

# Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19

## Pneumonia

Chengshui Chen<sup>1#</sup>, Feng Qi<sup>2#</sup>, Keqing Shi<sup>1#</sup>, Yuping Li<sup>1#</sup>, Ji Li<sup>1</sup>, Yongping Chen<sup>1</sup>, Jingye Pan<sup>1</sup>, Tieli Zhou<sup>1</sup>, Xiangyang Lin<sup>1</sup>, Jinsan Zhang<sup>1,3</sup>, Yongde Luo<sup>1,3</sup>, Xiaokun Li<sup>1,3\*</sup>, Jinglin Xia<sup>1,2\*</sup>

<sup>1</sup> The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China

<sup>2</sup> Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai 200032, China

<sup>3</sup> International Collaborative Center on Growth Factor Research, and School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou 325035, China

# Contributed equally

\* To whom correspondence should be addressed. E-mail: [xiajinglin@fudan.edu.cn](mailto:xiajinglin@fudan.edu.cn), [xiaokunli@wmu.edu.cn](mailto:xiaokunli@wmu.edu.cn)

**SUMMARY** A novel coronavirus strain (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in December 2019 and can cause acute respiratory distress syndrome and death. However, there are only limited therapy choices and no vaccine for SARS-CoV-2 is currently available. Here we report about a case of a SARS-CoV-2 caused pneumonia successfully treated with thalidomide. Thalidomide is an immunomodulatory and anti-inflammatory agent and was combined with a low-dose glucocorticoid. We suggest, that the effects of thalidomide might be related to regulating immunity, inhibiting the inflammatory cytokine surge, alleviating anxiety to reduce oxygen consumption, relieving vomit and lung exudation.

**KEYWORDS:** Coronavirus, SARS-CoV-2, COVID-19, Thalidomide, pneumonia

## Introduction

An epidemic illness caused by a novel coronavirus, now named Corona Virus Disease 2019 (COVID-19), occurred in Wuhan, China about 3 months ago<sup>1</sup>. The human-to-human contagious transmission of COVID-19 has been confirmed in multiple reports, leading to rapid spreading to tens of thousands of patients in China<sup>2,3</sup>. Organ dysfunction, including acute respiratory distress syndrome (ARDS), acute cardiac injury, shock, and death may occur. Therefore, many COVID-19 patients also suffered from anxiety, especially under treatment in intensive care units (ICUs). However, due to currently very limited treatment options and no developed vaccines available for COVID-19, new treatment approaches are urgently needed. Recently, several antiviral drugs with inhibitory effects against this novel coronavirus have been selectively tested in clinical trials, including remdesivir, favipiravir, and ritonavir<sup>4,5</sup>. Nevertheless, there were quite a few severe cases suffering from immune imbalance<sup>6</sup>, for which the efficacy of antiviral drugs might remain unsatisfactory or

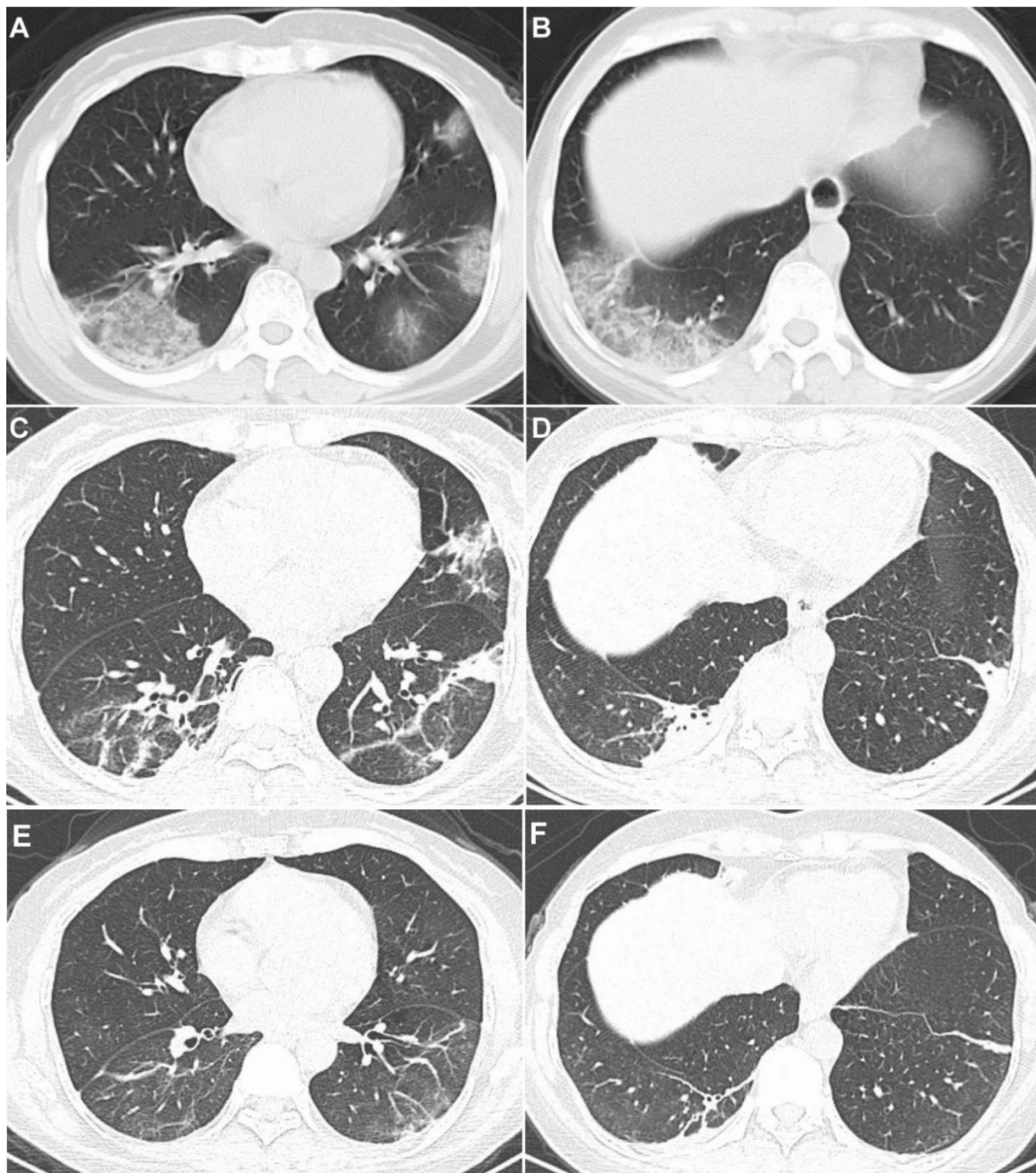
insufficient, especially in the later stages of disease progression. Thalidomide, as an immunomodulatory and anti-inflammatory agent, is known for its effects such as stimulating T cells, anti-inflammation, inhibiting cell proliferation, and reducing lung injury and pulmonary fibrosis. Here, we report the protective effect of thalidomide in combination with antiviral drugs and low dose glucocorticoid on lung injury and immunological stress caused by a COVID-19 pneumonia, shedding new light on an adjuvant treatment strategy for this potentially lethal viral disease.

## Case report

On January 31, 2020, a 45-year-old woman was admitted to a fever clinic of Wencheng County People's Hospital, in Wenzhou city, Zhejiang province, with a 5-day history of cough, fever, fatigue and diarrhea. She denied any recent travel to Wuhan, China, or close contact with infected persons or suspected cases. The patient exhibited no dyspnea. She was first treated with oral administration of ofloxacin and oseltamivir, but the condition deteriorated. The swab specimen

was tested positive for SARS-CoV-2 by real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) on February 1, 2020. Chest computerized tomography (CT) indicated signs of the subpleural effusions in the left upper and left lower lung (**Figure 1A, B**). Therefore, the patient was

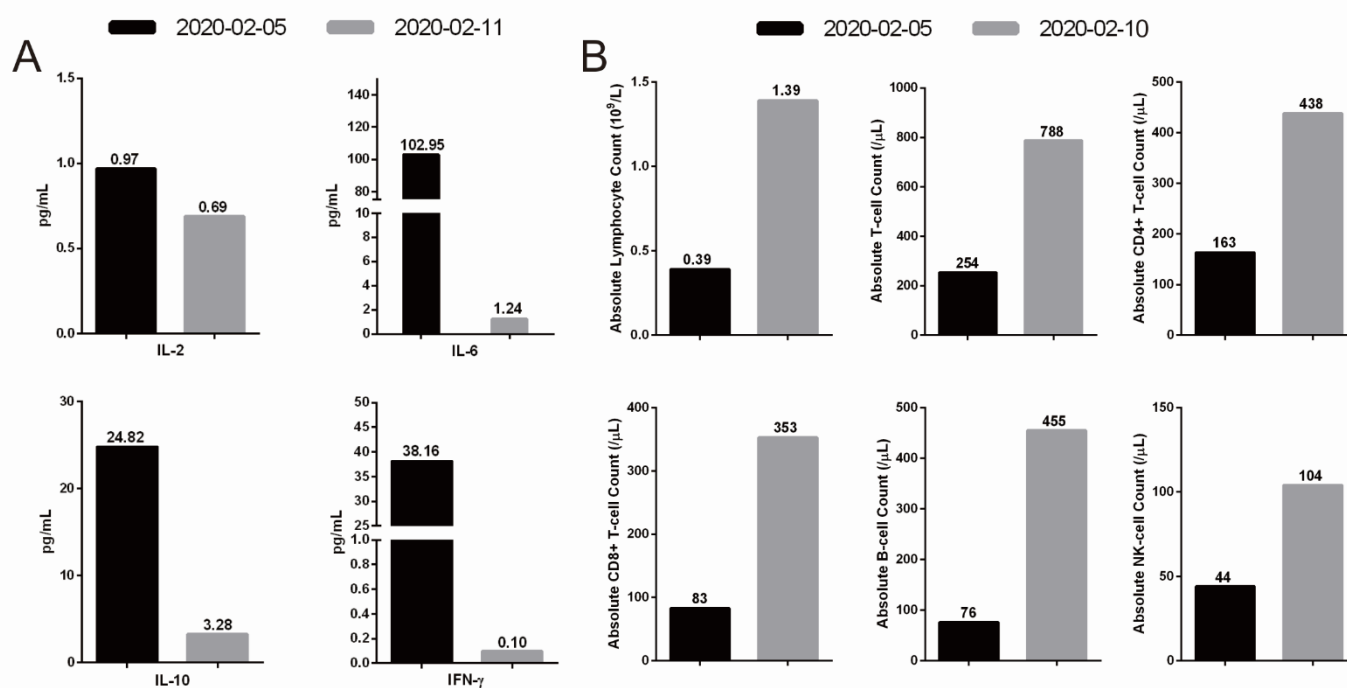
diagnosed with COVID-19 pneumonia, and treated with lopinavir/ritonavir. Due to the persistent hyperpyrexia, she was transferred to the isolation ward in our hospital on February 3, 2020 for further treatment.



**Figure 1.** Chest CT images. (A, B) subpleural exudation opacities in the lower right, left upper lung and left lower lung, on February 2, 2020; (C, D) fibrous lesions in the lower right, left upper lung and left lower lung, on February 11, 2020; (E, F) fibrous lesions in the lower right, left upper lung and left lower lung, on February 17, 2020.

The patient was healthy before this outbreak. Physical examination revealed a body temperature of 38.1°C, blood pressure of 117/78 mmHg, pulse rate 92 beats per minute, a respiratory rate of 20 breaths per minute and oxygen saturation of 93% while the patient was treated by nasal cannula delivery of oxygen at 3 L/minute. Laboratory studies revealed a significantly increased level of C-reactive protein (CRP) at

90.0 mg/L and cytokine levels including interleukin (IL)-6 at 102.95 pg/mL, IL-10 at 24.84 pg/mL and interferon (IFN)- $\gamma$  at 38.16 pg/mL (**Figure 2A**), as well as a significantly decreased T cell absolute value (254/ $\mu$ L), including CD4 + T cells (163/ $\mu$ L), CD8 + T cells (83 / $\mu$ L), NK cells (44 / $\mu$ L) and B cells (76 / $\mu$ L) (**Figure 2B**).



**Figure 2.** Inflammatory cytokines and Lymphocytes in the patient. A) Inflammatory cytokines in serum before and after thalidomide treatment. The normal ranges are IL-2 < 3.10 pg/mL, IL-6 < 3.00 pg/mL, IL-10 < 4.10 pg/mL, and IFN- $\gamma$  < 2.20 pg/mL. B) Lymphocytes in serum before and after thalidomide treatment. The normal ranges are: T-cell absolute value: 797-2370/ $\mu$ L, CD4+ T-cell absolute value: 432-1341/ $\mu$ L, CD8+ T-cell absolute value: 238-1075/ $\mu$ L, B-cell absolute value: 86-594/ $\mu$ L, NK-cell absolute value: 127-987/ $\mu$ L.

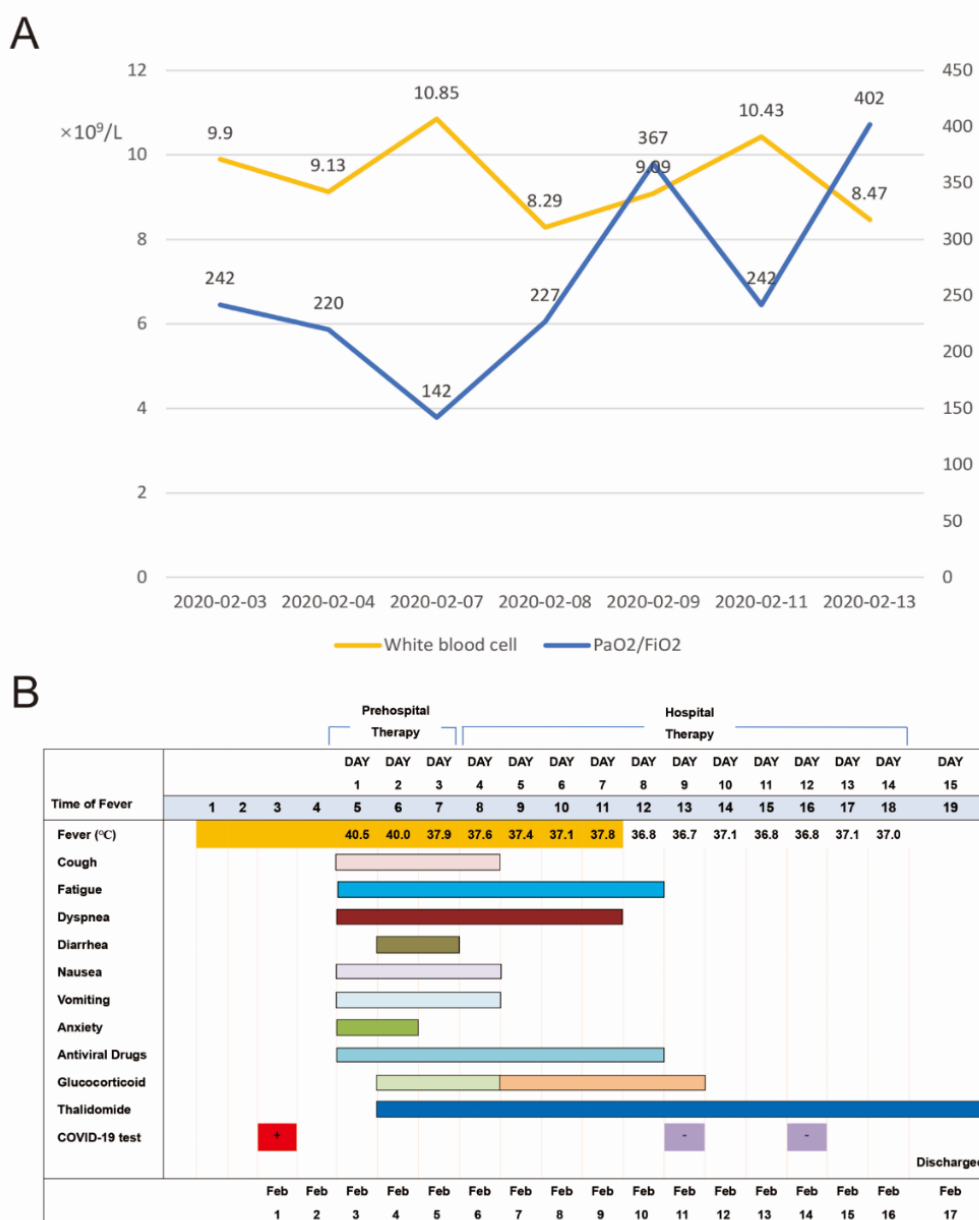
Note: IL, interleukin; IFN, interferon.

On admission, the patient's vital signs were initially stable. However, the patient continued to have a high fever, dyspnea and was obviously fatigued, accompanied by nausea and vomiting. Treatment during this period was primarily supportive and antiviral therapy. On hospital day 2 (illness day 6), arterial blood gas analysis indicated a deterioration of the oxygenation index (PaO<sub>2</sub>/FIO<sub>2</sub>: 220 mmHg) and laboratory results showed signs of lymphocytopenia. The patient was classified into the severe phenotype according to Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fifth edition) matching any of the following

conditions: respiratory rate  $\geq$  30 breaths per minute, oxygen saturation  $\leq$  93% at rest, and PaO<sub>2</sub>/FIO<sub>2</sub>  $\leq$  300 mmHg. Given the exacerbation of the patient's symptoms, treatment with thalidomide (Changzhou Pharmaceutical Factory Co., Ltd. Jiangsu, China) at 100 mg dose orally every 24 hours and low-dose methylprednisolone (40 mg administered intravenously every 12 hours for 3 days and then reduced to every 24 hours for 5 days) was initiated on February 5, 2020, hospital day 2. No adverse events were observed. The patient's clinical condition improved, including increased oxygen index, and disappearance of anxiety after 1 day and nausea and vomiting

3 days after thalidomide treatment was recorded. Furthermore, cytokine levels returned to the normal range including IL-6 at 1.24 pg/mL, IL-10 at 3.28 pg/mL and IFN- $\gamma$  at 0.10 pg/mL on February 11, 2020 (Figure 2A). The lymphocyte absolute value increased from  $0.39 \times 10^9/L$  to  $1.39 \times 10^9/L$ , T cells from 254 to 788/ $\mu L$ , CD4 + T cells from 163 to 438/ $\mu L$ , CD8+T cells from 83 to 353/ $\mu L$ , NK cells from 44 to 104/ $\mu L$  and B cells from 76 to 455/ $\mu L$  on February 10, 2020 (Figure 2B). The dynamic course of changes in the total amount of white blood cells, the absolute value of lymphocytes and the oxygen index

during hospitalization are shown in Figure 3A. As of February 12, 2020, the previous exudation of the left lung was decreased significantly (Figure 1 C, D) and the patient returned to afebrile, with all symptoms in remission regarding their degree of severity (Figure 3B). The SARS-CoV-2 tests in swab specimen on February 13, 2020 and on February 16, 2020, and in feces on February 2, 2020 were negative. The lesions in lung almost disappeared on February 17, 2020 (Figure 1 E, F), and the patient was discharged.



**Figure 3.** White blood cells, oxygen index, symptoms, body temperatures and drug use during the treatment. A) Dynamic course of the total number of white blood cells and the oxygen index during hospitalization. B) Symptoms, body temperatures and drug use according to the day of illness and day of hospitalization, February 3 to February 17, 2020.

## Discussion

It has been well documented that host immune responses are important factors leading to life-threatening ARDS in COVID-19 patients<sup>6</sup>. Given the reported anti-inflammatory and immunomodulatory effects of thalidomide, we sought to treat this patient who had developed a severe COVID-19 pneumonia with thalidomide in combination with low-dose glucocorticoid. We report here that this therapeutic strategy had a beneficial outcome in this patient with severe COVID-19 pneumonia.

In the current case, acute pulmonary effusion was observed due to markedly elevated inflammatory cytokine profiles in the serum including IL-6, IL-10 and IFN- $\gamma$ , manifesting as a cytokine surge. The cytokine surge is an inappropriate (exaggerated) immune response that is caused by rapidly proliferating and highly activated T cells. In this process, more than 100 inflammatory mediators are released, and subsequently lead to tissues damage and organs failure<sup>7</sup>. High doses of Glucocorticoid are usually used for suppressing cytokine surge. For instance, glucocorticoids were widely applied during the outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) corona virus (CoV) infections to suppress lung inflammation and immune responses<sup>8-10</sup>. However, it appeared to be associated with treatment side effects, such as secondary bacterial infection, osteoporosis and others. Therefore, glucocorticoid was not recommended for severe COVID-19 as used in SARS-CoV or MERS-CoV infections<sup>11</sup>, also due to its inhibition of immune responses and pathogen clearance. Interestingly, we found that after combined treatment of thalidomide with low-dose glucocorticoid, the pulmonary effusion symptoms and elevated inflammatory cytokines in the present patient were substantially reduced without any side effect. Simultaneously, the number of lymphocytes recovered. These results indicated that thalidomide could be used in conjunction with low-dose steroids to treat a COVID-19 pneumonia, likely based on its known anti-inflammatory and immunoregulatory effects.

Previous studies indicated that thalidomide inhibited lung injury in mice with H1N1 influenza virus, improved survival,

reduced inflammatory cell infiltration and inhibited cytokines (IL-6 and TNF- $\alpha$ ) and chemokines (RANTES)<sup>12</sup>. Since the outbreak of SARS in China in 2002, cytokine surge syndrome has been widely credited as the cause of multiple organ dysfunction, with a high mortality rate. Similar to SARS, the immune system of critically ill COVID-19 patients also present with episodes of lethal cytokine surges, and thus aggravated inflammation, tissue damage and function deterioration. In view of the effect of thalidomide in blocking NF- $\kappa$ B binding to its target gene promoter, further studies have found that thalidomide combined with dexamethasone could effectively inhibit the excessive inflammatory response caused by the mutation of ECSIT V140A in hemophagocytic syndrome<sup>13</sup>. In addition, it was shown that thalidomide could activate T cell receptors and T cells to enhance immune functions<sup>14</sup>. Therefore, thalidomide not only alleviates organ injury by inhibiting the cytokine 'storm' but also improves immune functions to reduce secondary bacterial infections.

Furthermore, the beneficial effect of thalidomide on COVID-19 might also be attributable to its sedative and antiemetic activities that help an anxious patient calm down to reduce oxygen consumption, and alleviate digestive symptoms in this patient. As shown in the present case, thalidomide also promoted the absorption of the extensive pulmonary exudation probably by inhibiting the growth of new blood vessels<sup>15</sup>.

In summary, in addition to its ability to inhibit cytokine surge<sup>13</sup> and regulate immune functions<sup>16</sup>, thalidomide could be used to calm patients down to reduce oxygen consumption, and relieve digestive symptoms in COVID-19 patients. Therefore, thalidomide may shed new light on an adjuvant treatment strategy for this potentially lethal viral disease. A randomized controlled trial to investigate the effectiveness of thalidomide combined with low-dose glucocorticoid for COVID-19 pneumonia treatment needs to be performed.

## Declarations of interests

The authors have no conflicts of interest to declare.

## Informed consent

Written informed consent was obtained from the participant included in this study.

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