly different under the oxygen saturation dimension between two groups ($p = 0.004$). However, time and group interaction were observed no significant difference ($p = 0.094$). After 14 days of treatment, the improvement ratio of the HSBD group over the conventional treatment group was 1.20 (95%CI, 0.89–1.61).

Conclusion: For severe COVID-19 patients, the HSBD has a tendency to shorten the time for relieving blood oxygen saturation. After taking a course of HSBD, the effect can be more obvious.

Introduction

The coronavirus disease 2019 (COVID-19) as an acute respiratory infection has become a major global public health event (Lai et al., 2020; Richardson et al., 2020). COVID-19 is a mild infection with dry cough

and malaise as primary symptoms (Huang et al., 2020) and it also has a good overall outcome (The Novel Coronavirus Pneumonia Emergency Response Epidemiology, 2020). However, severe patients may rapidly progress to acute respiratory distress syndrome (Chen et al., 2020), sepsis, acid-base imbalance, disturbance of blood coagulation, and

Abbreviations: ACE2, angiotensin I converting enzyme 2; COVID-19, coronavirus disease 2019; HSBD, *Huashibaidu* Formula; IQR, Interquartile Range; IL-6, Interleukin-6; NHC, National Health Commission.

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multi-organ failure (Wang et al., 2020c; Zhou et al., 2020) in one week after onset, previous study exemplified a mortality rate of approximately 25.7% in COVID-19 patients admitted to hospitals in United Kingdom (Horby et al., 2021). Unlike non-severe cases, Patients with severe COVID-19 mainly present with long hospital stays and high mortality rates. Dramatically, finger oxygen saturation less than 93% on air inhalation rest is a diagnostic criterion for severe COVID-19. Therefore, identifying effective treatments to relieve the oxygen saturation of patients is specifically significant for treating severe COVID-19 infections.

Although no specific drug for COVID-19, the pandemic has been well contained in China. Traditional Chinese Medicine (TCM) represented by the "3-drugs-3-formulas" has played a crucial role in controlling the epidemic. As one of the representatives of "3-drugs-3-formulas", HSB is a standard treatment for COVID-19 adopted by the National Traditional Chinese Medicine Medical Team at the Wuhan Jinyintan hospital. Previous studies found that it remarkably shortened the median duration of nucleic acid shedding and hospital stay of severe COVID-19 patients, improved clinical symptoms, and promoted the improvement of physical and chemical inspection indicators and pulmonary CT images (Shi et al., 2021; Wang et al., 2020b, 2021). HSB was approved by the National Medical Products Administration for marketing in China on March 2, 2021, confirming a full recognition of the clinical efficacy of TCM in containing the outbreak. On April 15, 2021, the National Health Commission (NHC) and the National Administration of Traditional Chinese Medicine of China jointly released the HSB as a therapeutic drug for severe COVID-19 in the "DTP for COVID-19 (Trial Version 8)". Although the mortality rate of severe COVID-19 varied across studies, ranging from 8.0 to 61.5%, it usually increases significantly among elderly patients who had severe pneumonia, compared with other age groups (Asselah et al., 2021; Bhatraju et al., 2020; Menzella et al., 2020; Wang et al., 2020a; Yang et al., 2020). Besides, oxygen saturation status is one of the most vital signs in COVID-19 patients, which directly affects the patients' prognosis. HSB could reduce the mortality of severe COVID-19 patients (Yang et al., 2020). Nonetheless, it remains unclear whether HSB can improve blood oxygen saturation and when it should be used with conventional therapies. Therefore, we conducted a retrospective cohort study to access the impact of the HSB on the oxygen saturation status of severe COVID-19 infections.

Methods

Subjects

Between January 24, 2020, and March 31, 2020, data were retrospectively collected from severe COVID-19 patients treated by the National Chinese Medical Team at Jinyintan hospital. Inclusion criteria: (1) Meeting the diagnostic criteria of severe COVID-19; (2) 18–95 years old; (3) Those with complete follow-up information. Exclusion criteria: (1) Incomplete clinical data; (2) Those with additional severe acute and chronic diseases significantly affecting the treatment and prognosis, including severe heart attack and cerebral infarction, liver and kidney insufficiency, and psychiatric diseases.

Study design: a single-center, retrospective cohort research

Data collection: We retrospectively collected data including demographic characteristics, epidemiological information, past medical history, clinical symptoms, and laboratory findings including local arterial oxygen pressure, oxygen saturation, complete blood count (leukocyte, lymphocyte, monocyte count, eosinophil count, neutrophil, lymphocyte ratio, hemoglobin level, and platelet count), serum biochemical tests (liver and renal function and lactate dehydrogenase), and coagulation indices.

Additionally, we carefully evaluated the patient's hospital history, including cardiovascular diseases, gastrointestinal diseases, endocrine diseases, malignancies, neurological diseases, and respiratory diseases.

Vital signs included body temperature, respiratory rate, heart rate, and blood pressure. Clinical symptoms included fever, chest pain, palpitations, dyspnea, cough, wheezing, fatigue, dry mouth, nausea and vomiting, diarrhea, anorexia, and medication. Medication included antivirals, antibiotics, immune intervention, and hormone usage.

The criteria for the timing of oxygen therapy were used to train doctors according to the *DTP for COVID-19*. Additionally, the physicians came from the same ward. Moreover, the instruments to test blood oxygen saturation were uniform.

All data information is obtained from the hospital inpatient medical record data information system and the laboratory test results database system, and reviewed by two physicians. If problems arise during the data verification, the information center would immediately be contacted for data source verification. This ensures the accuracy and completeness of data.

Definition

Severe COVID-19: according to the *DTP for COVID-19* (Trial Version 7) issued by the NHC of the People's Republic of China, severe cases should meet any of the following criteria: 1) shortness of breath, respiratory rate ≥ 30 beats/min; 2) during resting-state, oxygen saturation without oxygen uptake $\leq 93\%$; 3) arterial partial pressure of oxygen (PaO₂)/oxygen concentration ≤ 300 mmHg (1 mmHg = 0.133 kPa); 4) worsening progressive of clinical symptoms, lung imaging findings showed rapid progress $> 50\%$ during the past 24–48 h.

Oxygen saturation status by 6-point method (Wang et al., 2020d): 5 points - necessary to invasive ventilator; 4 points - necessary to high-flow humidified oxygen/high-frequency oxygen/non-invasive ventilator; 3 points - necessary to high-flow mask (> 5 l); 2 points - necessary to low-flow (1–5 l) mask/nasal cannula oxygen; 1 point-oxygen saturation above 93% without oxygen intaking; 0 points - discharge.

Time for relieving blood oxygen saturation (Wang et al., 2020d): The duration to decrease the oxygen saturation status score by 2 or more points.

The improvement ratio between groups: Group A to group B:

$$A|B = \frac{\frac{\text{Number of patients who improved in Group A}}{\text{Total number of people in Group A}}}{\frac{\text{Number of patients who improved in Group B}}{\text{Total number of people in Group B}}}$$

$$= \frac{\text{Improvement rate in Group A}}{\text{Improvement rate in Group B}}$$

Treatment and outcome measures

In the present study, the use of HSB was defined as receiving this medication for no less than six days during the hospitalization. HSB comprises 14 herbs of Chinese medicine, including Raw *ephra*, *Agastache*, Raw *gymsum*, Almond, *Rhizoma Pinellinae Praeparata*, *Magnolia Officinalis*, *Rhizoma atractylodis*, *Amomum tsao-ko*, *Poria cocos*, *Radix Astragali*, *Radix Paeoniae Rubra*, *lepidium* seed, rhubarb, and Licorice. Two or four formula a day, orally or by nasal feeding, at least 14 days for one course. We separated the patients into two groups according to the treatment they received: one group receiving HSB (HSB and conventional treatment group) and the other only receiving conventional treatment group.

Treatment regimens. (1) Conventional treatment group: medicines of conventional treatment were, according to *DTP for COVID-19* (Trial Version 7), except for using HSB, the use of antibiotics, antiviral drugs, hormones, other proprietary Chinese medicine preparations were all acceptable; (2) HSB group: The treatment method combining HSB with conventional treatment.

The outcome measures included the time for relieving blood oxygen saturation, blood oxygen saturation trend over time, and the improvement ratio between groups after 14 days of treatment (a course of

Chinese medicine).

Statistical analysis

Categorical variables were described as frequencies (percentage); Continuous variables were described as mean(SD) or median (IQR), based on whether they conformed to a normal distribution. Means for continuous variables were compared in groups using the *t*-test (normal distribution) or Wilcoxon rank-sum test (not normal distribution). Moreover, categorical variables were compared using the χ^2 test, when the data were limited the Fisher exact test was used. A repeated-measures design was used to count the status of oxygen saturation over the course of treatment. The data were analyzed by using the R software (3.6.2), invoking the ggplot2 package to graph the violin plots and the fit plots of locally estimated scatterplot smoothing (LOESS) regression. The test level α was 0.05, and the result was statistically significant when the *p*-value was less than 0.05.

Results

Study participants

307 cases were enrolled totally in the present study, 196 non-severe including mild and moderate cases were excluded. 111 cases were included in our analysis, of which 52 cases in the conventional treatment group, and 59 cases in the HSBD group. The mean age was 61.81 years, respectively 61.29 years in the conventional treatment group and 62.27 years in the HSBD group. A total of 22 women were in the conventional treatment group while 14 were in the HSBD group. The past medical history was dominated by cardiovascular diseases (44.1%). No statistically significant difference was noted in age and past medical history between the two groups ($p > 0.05$). In terms of clinical symptoms, fever (27.9%), cough (60.0%), and shortness of breath (34.2%) were predominant, whereas, there was no statistical difference between the two groups ($p > 0.05$). In the baseline oxygen saturation status score, no statistical difference was also observed between the two groups ($p > 0.05$) (Table 1).

Time for relieving blood oxygen saturation

Among 111 patients, the time for relieving blood oxygen saturation was 11 days (IQR, 8–14.25) in the conventional treatment group and 6 days (IQR, 3.25–10.75) in the HSBD group. The time for relieving blood oxygen saturation was 4.09 days reduced in the HSBD group (95%CI, 2.07–6.13; $p = 0.0001$), which was statistically significant (Fig. 1).

Blood oxygen saturation trend over time and the improvement ratio between groups

In severe patients, after repeated measurements, the main effect within times ($p < 0.001$) and the main effect between the two groups ($p = 0.004$) were significantly different under the oxygen saturation dimension. However, time and group interaction were no significant difference ($p = 0.094$) (Fig. 2). After one course of medication (14 days), the improvement ratio was 1.20 (95%CI, 0.89–1.61) in the HSBD over the Conventional treatment group (Fig. 3).

Treatment regimens and outcomes

Regarding medication, 23 (39.0%) and 40 (78.4%) patients used antivirals in the HSBD group and the conventional treatment group respectively ($p < 0.001$). A total of 33 (55.9%) and 46 (90.2%) patients used antibiotics in the HSBD group and the conventional treatment group, respectively ($p < 0.001$). Additionally, 111 patients were discharged from the hospital and no critically ill cases were reported during hospitalization.

Table 1

Characteristics between the two groups of severe patients.

	Total (n = 111)	Conventional treatment group (n = 52)	Huashibaidu group (n = 59)	<i>p</i>
Gender(Female, No., %)	36 (32.4%)	22 (42.3%)	14 (23.7%)	0.037
Age(year, $\bar{X} \pm S$)	61.81 (12.71)	61.29 (12.60)	62.27 (12.89)	0.686
Symptoms(No., %)				
Fever	31 (27.9%)	13 (25.0%)	18(30.5%)	0.519
Cough	66 (60.0%)	27 (51.9%)	39 (67.2%)	0.102
Tachypnea	38 (34.2%)	12 (23.1%)	26 (44.1%)	0.020
Coma	1 (0.9%)	0 (0.0%)	1 (1.7%)	>0.999
Sore throat	1 (0.9%)	1 (1.9%)	0 (0.0%)	0.473
Diarrhea	2 (1.8%)	0 (0.0%)	2 (3.4%)	0.497
Nausea and vomiting	1 (0.9%)	0 (0.0%)	1 (1.7%)	>0.999
Comorbidity (No., %)				
Cardiovascular diseases	49 (44.1%)	25 (48.1%)	24 (40.7%)	0.433
Digestive system disease	14 (12.6%)	6 (11.5%)	8 (13.6%)	0.749
Endocrine system disease	19 (17.1%)	8 (15.4%)	11 (18.6%)	0.649
Malignant tumor	6 (5.4%)	2 (3.8%)	4(6.8%)	0.683
Nervous system disease	2 (1.8%)	0 (0.0%)	2 (3.4%)	0.497
Respiratory system disease	8 (7.2%)	2 (3.8%)	6 (10.2%)	0.279
Vital signs				
Body temperature ($^{\circ}C$, $\bar{X} \pm S$)	36.90 (0.70)	36.95 (0.79)	36.86 (0.61)	0.669
Heart rate (beats/min, $\bar{X} \pm S$)	90.91 (11.96)	89.85 (12.06)	91.85 (11.89)	0.382
Respiratory rate (breaths/min, IQR)	22.00 (20.50, 23.00)	22.00 (20.50, 23.00)	22.00 (22.00, 22.50)	0.126
Systolic blood pressure (mmHg, $\bar{X} \pm S$)	130.59 (16.59)	126.44 (19.02)	135.88 (14.06)	0.022
Diastolic blood pressure (mmHg, $\bar{X} \pm S$)	81.86 (10.38)	78.75 (9.83)	85.24 (10.18)	0.008
Laboratory results				
White blood cell count ($10^{-9}/L$, IQR)	6.43 (5.04, 9.00)	6.56 (5.00, 8.88)	6.42 (5.04, 9.03)	0.951
Neutrophil cell count ($10^{-9}/L$, IQR)	5.08 (3.56, 7.49)	5.10 (3.53, 7.50)	4.89 (3.57, 7.40)	0.939
Lymphocyte count ($10^{-9}/L$, IQR)	0.90 (0.60, 1.29)	0.92 (0.65, 1.09)	0.84 (0.60, 1.33)	0.866
Immature granulocyte count ($10^{-9}/L$, IQR)	0.03 (0.01, 0.12)	0.03 (0.01, 0.12)	0.03 (0.01, 0.09)	0.929
monocytes count ($10^{-9}/L$, IQR)	0.41 (0.26, 0.53)	0.40 (0.30, 0.50)	0.41 (0.26, 0.57)	0.880
Eosinophils count ($10^{-9}/L$, IQR)	0.02 (0.00, 0.08)	0.01 (0.00, 0.06)	0.04 (0.01, 0.08)	0.141
Hemoglobin (g/L, $\bar{X} \pm S$)	123.19 (17.39)	121.12 (16.64)	125.02 (17.97)	0.238
Platelet count ($10^{-9}/L$, IQR)	217.00 (161.50, 280.00)	221.50 (154.75, 290.50)	215.00 (168.50, 271.00)	0.848
IL-6 (pg/ml, IQR)	8.99 (6.99, 12.80)	8.84 (6.55, 13.65)	9.19 (7.26, 11.90)	0.927
AmyloidA(mg/L, IQR)	179.00 (78.80, 245.64)	186.92 (146.75, 253.92)	172.10 (45.95, 225.10)	0.123
α -Rockulosidase (U/L, IQR)	22.00 (20.00,28.00)	22.00 (19.25, 26.00)	23.00 (20.00, 29.00)	0.298
	30.43 (3.78)	29.64 (3.61)	31.10 (3.82)	0.042

(continued on next page)

Table 1 (continued)

	Total (n = 111)	Conventional treatment group (n = 52)	Huashibaidu group (n = 59)	p
Albumin (g/L, $\bar{x} \pm s$)				
Prealbumin (mg/L, IQR)	131.00 (84.00, 192.00)	120.00 (85.25, 163.50)	137.00 (81.00, 221.00)	0.335
Aminotransferase alanine (U/L, IQR)	38.50 (22.50, 54.50)	41.00 (24.00, 54.00)	38.00 (21.00, 58.00)	0.721
Aminotransferase aspartate (U/L, IQR)	37.00 (29.00, 56.00)	39.00 (30.50, 55.00)	34.00 (26.00, 56.00)	0.591
Total bilirubin ($\mu\text{mol/L}$, IQR)	11.95 (9.15, 15.90)	11.10 (8.75, 13.75)	12.90 (9.80, 16.75)	0.178
Indirect bilirubin ($\mu\text{mol/L}$, IQR)	7.70 (5.62, 10.55)	7.50 (5.95, 9.25)	8.10 (5.05, 11.50)	0.708
Direct bilirubin ($\mu\text{mol/L}$, IQR)	4.10 (3.20, 5.40)	3.90 (3.00, 4.65)	4.45 (3.32, 5.88)	0.072
Lactate dehydrogenase (U/L, IQR)	339.00 (261.00, 451.00)	350.00 (275.75, 447.25)	304.00 (254.00, 449.00)	0.371
Uric acid ($\mu\text{mol/L}$, IQR)	225.00 (182.25, 299.50)	207.00 (168.50, 282.50)	233.00 (189.50, 335.50)	0.148
Creatinine ($\mu\text{mol/L}$, IQR)	70.50 (59.20, 83.57)	70.90 (56.85, 81.35)	70.10 (60.40, 90.80)	0.474
Blood urea nitrogen (mmol/L, IQR)	4.85 (3.92, 6.57)	5.00 (3.65, 6.65)	4.70 (4.20, 5.75)	0.895
D-dimer ($\mu\text{g/ml}$, IQR)	1.10 (0.56, 3.44)	1.08 (0.55, 1.95)	1.46 (0.64, 7.91)	0.118
Prothrombin time activity (% , IQR)	96.20 (78.30, 118.30)	96.20 (81.40, 116.50)	93.50 (76.75, 120.80)	0.511
Baseline oxygen saturation status (No., %)				
1	90	45	45	0.575
2	1(1.1%)	1(2.2%)	0(0%)	
3	3(3.3%)	2(4.4%)	1(2.2%)	
4	8(8.9%)	38(84.4%)	40(88.9%)	
		4(8.9)	4(8.9%)	
Medication (No., %)				
Antivirals	63(57.3%)	40 (78.4%)	23 (39.0%)	<0.001
Antibiotics	79 (71.8%)	46(90.2%)	33 (55.9%)	<0.001
Immune intervention IFN- γ	45 (17.1%)	18 (35.3%)	27 (45.8%)	0.318
Hormone usage	33 (30.0%)	18 (35.3%)	15 (25.4%)	0.365

Notes: P values were calculated by Pearson's chi-squared test or Fisher's exact test for Count Data, and t-test or Mann-Whitney test, as appropriate. P values denoted the comparison among Conventional treatment group and Huashibaidu group.

Discussion

In the study, we found that the HSBD appeared to improve oxygen saturation status and relieve clinical symptoms compared to conventional treatment. Remarkably, a dramatic decrease in lung function for gas exchange (Yang et al., 2020) causes exacerbation and even death of patients with severe COVID-19. Also, it could decrease oxygen saturation and oxygen partial pressure in patients relying on oxygen or ventilator-assisted gas exchange to sustain life. Moreover, autopsy analysis confirmed that the typical pathological features of severe COVID-19 included ischemic-hypoxic damage to pulmonary vascular endothelium (Buja et al., 2020). Therefore, protecting the ventilatory function of patients and improving their oxygen saturation status is vital to their treatment. The HSBD demonstrated that it alleviated oxygen saturation in COVID-19 patients. Latest studies indicated that Chinese medicine treatment represented by HSBD significantly alleviated the

clinical symptoms and improved quality of life in patients with COVID-19 (Yang et al., 2020). Besides, it can also improve the immunity of the patients and liver function, thereby improving the prognosis of patients to a significant degree (Fu et al., 2020; Hu et al., 2021; Yina et al., 2021)

HSBD has remarkable advantages in relieving blood oxygen saturation, which is consistent with its efficacy in other aspects including virus shedding time (Shi et al., 2021). Based on the improvement ratio, from day 1 to day 14, no significant difference was found between the HSBD and the conventional treatment group. Nevertheless, when the HSBD was used for one cycle (14 days), the improvement rate of the HSBD dramatically increased. This indicates that the TCM is a process that takes time, with an accumulation from quantitative changes to qualitative changes. Periodic use of HSBD combined with conventional treatment improves the ventilation function of patients and relieves respiratory distress. Nonetheless, the functional mechanism of the HSBD and how it synergistically functions with conventional treatments warrants additional investigations. Besides, the timing of its use and the presence of additional side effects should be confirmed by in-depth pharmacokinetic tests and molecular biological experiments.

HSBD is a core prescription summarized by the National Traditional Chinese Medicine Medical Team based on the early national recommended treatment plan combined with the clinical practice of Jinyintan hospital. In basic studies, the HSBD contains various active ingredients including *quercetin*, *lignan*, and *kaempferol* (Yizi et al., 2020). These ingredients potentially facilitate the reduction of excessive inflammatory response and oxidative stress. Moreover, these ingredients also lower ACE2 expression, ultimately alleviating clinical symptoms in severe patients (Xun et al., 2020; Yao et al., 2020). Previous researches demonstrated that the severity of SARS-CoV-2 infection in pulmonary bronchial epithelial cells was attached to the level of angiotensin I converting enzyme 2 (ACE2) expression (Jia et al., 2005), and a lack of ACE2 expression prevented SARS-CoV-2 infection (Hoffmann et al., 2020).

Previous studies focused on the role of HSBD in relieving clinical symptoms including fever, cough, sputum, chest tightness, negative conversion, and improving patients' lung CT performance (Han et al., 2020; Liu et al., 2021; Luo et al., 2021; Wang and Qi, 2020; Wang et al., 2021; Zhao et al., 2021). In this study, the main observation index was the time for relieving blood oxygen saturation, which is the most direct manifestation of COVID-19 patient and best reflects the severity of the patient's lung inflammation. Moreover, it is also the index most directly related to mortality (Lacasse et al., 2020; Spinner et al., 2020; Xie et al., 2020). Compared with other studies based on conventional therapies, this study focused on the performance of blood oxygen saturation after the combination of conventional treatment and HSBD, which represented the efficacy of HSBD and provided a foundation for further clinical trials.

There are several limitations in the present study. Firstly, our study was retrospective, and the completeness of medical records may affect the quality of data. Secondly, the relatively small sample size of 111 patients might cause biases on the conclusions. Thus, large-sample, multicenter, prospective studies should be conducted to further confirm our findings. Despite above limitations, there are some notable strengths. To the best of our knowledge, this is the first study to explore the impact of HSBD in blood oxygen saturation. We revealed statistically significant difference in the time for relieving blood oxygen saturation in the HSBD compared to the conventional treatment. Besides, the highest improvement ratio was observed after one course (14 days) of HSBD treatment, which was consistent with what was observed clinically. A pronounced improvement was noted in oxygen saturation with the combination of HSBD and conventional treatment. Our findings provided a reference for clinicians in treatment of severe COVID-19.

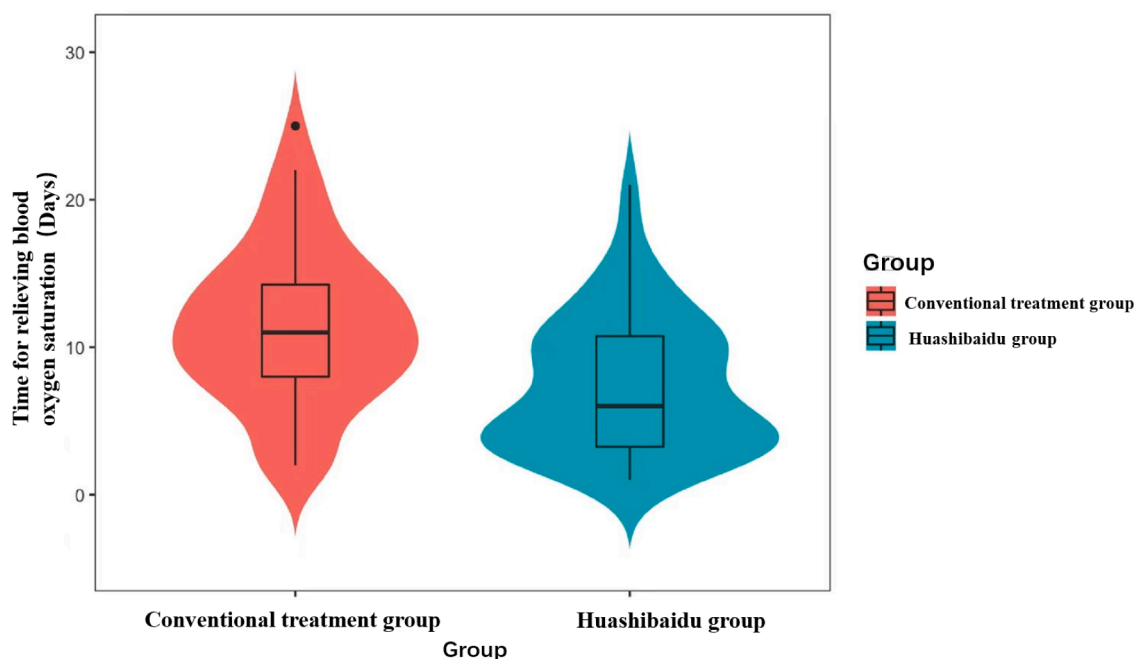


Fig. 1. Time for relieving blood oxygen saturation.

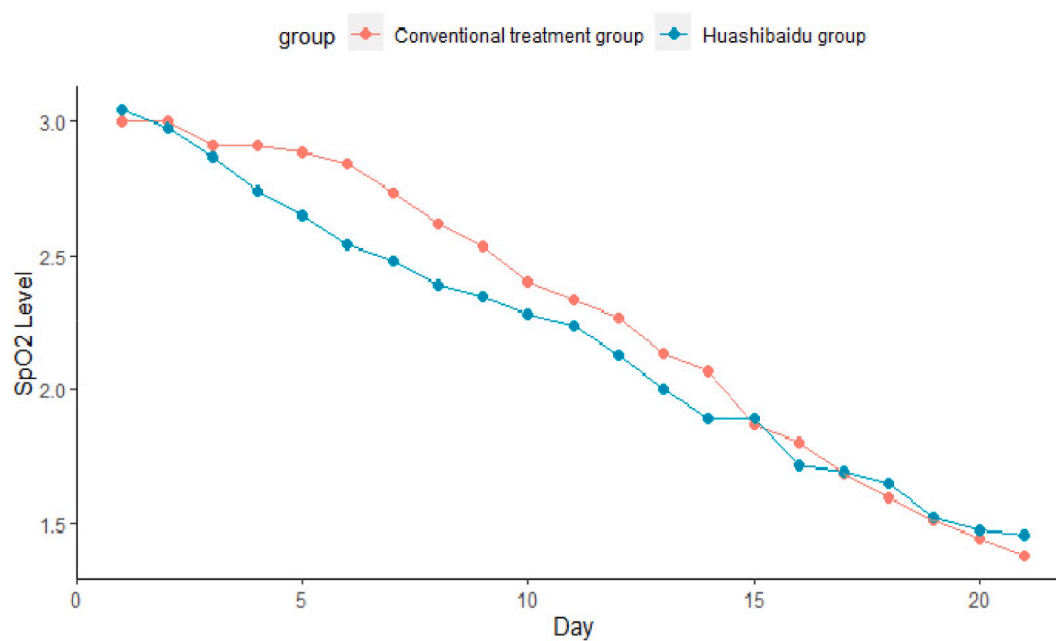


Fig. 2. Trend of blood oxygen saturation over time in two groups.

Author contributions

H.L.Q., L.C. and X.Y.B. designed the study. T.Y.X. carried out the statistical analysis. X.Y.B. and M.Y. wrote the manuscript. L.B. conducted data extraction. R.L.G and the members of the National Traditional Chinese Medicine Medical Team recruited patients. L.C. and H.L.Q revised the final paper. All data were generated in house, and no paper mill was used. All authors agree to be account able for all aspects of work ensuring integrity and accuracy.

Ethical approval

The study was approved by the ethical committee of Institute of the

Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences (Beijing, China) and Jinyintan hospital (Wuhan, China). The study was designed by the China center for Evidence-Based Traditional Chinese Medicine and implemented in partnership with Jinyintan hospital in Wuhan (CACMS-IRB2020-002-1).

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Disclosures: All authors have nothing to disclose.

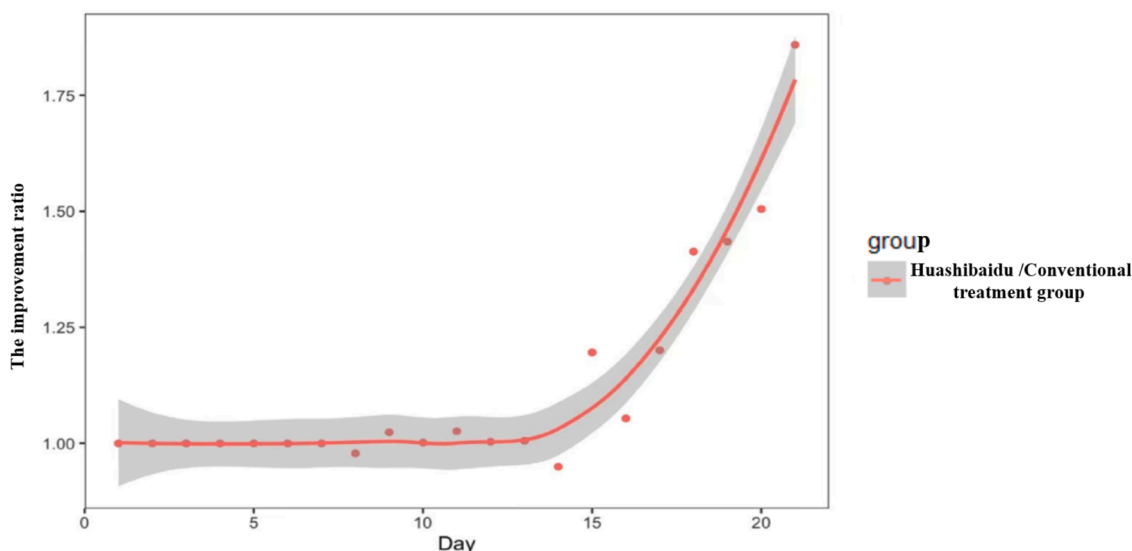


Fig. 3. The improvement ratio between groups.

Declaration of Competing Interest

All authors declare that no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. The authors declare no competing interests.

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. No pharmaceutical companies provided the study medication and financing for this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2021.153868.

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