

# Severe Community-acquired Pneumonia Caused by Type 7 Human Adenovirus in Immuno competent Adults

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## Research article

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# Abstract

## Background

Severe community-acquired pneumonia (SCAP) caused by human adenovirus type 7 (HAdV-7) in immunocompetent adults has been of increasing concern recently. Clinical understanding of SCAP caused by HAdV-7 in adults remains limited, though the pathogen has been adequately identified by metagenomic next-generation sequencing (mNGS).

## Methods

We conducted a retrospective review of all patients with SCAP caused by HAdV-7 in immunocompetent adults admitted to Nanjing Drum Tower Hospital, a tertiary hospital in Nanjing, China, between July 2017 and April 2020. Clinical manifestation, laboratory findings, serial radiological characteristics, mNGS results, treatments and outcomes of these patients were collected and analyzed.

## Results

A total of 7 SCAP patients with confirmed HAdV-7 infections were included. All patients were positive for HAdV-7 DNA fragments by mNGS for BALF and blood specimens. The median of the identified reads of two groups were 2783 and 1038, and the median coverage rates were 99.3% and 97.7%, respectively. All the patients were male and the median age was 23 years. High fever (100%), cough (57.14%) and dyspnea (100%) were the most frequent symptoms at admission. Laboratory data showed slightly decreased leucocytes but high procalcitonin and C-reactive protein levels. At early stage, with median 5 days from onset of illness, consolidation (85.71%) and patchy ground-glass opacity (GGOs) (85.71%) in unilateral lung were the most common findings in severe HAdV CAP. Within median 8 days after illness onset into progressive stage, consolidation developed and was the predominant finding in all patients, and 6 patients (85.71%) showed bilateral consolidations. In convalescent stage with median 18 days after illness onset, the parenchymal abnormalities began to absorb.

## Conclusions

MNGS of blood or BALF could identify HAdV-7 infection accurately. Doctors should be aware of SCAP caused by HAdV-7 infection and perform mNGS as soon as possible when patients had persistent high fever, cough, decreased WBC, high C-reactive protein and consolidation and GGO in unilateral or bilateral lungs shown by chest CT scan.

## Patients And Methods

Severe community acquired pneumonia (SCAP) requires admission to intensive care unit(ICU), occupying 20% of the admission of community-acquired pneumonia (CAP) and the core pathogens include streptococcus pneumoniae, atypical pathogens and so on[1].The case fatality rate of CAP is as high as 21% ~ 54%[2] and human adenoviruses (HAdVs) account for about 4.8% of CAP[3]. HAdVs pneumonia typically is limited to children, immunocompromised hosts, and usually a cluster erupts [4], but with the development of metagenomic next-generation sequencing (mNGS) technology, HAdVs pneumonia has been increasingly found to be involved in sporadic cases and outbreaks of SCAP in adults. Though it is generally self-limited, once it has progressed to severe pneumonia, the fatality rate is extremely high[5, 6].

HAdVs, ubiquitous in the environment, are non-enveloped, double-stranded DNA viruses, To date, 69 HAdVs genotypes have been recognized and are assigned to seven subgroups (A–G) according to genetic and biochemical characteristics. HAdV-3 and HAdV-7 in subgenus B were not only widespread, but also prone to severe pneumonia in children. HAdV-7 caused more severe clinical manifestations than HAdV-3, even leading to death[7, 8].

There are few international reports on the epidemiological and clinical features of adult severe adenovirus pneumonia[9, 10]. However, HAdV pneumonia in immunocompetent adults and risk factors of disease progression to SCAP have not been well studied. This paper reports 7 cases of adult severe HAdVs pneumonia confirmed by mNGS technology in Drum Tower Hospital affiliated to medical college of Nanjing University in Jiangsu Province, China, and analyzes their clinical features and prognosis.

## Patients and methods

### Study population

We conducted a retrospective review of 7 critically ill patients with severe HAdVs pneumonia admitted to Nanjing Drum Tower Hospital, a tertiary hospital in Nanjing, China, between July 2017 and April 2020. The requirement for informed consent by individual patients was waived given the retrospective nature of the study. The criteria for severe CAP was defined by modified American Thoracic Society criteria[11] and all patients were positive for Human adenoviruses (HAdVs) DNA fragments by mNGS in bronchoalveolar lavage fluid (BALF) and blood specimens.

### Mngs Technology

Sequencing were performed at BGISEQ-100 platform (Beijing Genomics Institute, Wuhan, China). MNGS was conducted using the following operational steps: Collection and management of specimens: After obtaining the informed consent of the patient and his/her family for blood and BALF mNGS, 3 mL of peripheral venous blood of the patient was extracted or 1.5 mL of BALF was collected. Blood samples were stored at room temperature for 3–5 min and centrifuged at 4,000 RPM for 10 min within 8 h. BALF samples: 1 g glass beads with a diameter of 0.5 mm were added and mixed for 30 min. After treatment,

the specimens were frozen at -20°C. DNA extraction: 0.3 ml of treated blood or alveolar lavage fluid was performed, and DNA extraction was performed using TIANamp Micro DNA Kit (Beijing Tiangen Biotechnology Co., LTD.). Library construction and sequencing: Agilent 2100 Bioanalyzer quality control library was used to insert 200 ~ 300 bp fragments, which were cycled to form a single-chain ring structure. The cycled library was replicated by rolling ring (RCA) to produce DNA nanospheres (DNB). The prepared DNB was loaded into the sequencing chip and BGISEQ50 was used for sequencing (BGI Shenzhen Co., LTD.). Data analysis and detection value significance: Low quality and < 35 bp in length sequencing data were removed using BWA software (HTTP: // Bio-BWA). Sourceforge.Net /) alignment removes human host sequences from high-quality data. After further removing the low-complexity sequence, it was compared with the dedicated microbial large database, and the compared data were classified and arranged according to viruses, bacteria, fungi and parasites, etc., to report the standard reference for pathogenic bacteria[12]. The database includes 6,350 species of bacteria whose sequences are known (including 174 species of Mycobacterium and 137 species of Mycoplasma/chlamydia/ricketia), 1,798 DNA viruses, 1,064 fungal species and 234 parasitic species.

## Diagnostic Criteria For Scap Caused By Hadv

Patients diagnosed with SCAP caused by HAdVs had to meet the following three criteria: (1) meet the criteria for SCAP[13]; (2) have specific fragment DNA of HAdVs in BALF and/or blood specimen identified using mNGS; and (3) excluded other etiological pathogen, including bacteria, fungi and other viruses, no other causative infectious location identified.

## Clinical Data Collection

Investigators collected clinical data through the electronic medical record system in Nanjing Drum Tower Hospital, a tertiary hospital in Nanjing, China, including demographic data (age, gender), underlying diseases, clinical symptoms, such as fever, cough, sputum, dyspnea, chest pain, dyspnea, diarrhea, myalgia and sore throat), laboratory findings, arterial blood gas analysis, the discovery of microorganisms (including HAdV type) and chest imaging data, drug therapy, respiratory support, complications, and overall prognosis were also recorded.

## Results

### Clinical characteristics

A total 7 cases were confirmed with HAdV-7 as the only pathogen of pneumonia and all were admitted to the intensive care unit (ICU) and fulfilled the criteria of SCAP. 100% cases were male and the median age was 23 (range 22–27) years (Table 1). All patients were positive for HAdV-7 DNA fragments by mNGS for BALF and blood specimens synchronously (Table 2). The median of the identified reads of the two groups were 2783 ( 1112-3319.5) and 1038 ( 383.5-1813.5), and the coverage rates were 99.3 ( 89.6–99.6) % and

97.7 (82.6–98.9) %, respectively. Meanwhile, systematic screening did not reveal any other respiratory pathogens and other infectious location on admission to our hospital.

Table 1

Demographic, clinical, laboratory and outcomes of patients with SCAP caused by adenoviruses

<b>Characteristics</b>	<b>Patients, n,(%)</b>	<b>Median value,(IQ range)</b>
Age,years		23 (22–27)
Male sex,%	7/7(100)	
Underlying disease	0/7(0)	
Days from onset of illness at admission		7 (4–8)
APACHEII score		12(10–21)
SOFA score		7(5–10)
<b>Clinical features</b>		
Tmax, °C	7/7(100)	39.8(39.2–40.5)
Cough	6/7(85.71)	
Purulent sputum	1/7(14.29)	
Bloody sputum	2/7(28.57)	
Dry cough	4/7(57.14)	
Chest pain	2/7(28.57)	
Dyspnea	7/7(100)	
Days from illness to dyspnea		7(5–7)
Diarrhea	1/7(14.29)	
Myalgia	2/7(28.57)	
Sore throat	1/7(14.29)	
Septic shock	1/7(14.29)	
<b>Laboratory finding</b>		
Decreased leukocyte (normal 4–10, × 10 <sup>9</sup> /L)	5/7(71.43)	3.8(2.2-6.0)
Increased PCT (normal 0-0.5 ng/mL)	5/7(71.43)	1.14(0.4–9.82)
Elevated CRP (normal 0–8 mg/L)	7/7(100)	142(74–208)

SCAP, severe community-acquired pneumonia, APACHEII, acute physiology and chronic health evaluation II; SOFA, simplified acute physiology score; PCT, procalcitonin, CRP, C-reactive protein, AST, aspartate aminotransferase, ALT, alanine aminotransferase;LDH, lactic dehydrogenase; CK, creatine kinase; mHLA-DR, monocyte human leukocyte antigen-DR; HFNC, high-flow nasal cannula oxygen therapy; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement treatment.

<b>Characteristics</b>	<b>Patients, n,(%)</b>	<b>Median value,(IQ range)</b>
Elevated AST (normal 0–40 U/L)	7/7(100)	210.5(117.5-978.5)
Elevated ALT (normal 0–40 U/L)	6/7(85.71)	108.0(57.75-393.25)
Elevated LDH(normal 109–245 U/L)	7/7(100)	2150(1381–2150)
Elevated CK (normal 30–135 U/L)	7/7(100)	1648.5(1246.75-20674.25)
Decreased CD4 + T cell(normal 500–1100, × 10 <sup>6</sup> /L)	7/7(100)	173(108–258)
Decreased mHLA-DR, % (80–100%)	3/7(42.85)	52.2(48.5–87.0)
<b>Respiratory support</b>		
HFNC	1/7(14.29)	
Noninvasive ventilation	1/7(14.29)	
Mechanic ventilation	5/7(71.43)	
ECMO	3/7(42.85)	
<b>CRRT</b>	4/7(57.14)	
<b>Antiviral therapy</b>		
Ribavirin	6/7(85.71)	
Cidofovir	1/7(14.29)	
<b>Outcomes</b>		
Length of ICU stay, days		14(10–25)
Length of hospital stay, days		20(15–40)
In-hospital mortality	7/7(100)	
<p>SCAP, severe community-acquired pneumonia, APACHEII, acute physiology and chronic health evaluation II; SOFA, simplified acute physiology score; PCT, procalcitonin, CRP, C-reactive protein, AST, aspartate aminotransferase, ALT, alanine aminotransferase;LDH, lactic dehydrogenase; CK, creatine kinase; mHLA-DR, monocyte human leukocyte antigen-DR; HFNC, high-flow nasal cannula oxygen therapy; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement treatment.</p>		

Table 2  
Synchronous HAdV-7 mNGS results of blood and BALF specimens of severe CAP caused by adenoviruses (median, range)

Specimen type	Days from onset to specimen acquisition	mNGS	
		Identified reads	Coverage rates (%)
BALF(n = 7)	8(5–9)	2783(1112-3319.5)	99.3(89.6–99.6)
Blood(n = 7)		1038(383.5-1813.5)	97.7(82.6–98.9)

mNGS, metagenomic next-generation sequencing; BALF, bronchoalveolar lavage fluid; CAP, community-acquired pneumonia

As shown in Table 1, flu-like symptoms, such as fever, cough, especially dry cough (57.14%) were the most commonly observed from the onset of illness. All patients presented with a high fever with a median highest temperature of 39.8 °C (range 39.2 °C to 40.5 °C). Other symptoms included diarrhea (14.29%), myalgia (28.57%) and sore throat (14.29%). all patients (100%) showed apparent dyspnea at admission, with median oxygen index (OI)120 mmHg (range 89–152 mmHg). The median time from onset to ICU admission was 7 days, with mean Acute Physiology and Chronic Health Evaluation and Sequential Organ Failure Assessment scores of 12 and 7, respectively.

Laboratory findings at admission were showed in Table 1. 5 of 7 cases had decreased leukocyte, with a mean white blood cell count of  $3.8 \times 10^9/L$ , percentage of neutrophils, 71.43%. all cases had elevated C-reactive protein (CRP) level of median 142 mg/L, and 5 cases had elevated procalcitonin (PCT) level of median 1.14 ng/ml. Serum aspartate aminotransferase (AST), aspartate aminotransferase( ALT),lactate dehydrogenase (LDH) and creatinine phosphokinase (CK) levels were elevated almost in all cases. CD4 + T cell count were all dramatically decreased to median  $173 \times 10^6/L$  (range 108–258  $\times 10^6/L$ ) and 3 cases (42.85%) had decreased monocyte human leukocyte antigen-DR (mHLA-DR), with median 52.2%.

All the patients had type I respiratory failure and received different oxygen therapy at admission, 1 with high-flow nasal cannula (HFNC), 1 with noninvasive ventilation, other 5 with tracheal intubation and mechanic ventilation. Among them, 3 patients deteriorated rapidly and received extracorporeal membrane oxygenation (ECMO) treatment.

4 cases (57.14%) had acute kidney injury and received continuous renal replacement treatment (CRRT). All the 7 patients had received antiviral treatment, 6 cases with riboviron (85.71%) and 1 with cidofovir (14.29%), which remains side effect of chronic renal failure. The median period of treatment was 7 days. All patients were survived, with median 14 days of ICU stay and median 20 days of hospital stay.

## Radiographic Features

CT scan changes at different stages with SCAP caused by HAdVs were showed in Table 3 and Fig. 1. At early stage, with median 5 days from onset of illness, consolidation (85.71%) and patchy ground-glass opacity (GGOs) (85.71%) were the most common findings in severe HAdV CAP. Small nodules were revealed as predominant in two patients (28.57%). Lesion involvement was often limited to unilateral lung and the most commonly involved lobe was the right lower lobe (n = 4, Figs. 2A), followed by the left lower lobe (n = 3, Figs. 1A). Within median 8 days after illness onset into progressive stage, consolidation developed and was the predominant finding in all patients, and 6 patients showed bilateral consolidations accompanied by GGOs in 3 patients (Figs. 1B and 2B). In convalescent stage with median 18 days after illness onset, the parenchymal abnormalities began to absorb (Figs. 1C, 2C and 2D). Follow-up radiologic findings after 3 months of discharge, lesions continued to absorb with appearances of fibrosis (Figs. 1D).

Table 3  
CT scan changes at different stages with severe CAP caused by adenoviruses

Characteristic	Early stage	Progressive stage	Convalescent stage
Day from onset, median(range)	5(3–5)	8(7–9)	18(14–22)
<b>Dominant pattern, n,(%)</b>			
Lobar consolidation	6/7(85.71)	7/7(100)	6/7(85.71)
Small nodules	2/7(28.57)	1/7(14.29)	2/7(28.57)
Patchy ground glass opacity	6/7(85.71)	3/7(42.85)	5/7(71.43)
<b>Laterality, n,(%)</b>			
Unilateral	7/7(100)	1/7(14.29)	2/7(28.57)
Bilateral	/	6/7(85.71)	5/7(71.43)
<b>Lung zone, n,(%)</b>			
Lower	7/7(100)	5/7(71.43)	6/7(85.71)
Upper	/	/	/
Random	/	/	/
Both upper and lower		2/7(28.57)	1/7(14.29)
<b>Location of mainly involved lobe, n,(%)</b>			
Left upper lobe	/	3/7(42.85)	2/7(28.57)
Left lower lobe	3/7(42.85)	4/7(57.14)	4/7(57.14)
Right upper lobe	/	/	/
Right lower lobe	4/7(57.14)	7/7(100)	5/7(71.43)

## Discussion

In the absence of appropriate diagnostic methods, the incidence of CAP due to virus infection is far underestimated[14]. In recent years, with the development of molecular diagnostic methods, more and more CAPs caused by viruses have been recognized. HAdV-caused CAP has been confirmed to account for 1–7% in immunocompetent adults = [4]. In this study, all the patients confirmed HAdV-7 infection through mNGS in BALF and blood specimens and clinically characterized by SCAP.

Severe adenovirus CAP is clinically difficult to differentiate from bacterial and mycoplasma pneumonia. Combine age, season, underlying disease and risk factors, clinical symptoms or signs, chest imaging features, laboratory tests, etc., to preliminarily infer the possible pathogen in clinical practice. Studies have shown that the immunocompetent HAdV SCAP patients, mainly for different degrees of fever, irritation dry cough, and headache, fatigue, chest tightness, poor appetite, diarrhea and other non-specific systemic toxemia. Most of the symptoms are not serious, a few can quickly progress to severe pneumonia[15, 16]. Common laboratory findings include leukopenia, lymphopenia, elevated transaminases and occasionally leukocytosis with neutrophilia[17]. From above all, these symptoms and laboratory findings are common in severe viral infections and lack specificity.

Therefore, in the absence of etiological detection, the diagnosis of adenovirus pneumonia is mainly dependent on imaging features. It has been reported that GGO is the early characteristic imaging feature and consolidation is the typical CT appearance in HAdVs pneumonia[18]. The patient's imaging abnormalities in this study appeared early and advanced rapidly. In early stage from onset, CT scans showed the lesion were dominated by consolidation, GGO and other focal morphology, mostly in the lower lobes in unilateral lung. As the disease progressed, the lesions spread from unilateral to bilateral lungs, and the consolidation shadow enlarged and becomes the most prominent feature in progressive stage. After about two weeks, the patient's condition gradually improved and the lesions gradually absorbed, partly remaining fibrous lesions.

Currently, clinical HAdVs diagnosis mainly relies on specific nucleic acid sequence PCR and antibody detection, but low positive rate and often difficulty in differentiating clinical subtypes[19]. MNGS technology, a new type of pathogen detection technology, collects the wall of segments of nucleic acid in specimen, amplification detection after its sequence, then through bioinformatics analysis and the quantitative analysis of sequence number and coverage can be obtained. MNGS has the merit of high sensitivity, fast screening and has been widely used in bacteria, fungi, virus and mycoplasma detection[20, 21]. HAdV-7 was identified in blood and BALF of these 7 patients in this study by mNGS, with high median DNA detection sequence and mean coverage above 90%, indicating that mNGS has good credibility in detecting HAdV-7. It is indicated that HAdV ran into the bloodstream after pulmonary infection to cause systemic symptom, so DNA sequence of digits and coverage in BALF were more than those in blood HAdV-7 detection, even so, the median detection sequence in blood specimen is still up to 1038, average coverage of 97.7%, suggesting even in blood high sensitivity of mNGS for HAdV-7 were obtained.

The optimal treatment for severe adenovirus infections has not been established. Cidofovir has been proven to be effective in treating adenovirus pneumonia.[9, 22–24]. However, it is expensive, difficult to obtain in China, and has serious side effects, mainly including renal and hematological toxicity. Ribavirin is a broad-spectrum antiviral drugs of nucleoside analogues that are less toxic and have shown efficacy in treating severe adenovirus infections in children and immunocompromised adults[4, 25]. In this study, 6 patients were treated with ribavirin and 1 with cidofovir for antiretroviral therapy, with no significant difference in efficacy and mortality. All 7 patients were survived, but patients treated with cidofovir had complications of chronic renal failure and required long-term dialysis.

The pathogenesis of severe adenovirus pneumonia in adults is still unclear. The possible mechanism is that HAdV could bind to the cell receptors of target cells, causing the expression and release of inflammatory mediators such as interleukins and chemokines. Excessive release of pro-inflammatory cytokines (such as IL-6, IL-10, TNF-, IFN-, etc.) can cause tissue damage, leading to acute lung injury and multiple organ dysfunction[26]. All the 7 patients in in this study were healthy young healthy adults before their illness and had no underlying disease. However, the count of CD4 + T cell and mHLA-DR% dramatically decreased at admission, suggesting that both cellular immunity and humoral immunity were both impaired. Previous studies have shown that most of the acute damage for body caused by adenovirus infection may be due to immune system disorders[27, 28].These findings may partly explain the self-limiting nature of severe HAdV infection whatever antiviral therapy use, and suggest that host immune response to infection is a major factor in the pathogenesis of lung injury. But the mechanism by which adenovirus impairs cellular and humoral immunity in a healthy body is not clear and further research is needed.

Our study has several limitations. First, there were a relatively small number of cases because of the relatively low incidence of in immunocompetent adults. Second, the study was a retrospective study, no dynamic monitoring of laboratory tests and viral loading were made. Finally, the study is a single-center study and the results may be limited.

In conclusion, the number of adenovirus pneumonia in adult patients has been increasing in recent years. It is recommended to routinely conduct chest CT scan for suspected adenovirus patients to detect early pulmonary lesions, and pay attention to pathogenic screening, especially mNGS technology, for timely detection, early antiviral and respiratory function support treatment.

## **Declarations**

## **Conflict of interest statement**

All work has been approved by all co-authors. Ying Xu and Qin Gu made substantial contributions to the conception and design; the acquisition of data was performed Ying Xu; the analysis and interpretation of data were performed by Ying Xu and Ning Liu; Ying Xu and Qin Gu wrote the draft of the article and

revised it critically for intellectual content. Mingran Shao re-evaluated and added content on the CT imaging outcomes. The final version was approved by all authors. No conflicts of interest exist in the submission of this manuscript. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part.

## Ethical approval

This study was approved by the Ethical Committee of Drum Tower Hospital affiliated with the Medical School of Nanjing University.

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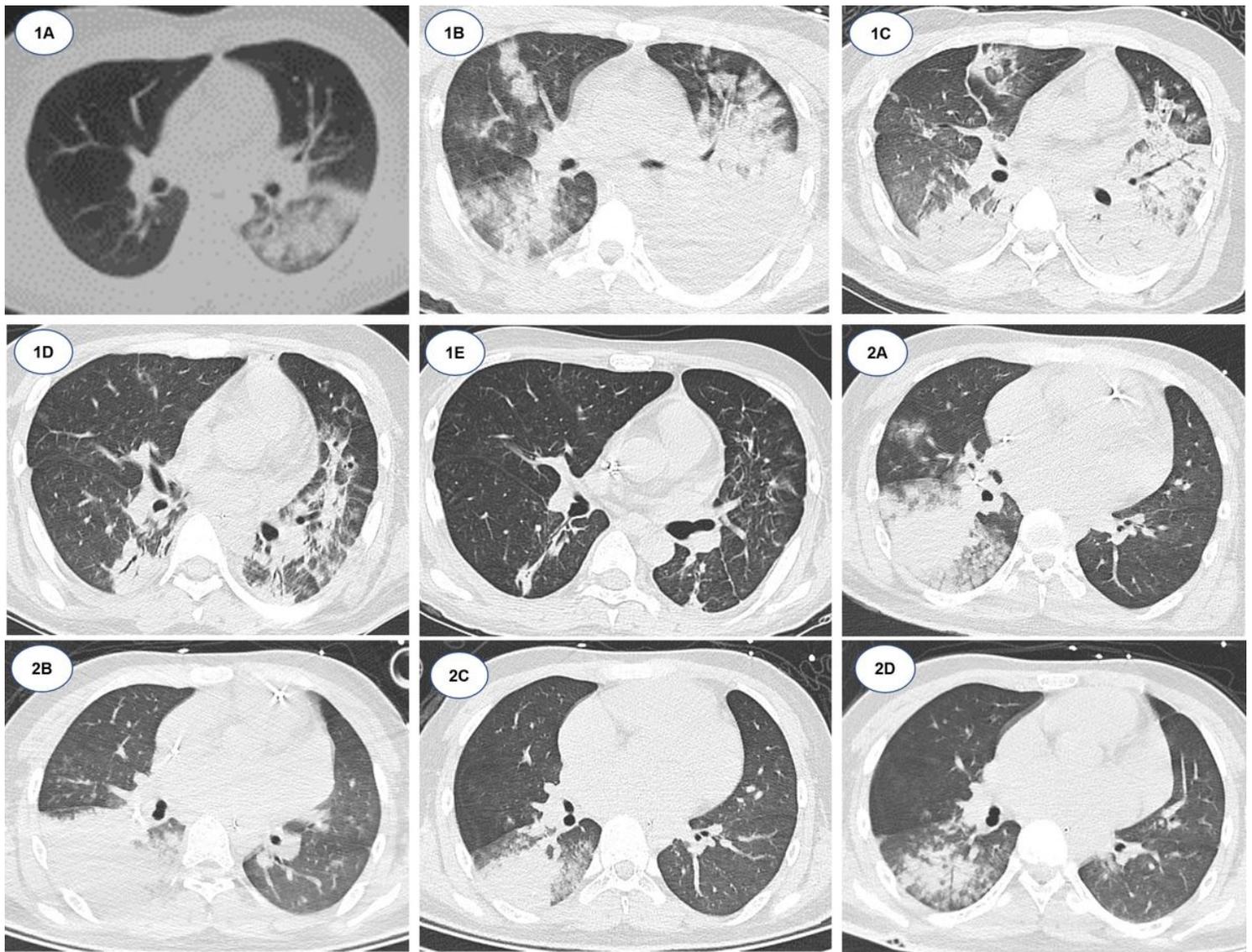
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## Figures



**Figure 1**

1A-1E A 24-year-old male patient was admitted due to "fever for 8 days, cough and wheezing for 2 days". A chest CT scan showed lamellar ground glass opacities (GGOs) of the left lower lung on day 6 after onset (1A). On the 8th day after onset, there were large consolidation shadows in the left lung and multiple GGOs in the right lung (1B). The oxygenation index (OI) was 72 mmHg (1 mmHg = 0.133 kPa), and ECMO treatment was performed. On the 18th day after onset, the left lung consolidation had undergone absorption, and the right lower lung had developed small consolidation shadows (1C). The patient was weaned from ECMO. On the 32nd day after onset, the shadows of the bilateral lung consolidation had undergone more absorption, and remaining fibrous foci were observed (1D). At the follow-up 3 months after discharge, the bilateral lung lesions had mostly dissipated, leaving a few fibrous foci (1E). 2A-2D A 14-year-old male patient was admitted due to "fever for 5 days, chest tightness for 3 days". A chest CT scan showed consolidation of the lower lobe of the right lung with multiple GGOs on the 5th day after onset (2A). On the 8th day after onset, consolidation was more advanced in the right middle and lower lobe, and few GGOs appeared in the left lung (2B). The OI was 162 mmHg. On the 14th

day after onset, the consolidation in the right lung had undergone more absorption (2C). On the 21st day after onset, the consolidation in both lungs was more diffuse (2D).