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CASE REPORT

Successful management of seven cases of critical COVID-19 with early noninvasive–invasive sequential ventilation algorithm and bundle pharmacotherapy

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Abstract **We report the clinical and laboratory findings and successful management of seven patients with critical coronavirus disease 2019 (COVID-19) requiring mechanical ventilation (MV). The patients were diagnosed based on epidemiological history, clinical manifestations, and nucleic acid testing. Upon diagnosis with COVID-19 of critical severity, the patients were admitted to the intensive care unit, where they received early noninvasive–invasive sequential ventilation, early prone positioning, and bundle pharmacotherapy regimen, which consists of antiviral, anti-inflammation, immune-enhancing, and complication-prophylaxis medicines. The patients presented fever (n = 7, 100%), dry cough (n = 3, 42.9%), weakness (n = 2, 28.6%), chest tightness (n = 1, 14.3%), and/or muscle pain (n = 1, 14.3%). All patients had normal or lower than normal white blood cell count/lymphocyte count, and chest computed tomography scans showed bilateral patchy shadows or ground glass opacity in the lungs. Nucleic acid testing confirmed COVID-19 in all seven patients. The median MV duration and intensive care unit stay were 9.9 days (interquartile range, 6.5–14.6 days; range, 5–17 days) and 12.9 days (interquartile range, 9.7–17.6 days; range, 7–19 days), respectively. All seven patients were extubated, weaned off MV, transferred to the common ward, and discharged as of the writing of this report. Thus, we concluded that good outcomes for patients with critical COVID-19 can be achieved with early noninvasive–invasive sequential ventilation and bundle pharmacotherapy.**

Keywords COVID-19; noninvasive–invasive sequential ventilation; bundle pharmacotherapy

Introduction

The transmission of pathogens from animals to humans and resultant zoonotic infectious diseases have been associated with several major global outbreaks and constitute global public health burden. Generally, coronaviruses (CoVs) are enveloped RNA viruses that can cause respiratory and intestinal infections in humans and other animals. Human infections with CoVs had been associated with mild upper respiratory disease before the 2003 outbreak of severe acute respiratory syndrome (SARS) [1]. However, the discovery that SARS is caused by a new CoV, SARS-CoV, redefined our understanding of CoVs [2]. The potential pathogenicity of CoVs was further elucidated by the 2012 Middle East respiratory syndrome (MERS) outbreak, which is attributed to infection with yet another new CoV, MERS-CoV. MERS, which presents as acute pneumonia and occasional renal failure in severe cases, had an alarming 30% mortality rate in the 2012 outbreak [3]. The severe morbidities of CoV diseases over the past two decades have shown that CoVs represent a serious infectious disease concern.

In December of 2019, a cluster of patients with pneumonia of unknown cause was linked to transmission

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at a seafood wholesale market in Wuhan, China. A previously unknown β-CoV was discovered in samples from affected patients. The 2019 novel CoV causing the ongoing pneumonia pandemic was identified to be of the same genus as the SARS-CoV and the seventh CoV known to infect humans following 229E, NL63, OC43, HKU1, MERS-CoV, and SARS-CoV [4,5]. This causative virus was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The relevant infectious disease was named as coronavirus disease 2019 (COVID-19) by the World Health Organization [6].

The cases of COVID-19 can be classified as mild, moderate, severe, or critical based on clinical symptoms and radiologic images [7]. A total of 87 137 confirmed cases globally, including 79 968 confirmed cases in China and 7169 outside China, with 2977 deaths (3.4%) had been reported by the World Health Organization as of March 1, 2020 [8]. SARS-CoV-2 exhibits rapid transmission and causes atypical clinical symptoms, including fever, cough, myalgia, weakness, and dyspnea, as well as clinical signs recognizable in chest images that may be helpful for the early detection of emergent COVID-19 [9].

Patients with COVID-19 who become critically ill and require mechanical ventilation (MV) have a particularly high mortality risk. Therefore, an effective standard treatment regimen for COVID-19 that can limit disease severity should be established to quell public panic. Here, we report the successful management of seven critically ill patients diagnosed with COVID-19 who suffered acute respiratory failure.

Case report

We collected the clinical and laboratory data of the seven critically ill patients admitted to the intensive care unit (ICU) of the Third People's Hospital of Shenzhen. Respiratory specimens (nasopharyngeal swabs, sputum, or bronchoalveolar lavage) from each patient were tested for SARS-CoV-2 with real-time reverse-transcriptase polymerase chain reaction testing.

The patients who presented the clinical symptoms of COVID-19 sought care in our hospital from January 20 to February 6, 2020. Suspected diagnoses of COVID-19 were made based on clinical symptoms and then confirmed based on white blood cell count (WCC)/lymphocyte count, chest computed tomography (CT) images, and nucleic acid test results. The patients were treated in the ICU for COVID-19. At present, these seven critically ill patients who suffered respiratory failure and required MV were treated successfully and discharged.

The seven critically ill patients (four women; 57.1%), who are the subjects of this case series, had a median age of 56 years (interquartile range (IQR), 41–65 years; range, 36–71 years). The group included four patients (57.1%) with body mass index > 25, three patients with pre-existing chronic diseases (42.9%), and six patients with Wuhan contact history (85.7%). All seven patients had fever (100%), three had dry cough (42.9%), two experienced weakness (28.6%), one had chest tightness (14.3%), and one reported muscle pain (14.3%). The demographic and clinical characteristics of these patients are summarized in Table 1. Laboratory tests (results reported in Table 2) showed that all seven patients (100%) had normal or lower than normal WCCs and lymphocyte counts, as well as bilateral patchy shadows or ground glass opacity in the lungs visible in chest CT scans (Fig. 1).

All the patients (100%) were treated with the following bundle pharmacotherapy regimen: lopinavir/ritonavir tablets (500 mg every 12 h) plus α-interferon (5.0 MU atomized inhalation every 12 h) as an antiviral treatment, thymosin α1 (1.6 mg/day subcutaneous injection) to enhance immunity, methylprednisolone (40 mg/day for the first 3 days) to reduce pulmonary exudation, traditional

Table 1 Patients' demographic and clinical characteristics

Characteristic	Patient						
	1	2	3	4	5	6	7
Age (year)	65	57	64	46	56	71	36
Gender	F	F	F	M	M	M	F
Body mass index	22	23	21	25	25	25	28
Underlying disease	Diab, 15 years	No	No	No	Hypt, 30 years	Hypt, 6 months	No
Wuhan contact	Yes	Yes	Yes	Yes	No, but subway worker	Yes	Yes
Symptoms							
Fever	+	+	+	+	+	+	+
Dry cough	+	−	−	+	−	−	+
Weakness	−	−	−	+	+	−	−
Chest tightness	+	−	−	−	−	−	−
Muscle pain	−	−	−	+	−	−	−

F, female; M, male; Diab, diabetes; Hypt, hypertension.

Table 2 Patients' laboratory and CT manifestation findings

Parameter	Patient						
	1	2	3	4	5	6	7
WCC ($\times 10^9$/L)	5.89	9.14	5.39	6.64	6.51	5.64	3.81
Neutrophil count ($\times 10^9$/L)	5.35	7.34	4.25	4.38	5.36	3.98	2.37
Lymphocyte count ($\times 10^9$/L)	0.42	1.42	0.90	0.83	0.93	0.79	1.08
Hemoglobin (g/L)	118	143	125	159	124	142	92
Platelet ($\times 10^9$/L)	118	175	176	171	153	191	282
PaO_2/FiO_2 ratio before intubation (mmHg)	136	165	118	150	116	110	141
Lactate (mmol/L)	2.7	2.3	2.1	2.6	2.6	1.9	1.4
Creatinine (μmol/L)	54.1	38.3	54	86	94.6	78.9	42
Urea (mmol/L)	4.48	3.71	6.35	4.36	8.48	5.78	4.13
Albumin (g/L)	34.6	37.9	39	46.6	35.5	40.8	41.3
Alanine aminotransferase (U/L)	15.7	19.7	33.3	12	34.8	26.8	15
Total bilirubin (μmol/L)	8.4	12.1	10.8	11.9	12.2	33.6	7.7
CT lung changes	+	+	+	+	+	+	+
Respiratory nucleic acid result	+	+	+	+	+	+	+

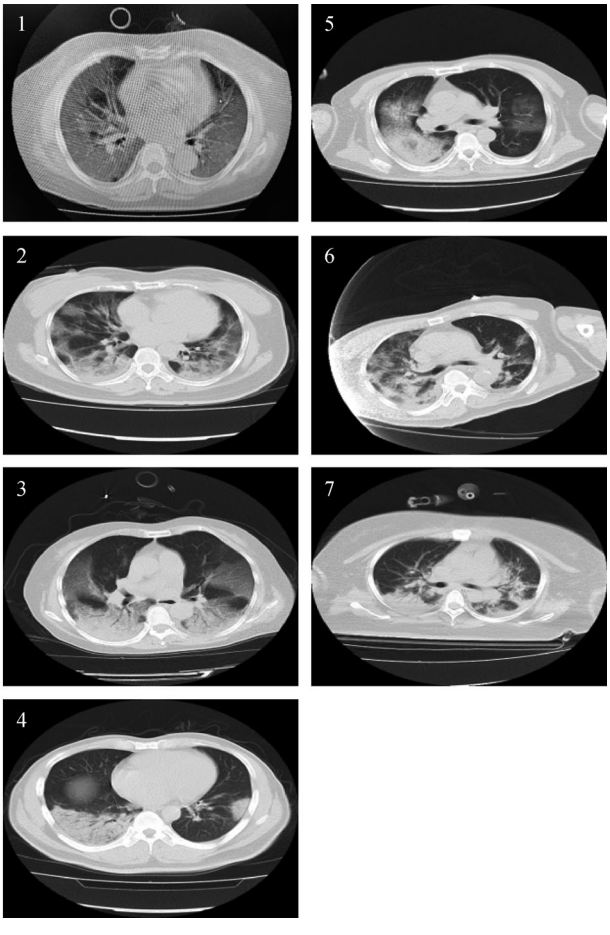

Fig. 1 Pretreatment chest CT scans for patients 1–7. Patient numbers are indicated in the upper left of each image.

Chinese medicine *Xuebijing* (100-mL injection every 12 h) to attenuate inflammation, and low-molecular-weight heparin (4.0 kIU subcutaneous injection each day) to prevent deep vein thrombosis. The drugs (lopinavir/ritonavir and α-interferon) were stopped when two consecutive negative respiratory sample nucleic acid tests with a sampling interval of $\geqslant$ 1 day were achieved.

The patients received noninvasive ventilation (NIV) with 60% oxygen absorption concentration (FiO_2) and inspired/expiratory positive airway pressure (IPAP/EPAP) levels of 8–12 and 6 cmH_2O, respectively. However, the patients' conditions were not relieved in 2 h (PaO_2/FiO_2 ratio reported in Table 2). Subsequently, all the patients were advanced to invasive MV with prone positioning (12–14 h/day) in the first 3–5 days. The median MV duration was 9.9 days (IQR, 6.5–14.6 days; range, 5–17 days). The MV start and end dates and duration for each patient, as well as ICU admission and transfer-out dates and duration of ICU stay, are reported in Table 3. None of the patients received extracorporeal membrane oxygenation.

All seven patients were extubated and weaned off their ventilators by February 25, 2020 and exhibited clinically smooth breathing without fever or any other COVID-19 symptoms. Additionally, chest CT scans showed absorption of the aforementioned lung changes in all cases (Fig. 2). The patients were thus transferred from the ICU to the common ward. The patients had a median ICU stay of 12.9 days (IQR, 9.7–17.6 days; range, 7–19 days; Table 3) and were discharged as of the writing of this report.

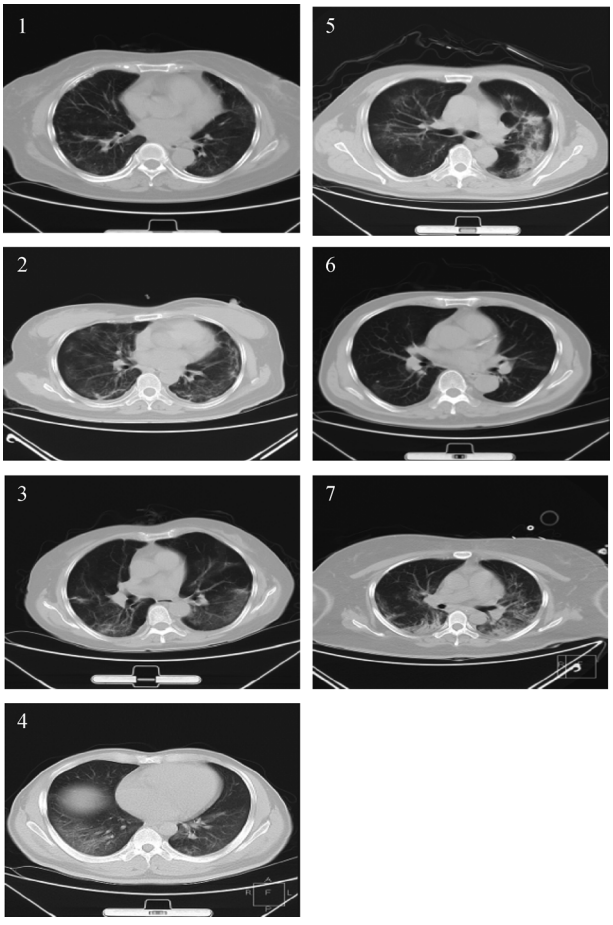

Fig. 2 Post-treatment chest CT scans for patients 1–7. Patient numbers are indicated in the upper left of each image.

Discussion

SARS-CoV-2, the underlying causative agent of COVID-19, can be transmitted from person to person; thus, SARS-CoV-2 and COVID-19 has rapidly spread [10,11]. Patients infected with SARS-CoV-2 have since been found in China, other countries in Asia, the Middle East, Europe, and North America [12]. Thus, an urgent international need for the establishment of effective therapeutic strategies has emerged to achieve the rapid control of SARS-CoV-2 infection and COVID-19.

According to China's national guidelines for the diagnosis of COVID-19 (summarized in Fig. 3) [7], these seven cases were diagnosed with COVID-19 because of the positive nucleic acid affirmation of SARS-CoV-2 in their respiratory samples (Table 2). COVID-19 can be classified as mild, moderate, severe, or critical. Mild COVID-19 is characterized by mild clinical symptoms without signs of pneumonia on imaging. Moderate COVID-19 is characterized by fever, respiratory symptoms, and imaging manifestations of pneumonia. Moderate-type COVID-19 is elevated to severe-type if the patient shows respiratory distress (defined by a respiratory rate of $\geqslant$ 30 breaths/min, a resting oxygen saturation rate of $\leqslant$ 93%, or a partial arterial oxygen pressure (PaO_2)/FiO_2 $\leqslant$ 300 mmHg). Severe COVID-19 is considered to have progressed to critical COVID-19 if the patient develops respiratory failure requiring MV, sepsis, or combined with organ failure requiring ICU monitoring and care. The seven cases of COVID-19 presented in this paper exhibited respiratory failure requiring invasive MV and thus were classified as critical-type COVID-19.

Our department is focused on the early diagnosis and severity typing of COVID-19. Our management plan upon confirmation of a COVID-19 diagnosis includes the immediate treatment of symptoms and the delivery of a comprehensive bundle pharmacotherapy. Monitoring and supportive treatment is usually sufficient in patients with mild or moderate COVID-19 to ensure good outcome. We provide close monitoring and bundle pharmacotherapy, as well as supplemental oxygen therapy, in patients with

Table 3 Patients' MV care spans, ICU admission spans, and notable case characteristics

Parameter	Patient						
	1	2	3	4	5	6	7
MV start date (in 2020)	Jan 24	Jan 27	Jan 31	Feb 1	Feb 3	Feb 4	Feb 6
MV end date (in 2020)	Feb 1	Feb 12	Feb 7	Feb 6	Feb 10	Feb 13	Feb 23
MV duration (day)	8	16	7	5	7	9	17
ICU admission date (in 2020)	Jan 24	Jan 26	Jan 28	Feb 1	Feb 3	Feb 4	Feb 6
ICU transfer out date (in 2020)	Feb 6	Feb 13	Feb 9	Feb 8	Feb 12	Feb 16	Feb 25
ICU stay (day)	13	18	12	7	9	12	19
Notable case characteristics	Sulp for ↑sputum, cultures negative	VAP; sepsis; NE; sputum; culture *Pm*, ESBL + *E. coli*; AB: Taz, Mer, Cef	–	Sulp for ↑sputum, cultures negative	Sulp for ↑sputum, cultures negative	–	VAP; sputum culture MDR *Pm*; AB: Mer, Taz, Ami

Jan, January; Feb, February; Sulp, sulperazone; VAP, ventilator-acquired pneumonia; NE, norepinephrine (low-dose acute treatment in this case); *Pm*, *Pseudomonas*; ESBL +, extended spectrum beta-lactamase positive; AB, antibiotic drugs administered; Taz, tazocin; Mer, meropenem; Cef, ceftazidime; MDR, multi-drug resistant; Ami, amikacin.

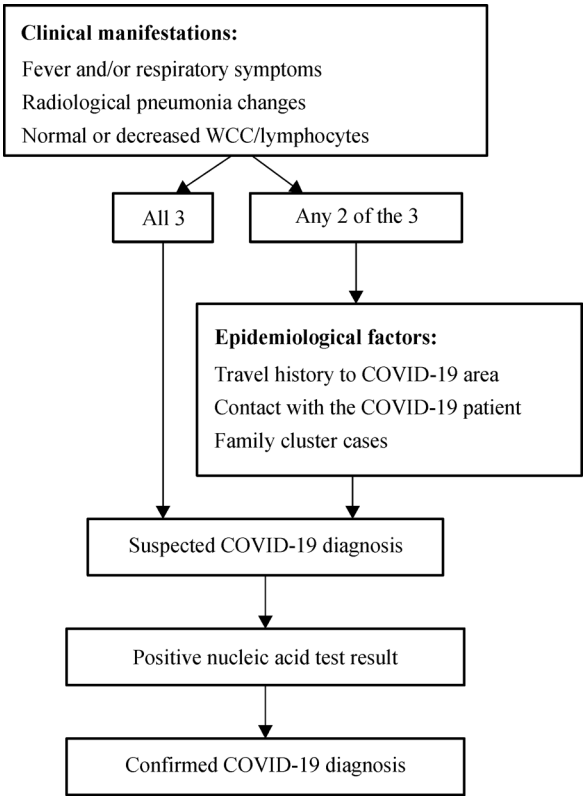

Fig. 3 COVID-19 diagnoses algorithm.

severe COVID-19 to avoid the progression of COVID-19 to critical level, which can be fatal. Therapy plans may be individualized depending on the particular characteristics of individual patients (Table 3).

The patients with critical COVID-19 were weaned off MV successfully, transferred to the common ward, and subsequently discharged. Our experience with the concentrated treatment of this patient population from Shenzhen, China has yielded three noteworthy lessons explained below.

First, we found that the early determination of COVID-19 severity is of utmost importance. Missed diagnosis and misdiagnosis caused by atypical symptomology results in the loss of opportunity for early intervention [9]. Patients with the following factors are at risk of severe or critical COVID-19 [13,14]: age $>$ 60 years; body mass index $>$ 25; underlying chronic disease; low lymphocyte count ($< 0.95 \times 10^9$/L); and nasopharyngeal swab viral nucleic acid value $<$ 30 or positive results with blood, stool, urine, or tear specimen. We believe that the most important among these factors may be lymphopenia. Three among the seven patients described in this report were over 60 years old with a chronic underlying disease and lymphocyte counts $< 0.95 \times 10^9$/L, which indicate a less than robust immunocompetence. Patients with lymphopenia tend to have the most serious symptoms, especially severe hypoxemia, and are prone to developing sepsis or multiple organ failure.

Second, early sequential noninvasive–invasive respiratory support and early prone position are effective measures for improving outcomes. Respiratory support is a very important technique that can save patients with severe COVID-19 who suffer from respiratory failure by improving oxygenation to reduce mortality. Therefore, appropriate respiratory support technique is the key point related to its success or failure [15]. Early respiratory support can facilitate disease recovery and improve prognosis [16]. We have come to favor a sequential noninvasive–invasive ventilation algorithm (summarized in Fig. 4), wherein patients with COVID-19 are started on NIV (IPAP, 8–12 cmH_2O; EPAP, 6 cmH_2O; FiO_2, 60%) if they have a PaO_2/FiO_2 ratio of $\leqslant$ 200 mmHg (patients alert, hemodynamically stable). If the patients' symptoms showed no improvement after 2 h of NIV, then they are advanced to MV (parameters in Fig. 4). We restricted the duration of NIV to $\leqslant$ 2 h because respiratory failure cannot be relieved with NIV and the patients will continue to incur further oxygen debt if they have massive lung consolidation. MV with sedation and analgesia allows patients with critical COVID-19 to rest while giving time for our comprehensive pharmacotherapy regimen to exert therapeutic efficacy in the lungs. The patients were rested in prone position to ensure that the diaphragm is in a favorable position to enable its movement while reducing the pressure gradient in the chest cavity. This position

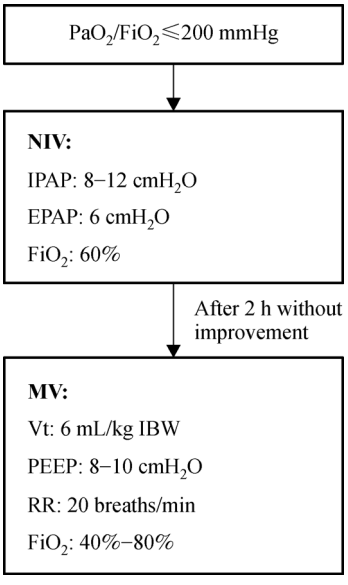

Fig. 4 Sequential noninvasive–invasive ventilation process. Vt, tidal volume; PEEP, positive end-expiratory pressure; RR, respiratory rate; IBW, ideal body weight.

increases the functional residual capacity of the lungs, which improves oxygenation by improving the ventilation-to-blood flow ratio and enhancing secretion drainage and fluid movement in the lungs.

Third, the administration of a bundle pharmacotherapy can support recovery from COVID-19. We recommend a bundle therapy (see case report text for dosage information) with three principal components: (1) antiviral (lopinavir/ritonavir plus α-interferon) and anti-inflammation drugs (methylprednisolone and *Xuebijing*), (2) immune system support (thymosin α1), and (3) prevention/treatment of complications (low-molecular-weight heparin). All seven patients were treated with this bundle pharmacotherapy while receiving respiratory support and recovered well. All of them have been discharged as of the writing of this report. Our discharge criteria for patients recovering from COVID-19 are: normal body temperature for $\geqslant$ 3 days; alleviation of respiratory symptoms; majority resolution of radiological lung changes; and two consecutive negative respiratory sample nucleic acid tests with a sampling interval of $\geqslant$ 1 day [7].

Among the seven critically ill patients whose cases are described in this report, five patients had MV durations of 5–9 days, and two patients required extended MV durations (16 and 17 days) because of ventilator-acquired pneumonia infections, which caused sepsis in one case (see Table 3 for bacteria identified from sputum cultures and individualized treatments). Consistent with the findings, we found that complications due to secondary infection are rare if the period of disease requiring MV is within a week or so. Conversely, patients requiring 2 weeks or more of MV become exposed to greater risk of acquiring negative bacilli, positive cocci, and fungal infections, which make the patients at increased risk of systemic infection, sepsis, multiple-organ dysfunction, and death. Thus, the strict control of hospital-acquired infections is of utmost importance in patients requiring MV to improve their likelihood of achieving rescue success. We aim to facilitate such success in part by enhancing patient immunity as discussed above.

This report has a notable limitation in that only seven cases of successfully treated critical ill patients with COVID-19 were included. More cases are needed to further confirm the effectiveness of our recommended treatment regimen. We hope that our treatment protocol will be applied to patients more broadly to collect data on its efficacy from broader populations.

Conclusions

Good treatment outcomes can be achieved for critically ill patients with COVID-19 with early sequential non-invasive–invasive ventilation and bundle pharmacotherapy, which comprises antiviral and anti-inflammation medicines, immune system support, and prophylaxis for vascular complications.

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Compliance with ethics guidelines

Mian Peng, Xueyan Liu, Jinxiu Li, Di Ren, Yongfeng Liu, Xi Meng, Yansi Lyu, Ronglin Chen, Baojun Yu, and Weixiong Zhong declare no conflict of interest. Written informed consent was obtained from all the patients.

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