Restricting activity and earlier oxygen supplementation may reduce adverse outcomes in patients with COVID-19 (Review)

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Abstract. Coronavirus disease 2019 (COVID-19) has spread rapidly worldwide and the number of confirmed cases and deaths is increasing rapidly. Approximately one quarter of patients infected with COVID-19 require ICU care, and among these patients, the mortality increases to 49%. Comparative clinical studies have demonstrated that severe and critical disease in patients with COVID-19 is associated with the time from the onset of symptoms to hospital admission. Similarly, an effective quarantine policy that isolates or hospitalizes diseased individuals as soon as possible, to limit their activity, is an important reason for the reduction in the rates of severe and critical disease in China. A number of patients with COVID-19 present mild symptoms at the early stages, while subsequently experiencing rapid deterioration with severe pneumonia and acute respiratory distress syndrome (ARDS). Before the virus invades the lungs and hypoxemia occurs, it is necessary to increase the oxygen supply, which enables the body to fight the virus. Lower oxygen reserves, which are influenced by factors, such as excess activity or changes in vital signs, can increase oxygen consumption, and shifts in the balance of oxygen supply and demand and can lead to critical illness and death. The present review article discusses whether early oxygen supplementation, and reducing the oxygen demand may result in a better prognosis of patients with COVID-19.

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Contents

1. Introduction

As of September 19, 2020, the coronavirus disease 2019 (COVID-19) pandemic has spread globally, leading to >30 million confirmed cases and 943,433 deaths (1). A large-scale analysis from China found that 81% of those infected were either asymptomatic or had mild disease, with a case fatality rate of 2.3%. However, patients requiring intensive care unit (ICU) care and those with acute respiratory distress syndrome (ARDS) had high fatality rates of 49 and 52.4%, respectively (2-4). Although there are different therapies available for the management of patients with COVID-19, no specific antiviral therapy exists thus far. The various therapeutic interventions are mostly supportive therapies. Due to the extreme shortage of medical resources, the treatment of patients critically ill with COVID-19-associated pneumonia remains a major challenge for clinicians. Since the adverse outcomes of patients with COVID-19 are the main cause of medical burden (2), the key intervention for the control of COVID-19 is to reduce the occurrence of adverse outcomes.

It has been reported that severe acute respiratory syndrome (SARS) coronavirus and SARS-CoV-2 have 79.5% genetic homology and similar clinical manifestations characterized by rapid progression to ARDS (5). However, at the early stages, a number of patients with COVID-19 present with atypical symptoms, including mild pharyngeal pain, dizziness, anorexia and silent hypoxemia, without significant signs of respiratory distress (6). In effect, this delays treatment, aggravates the disease progression of COVID-19, and increases the risk of disease transmission to others, including

healthcare workers, as vigilance is relaxed (7-9). In addressing this clinical dilemma, it was found that early oxygen therapy and less activity during the asymptomatic period may reduce the chances of the deterioration of the condition of patients before viral shedding begins.

While performing tracheal intubation in a patient considered to be a super-spreader of SARS coronavirus in 2003, the author, XL, became infected. She received continuous oxygen therapy as soon as possible and remained in bed. She had no obvious symptoms of respiratory distress, inconsistent with her progressing and severe chest X-ray manifestations, which were similar to those of patients with COVID-19 reported by Pan *et al* (7). Some patients in the same ward considered it unnecessary to receive oxygen therapy and remain in bed, as they felt relatively well. However, they developed marked respiratory distress and were subsequently admitted to the ICU. This suggested that further attention should be paid to activity restriction and early oxygen therapy during the asymptomatic period.

2. Link between activity restriction and the severity of COVID-19

Wang *et al* (9) reported that patients with severe COVID-19 in Wuhan who required care in the ICU were of an older age than patients with mild COVID-19, were more likely to have dyspnea and anorexia, and had more underlying comorbidities, including hypertension, diabetes, cardiovascular disease and cerebrovascular disease. Moreover, in the early stages of infection, the severe cases exhibited milder atypical symptoms and a longer interval from disease onset to hospital admission. Although many patients with COVID-19 are asymptomatic, and they do not undergo any activity restriction prior to exhibiting profound symptoms of hypoxemia, rapid deterioration can occur without proportional signs of respiratory distress, which is known as 'happy' hypoxemia (10). Thus, inadequate attention may be paid to critically ill patients who present with atypical symptoms in the early stages, resulting in a lack of sufficient rest and oxygen therapy.

By contrast, numerous patients with an exposure history from Wuhan and/or contact with confirmed cases were diagnosed with COVID-19. The time from the onset to the confirmation of infection was shorter in patients with mild disease, and this may be attributable to the policy on isolation and medical observation that restricted patient activity, and ensured rapid diagnosis (11). Moreover, the rate of severely affected cases significantly increased when hospital admission was delayed (9,12-18); this inspired the research interests of the authors, since hospitalization is associated with limited patient activities and oxygen treatment is available (Table I). Patients with infection are 'hypermetabolic' in the early stages of the insult as the body initially fights to defend itself (19). However, with a prolonged insult, there is a progressive reduction in oxygen consumption in severely affected patients (20). The restriction of activity in the early stages of infection helps to attenuate oxygen consumption and ensure sufficient energy supply to important organs. This may provide an explanation for the effectiveness of the quarantine policy in China, which recommends rapid isolation or the hospitalization of patients to limit their activity and oxygen consumption, resulting in the current reduction in severe and critical cases of COVID-19 in China.

As shown in Figs. 1 and 2, the highest case fatality rate in Hubei Province was 6.62%. However, the highest case fatality rate in other provinces was only 0.9% during the same period. After the COVID-19 outbreak in Hubei Province, other provinces adopted strict anti-epidemic measures. Those who had been in contact with confirmed cases were rapidly isolated. With the strengthening of the quarantine measures in Hubei Province in the later period of the epidemic, both the new cases and the case fatality rate decreased. Thus, the disease severity of patients with COVID-19 may be related to activity restriction (Fig. 2).

3. Importance of atypical symptoms and earlier oxygen inhalation

Although oxygen therapy has been repeatedly emphasized in patients with COVID-19, the optimal timing of oxygen administration remains unclear (21); many clinicians still base their treatment decisions on their experience and the criteria for oxygen administration in other respiratory diseases. Xu *et al* (22) reported the pathological course of a fatal case who initially exhibited mild chills and dry cough and continued to work. Although the patient in question underwent high-flow oxygen therapy after developing hypoxemia, he had impaired gaseous exchange in the lungs, which eventually caused his death. SARS-CoV-2 mainly affects the lungs, resulting in diffuse alveolar damage and a gelatinous mucus secretion of hyaline membrane, thereby inhibits alveolar gas exchange (22). Once a patient develops significant hypoxemia, it may be too late to provide oxygen therapy (non-invasive or invasive ventilation); therefore, the optimum timing of oxygen inhalation is critical. It is necessary to increase the oxygen supply at an early stage before the virus invades the lungs and hypoxemia occurs (1,8).

As mentioned above, numerous patients with COVID-19 only present atypical symptoms at the early stages of infection, including silent hypoxemia without any significant signs of respiratory distress (6). As a result, such patients receive inadequate attention, leading to rapid deterioration. It was hypothesized that the lack of timely oxygen therapy and activity restriction was one of the main causes of deterioration. Previous studies have confirmed that early oxygen support may improve asymptomatic hypoxemia and reduce adverse prognosis in infants hospitalized for acute lower respiratory tract disease or laboratory animals under anesthesia (23,24). Since the majority of patients with COVID-19 have a fever that leads to partial energy loss and a high oxygen demand, the of activities of patients should be restricted and pre-oxygenation should be performed to ensure sufficient energy and oxygen supply to vital organs (25). The successful experience in China has indicated that aggressive oxygen therapy to combat hypoxia is critical for the successful management and treatment of patients with COVID-19 and for the reduction of mortality.

4. Psychotherapy and music therapy for the reduction of oxygen consumption

With limited knowledge about COVID-19, fear, despair, anxiety, depression and irritability may prevail among patients

Table I. Adverse outcomes of patients with COVID-19 (rates of severe and critical cases and mortality).

Author	Total cases (n)	Study type	Study date range	Location	Groups (no. of patients)	Proportion of severe and critical cases	Mortality/%	OSTHA, median (IQR), days	(Refs.)
Zhou *et al*	191	Retrospective	December 29, 2019 to January 31, 2020	Wuhan	Non-survivor (54) vs. survivor (137)	63% Severe (35%) Critical (28%)	28.3%	11 (8-14)	(13)
Huang *et al*	41	Retrospective	December 31, 2019 to January 2, 2020	Wuhan	ICU (13) vs. non-ICU (28)	32%	15%	7 (4-8)	(14)
Wang *et al*	138	Retrospective	January 1, 2020 to January 28, 2020	Wuhan	ICU (36) vs. non-ICU (102)	26.1%	4.3%	7 (4-8)	(9)
Guan *et al*	1,099	Retrospective	Through January 29, 2020	31 Provinces	Severe (173) vs. non-severe (926)	15.7%	1.36%	3 (0-8)	(15)
Han *et al*	108	Retrospective	January 4 to February 3, 2020	Wuhan	All mild	0%	0%	1 (1-3)	(16)
Qian *et al*	91	Retrospective	January 20 to February 11, 2020	Zhejiang	Severe (9) vs. mild (82)	10%	0%	1 (1-2)	(17)
Xu *et al*	51	Retrospective	January 23 to February 18, 2020	Changzhou	Imported (15) Secondary (17) Tertiary (19)	0%	0%	CT was performed immediately after symptom onset	(18)
Xu *et al*	1	Case report	January 21 to February 3, 2020	Wuhan		Critical disease and death		9	(22)

OSTHA, onset of symptoms to hospital admission (or confirmed disease); CT, computed tomography; IQR, interquartile range.

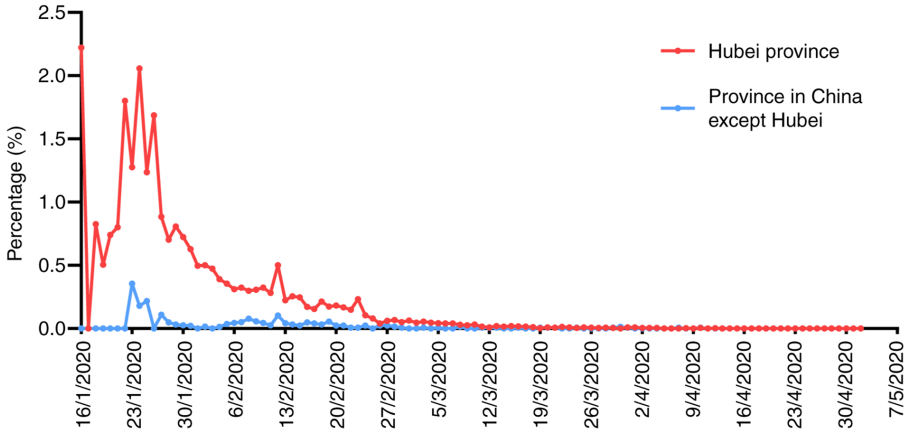

Figure 1. New fatalities/cumulative number of cases.

Figure 2. Fatality rate of COVID-19 in Chinese provinces on May 2, 2020. The numbers next to the color key indicate the fatality rate ranges.

with COVID-19 (26). Negative emotions and psychological diseases may not only delay recovery, but also pose challenges to treatment due to the possibility of extreme behaviors, such as non-cooperation during treatment (5). Psychotherapy and music therapy may help patients to remain calm and may enhance their confidence in overcoming the disease (27).

The 'Voice of the Square Cabin' music therapy has been used by the Third Affiliated Hospital of Sun Yat-sen University since the outbreak of the COVID-19 pandemic. The program provides personalized online music therapy by utilizing music artificial intelligence to provide all-round help to patients, in combination with online psychotherapy and disease consultations. Tranquilizing music can eliminate anxiety, dispel depression, and reduce the heart rate and respiratory rate, thereby reducing oxygen consumption (28). Moreover, psychological counseling and proper nutrition are necessary to provide in-depth treatment of COVID-19 patients.

5. Conclusions and future perspectives

The global COVID-19 pandemic will continue to affect humanity until the development of an effective vaccine or specific therapeutic drugs are made available. The present review article provides new insight which may help minimize the loss of life and prevent the development of severe disease. The present review article discusses the hypothesis that restricting patient activities, providing oxygen inhalation at the earlier stage of infection, and reducing oxygen consumption, such as by reducing the heart rate and respiratory muscle work, may result in a better prognosis of patients with COVID-19.

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Availability of data and materials

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Authors' contributions

XL and ZH contributed to the study design. XL and CC wrote the manuscript. YG contributed to literature retrieval and manuscript writing and to the preparation of the tables. JW performed the literature search, figure production and manuscript editing. YZ revised the manuscript. WY and ZH revised and edited the manuscript. The manuscript has been read and approved by all the authors; the requirements for authorship have been met; and each author believes that the manuscript represents honest work.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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