Acute Respiratory Distress Syndrome Caused by Human Adenovirus in Adults: A Prospective Observational Study in Guangdong, 2019–2020

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Research

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Abstract

Background: Viral causes of acute respiratory distress syndrome (ARDS) are mostly limited to influenza. However, adenovirus has been emerging as a cause of ARDS with a high mortality rate and described in adults are rare.

Methods: We conducted a prospective, single-center observational study of viral pneumonia with ARDS and confirmed adenovirus-associated ARDS in adults at our quaternary referral institution between March 2019 and June 2020. We prospectively analyzed clinical characteristics, laboratory test results, radiological characteristics, viral load from nasopharyngeal swabs and endotracheal aspirates, treatments, and outcomes for the study participants.

Results: The study enrolled 143 ARDS patients, including 47 patients with viral pneumonia-related ARDS, among which there were 14 adenovirus-associated ARDS patients, which accounted for 29.79% of the viral pneumonia-related ARDS cases. Among the adenovirus-associated ARDS patients, 78.57% were men with a mean age of 54.93 ± 19.04 years. Adenovirus-associated ARDS patients had no specific clinical characteristics, but they presented with shortness of breath and fever, and their initial chest radiographic findings were multifocal or showed diffuse opacity. The viral load and the positivity rate in the lower respiratory tract were higher than that of the upper respiratory tract in the patients with adenovirus-associated ARDS, and 85.71% of the patients had a significant decrease in the number of CD3+CD4+ T cells during the early stage. All patients required invasive mechanical ventilation treatment. The average time from shortness of breath to the application of invasive ventilation was 24 hours. The median duration of invasive mechanical ventilation was 22 days (14–75 days). Six patients (42.86%) required renal replacement therapy, and three patients (21.43%) required extracorporeal membrane oxygenation support. Additionally, 85.71% of the 14 adenovirus-associated ARDS patients survived.

Conclusion: Adenovirus infection is an important cause of virus-related ARDS. The positivity rate of adenovirus infection in lower respiratory tract secretions was higher than that in upper respiratory tract secretions in these patients. Most of the patients had a significant decrease in the number of CD3+CD4+ T cells during the early stage. Early identification and intervention to prevent disease progression are essential for reducing the mortality rate in these patients.

Background

Acute respiratory distress syndrome (ARDS) is a rapid inflammatory lung injury with a high mortality rate that ranges from 30.0–46.0% [1–3]. Infectious pneumonia is the most common disease leading to ARDS, with viral infection accounting for approximately 22–40% of cases [4, 5]. Influenza and rhinovirus have been most commonly detected in viral pneumonias followed by parainfluenza, adenovirus, respiratory syncytial virus, coronavirus, and human metapneumovirus [4, 6]. However, the proportion of viral pneumonia leading to ARDS is unknown. Some viral infections, such as influenza A H1N1, H5N1, and H7N9 and the coronaviruses severe acute respiratory syndrome (SARS), severe acute respiratory

syndrome coronavirus-2 (SARS-CoV-2), and Middle East Respiratory Syndrome (MERS), are associated with a high incidence of ARDS and increased mortality [7, 8]. An increased number of adenoviruses has been isolated from patients in recent years due to the development of molecular diagnostic technology [9]. Adenovirus-associated ARDS has been reported in adult patients with rapid progression to multi-organ failure and death, which has raised concerns. Additionally, there is limited information on ARDS and no consensus on its management [10].

Human adenoviruses (HAdVs) are non-enveloped DNA viruses that are associated with a wide range of clinical manifestations [11]. Adenovirus infection that causes severe fatal pneumonia has been well described in infants and children, but reports in adults are rare [12]. HAdV-associated ARDS infection is a devastating disease with rapid progression to multi-organ failure and death, and it can be fulminant with a mortality rate of approximately 40% in adult patients who require mechanical ventilation [13]. Patients with HAdV-associated ARDS have a poor survival rate.

Here, we performed a prospective, observational study to evaluate the proportion of viral pneumonia leading to ARDS in adult patients. We reported the cases patients with adenovirus-associated ARDS who required mechanical ventilation in the medical intensive care unit at our quaternary referral institution between November 2019 and December 2020. We analyzed clinical test results, laboratory test results, radiological characteristics, sequential viral load test results on nasopharyngeal swabs and endotracheal aspirates, treatments, and outcomes in these patients.

Methods

Study design and population

We performed a prospective, single-center observational study in adult patients with viral pneumonia with ARDS who were admitted to our respiratory intensive care unit (ICU) between March 2019 and June 2020. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. All patients provided written informed consent for their data to be used for research.

Severe ARDS was diagnosed in accordance with the Berlin definition [2], as follows: (1) developing within 1 week of a known clinical insult or new or worsening respiratory symptoms; (2) bilateral opacities not fully explained by effusions, lobar and/or lung collapse, or nodules; (3) respiratory failure not fully explained by cardiac failure or fluid overload; (4) partial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ≤ 100 mmHg with positive end-expiratory pressure (PEEP) ≥ 5 cmH_2O; and (5) a chest radiograph with three or four quadrants with opacities. Patients with HAdV-55 infection and severe ARDS who failed conventional non-invasive positive pressure ventilation and invasive mechanical ventilation (IMV) were included in the analysis.

Clinical data collection

A standardized electronic case report form was used to prospectively collect the study data. The following data were obtained: age, sex, body mass index (BMI), preexisting comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHEII) score, daily Sequential Organ Failure Assessment (SOFA) score, and clinical pulmonary infection score (CPIS). Clinical symptoms (fever, cough, sputum, and dyspnea), signs (body temperature, heart rate, respiratory frequency, and blood pressure), and laboratory data (procalcitonin, white blood cell count, lymphocyte, platelet count, and creatinine level), microbiological findings, and images of the lung (chest X-ray and computed tomography) were also collected. Additionally, complications, treatments, respiratory support, and clinical outcomes were recorded.

Molecular assay for respiratory virus detection

Nasopharyngeal swabs and endotracheal aspirates (ETA) were collected at admission and during hospitalization and stored at − 80°C until testing. All nasopharyngeal swabs and ETA samples were analyzed using multiplex quantitative polymerase chain reaction (Q-PCR) technology. This assay tested for 24 respiratory viruses (adenovirus; influenza virus type A H1N1, H3N2, H1N1 2009, H5N1, and H7N9; influenza virus type B; respiratory syncytial virus types A and B; parainfluenza viruses type 1, 2, 3, and 4; metapneumovirus; coronavirus OC43, 229E, NL63, HKU1, SARS, and MERS; rhinovirus; bocavirus; Nipah virus; and circovirus).

The viral load was indicated as the cycle threshold (Ct) value. Ct values were used to analyze each patient's viral load. Ct values were inversely correlated to the quantity of RNA target present in the specimen. A Ct value of < 40 was defined as positive for the viruses and > 40 was defined as a negative result. Samples with a Ct value between 37 and 40 were retested at least twice.

Statistical analysis

Measurement variables were summarized using the median (interquartile range) or the mean and range,. and enumeration variables were presented using the frequency and percentage. The Student's *t*-test or the Mann–Whitney U-test was used to compare the measurement variables, and $p < 0.05$ was considered to be significant. Statistical analysis was performed using GraphPad Prism 7.0.

Results

The study included 143 patients, including 47 patients (32.87%) with viral pneumonia-related ARDS and 14 adenovirus-positive ARDS patients, which accounted for 29.79% of viral pneumonia-related ARDS (Fig. 1).

The general condition and clinical characteristics of the patients with adenovirus-associated ARDS are shown in Table 1. The mean age was 54.93 ± 19.04 years, and 78.57% were males, 50% were smokers, and 71.43% had high nutritional risk (Table 1). In addition, 28.57% of the patients had concurrent lung diseases, and 28.57% of the patients also had an immunodeficiency. All patients had cough, sputum expectoration, and shortness of breath, and 92.86% of them had a fever. Most patients presented with a

low-grade fever. As shown in Table 2, the PaO_2/FiO_2 for 64.29% of the patients was between 150 and 200 mmHg. Most of the patients had normal blood CO_2, manifesting as type I respiratory failure. The average time from the onset of shortness of breath to tracheal intubation was 24 hours. Hypoproteinemia occurred in 85.71% of the patients, and abnormal coagulation function occurred in > 60% of the patients. At the time of enrollment, 64.29% of the patients had a low total number of white blood cells, and more than 70% of the patients had a decrease in the total number and percentage of lymphocytes. Additionally, 85.71% of the patients had a significant decrease in the number of CD3 + CD4 + T cells during the early stage and an increase in interleukin (IL)-6 levels. Most of the patients had diffuse infiltrates in both lungs. Three (21.43%) of the patients had interstitial abnormalities. Five patients (35.71%) had pleural effusions. Only a few patients showed ground-glass opacity (Fig. 2).

Table 1
Demographic data and clinical characteristics of the patients with adenovirus-associated ARDS

	Mean ± Standard Deviation,n(%)
Sex(male)	11(78.57%)
Age(years)	54.93 ± 19.04
BMI(kg/m^2)	20.30 ± 3.03
APACHEII Score	19.14 ± 7.35
SOFA Score	10.50 ± 4.09
CPIS Score	6.50 ± 1.15
Smoking	7(50%)
Nutrition Score	5.64 ± 2.31
High Nutritional Risk	9(64.29%)
Underlying lung disease	
COPD	2(14.28%)
Bronchiectasis	1(7.14%)
Interstitial lung disease	1(7.14%)
Immunodeficiency	4(28.57%)
Symptoms	
Fever	13(92.86%)
Cough	14(100.00%)
Shortness of breath	14(100.00%)
Temperature(℃)	
36.0-37.2	7(50%)
37.3–38.0	5(35.71%)
38.1–39.0	1(7.14%)
39.1–41	1(7.14%)
Heart rate(bpm)	98.36 ± 24.11
Respiratory Rate(bpm)	22.93 ± 6.96
MAP(mmHg)	75.86 ± 12.27

	Mean ± Standard Deviation,n(%)
Co-infection	
Other viruses	
Influenza Virus	2(14.29%)
Human Coronavirus OC43	1(7.14%)
Human Rhinovirus	1(7.14%)
Bacteria	10(71.43%)
Acinetobacter baumannii	6(42.86%)
Stenotrophomonas Maltophilia	3(21.43%)
Klebsiella pneunoniae	2(14.29%)
Other bacteria	4(28.57%)

Table 2
Laboratory findings and radiographic results for patients with adenovirus-associated ARDS

Characteristic	Mean ± Standard Deviation,n(%)
White blood cell count,×10⁹ /L	12.66 ± 6.40
< 4	0
> 10	9(64.29%)
Platelet count,×10⁹ /L	165.43 ± 103.26
≤100	5(35.71%)
Lymphocyte, ×10⁹ /L	0.64 ± 0.49
≤0.9	10(71.43%)
CD3 + CD45 + T, Cell/UL	278.00(171.50–634.00)
≤955	12(85.71%)
CD3 + CD4 + T, Cell/UL	148.00(106.00-365.00)
≤550	12(85.71%)
CD3 + CD8 + T, Cell/UL	120.00(57.50–282.00)
≤320	11(78.57%)
Interleukin-6,pg/ml	39.37(12.53-143.06)
≤5.3	12(85.71%)
Procalcitonin, ng/mL	0.38(1.90–4.66)
≤0.05	14(100.00%)
Arterial blood gas analysis:	
pH	7.37 ± 0.09
pCO_2,mmHg	44.12 ± 6.83
P/F	168.59 ± 41.77
≤150	5(35.71%)
150–200	9(64.29%)
Albumin, g/L	30.96 ± 10.14
≤35	12(85.71%)
Prothrombin time, s	16.06 ± 2.73

Characteristic	Mean ± Standard Deviation,n(%)
≥14.5	10(71.43%)
Activated partial thromboplastin time,s	51.23 ± 28.21
≥42.8	9(64.29%)
Creatinine, umol/L	162.55(87.50-282.50)
≥133	9(64.29%)
Abnormalities on chest radiograph	
Ground-glass opacity	2(14.29%)
Bilateral patchy shadowing	14(100%)
Interstitial abnormalities	3(21.43%)
Pleural effusions	5(35.71%)

Within 48 hours of enrollment, paired upper respiratory tract (URT) samples (nasopharyngeal swab) and lower respiratory tract (LRT) samples (sputum and bronchoalveolar lavage) were collected from the patients to detect the virus using multiplex Q-PCR. As shown in Table 3, the LRT samples showed a significantly higher positive rate (100%, 14/14) than URT samples (64.29%, 9/14) for detecting respiratory viruses ($p < 0.001$), and LRT samples had higher levels of detection using a Ct value of 31.66 (20.56–34.78) compared with URT sampling using a Ct value of 39.14 (27.95–40) (Fig. 3). On average, URT sites cleared faster than LRT sites (Fig. 4). Detection of other viruses, fungi, and bacteria from the sputum collected from patients within 48 hours of enrollment showed that four patients (28.57%) also had another viral infection, and among these patients, the most common virus was the influenza virus that accounted for 14.29% of viral infections. Nine patients (64.29%) had positive bacterial cultures in the sputum, with the highest positivity rate for *Acinetobacter baumannii*, which was detected in six patients (42.86%). All patients had a negative fungal culture from the sputum, blood, and bronchoalveolar lavage fluid in (1–3)-β-D-glucan (G) and galactomannan (GM) tests.

Table 3
Comparison of multiplex Q-PCR results between URT and LRT samples

	URT	LRT	*P* value
Detected n (%)	9(64.29%)	14(100%)	< 0.001
Undetected n (%)	5(35.71%)	0	< 0.001
Time of virus clearance(days)	15.16(4–37)	24.17(6–42)	< 0.001

All patients received antiviral therapy, including ganciclovir (5 mg/kg intravenously every 12 hours) and oseltamivir. Considering that bacterial coinfection may combine with a severe viral infection, broad-

spectrum intravenous antibiotics were administered to all patients. Additionally, 78.57% of the patients received immunoglobulin. All patients required invasive ventilation, and the median duration of mechanical ventilation was 22 days (interquartile range [IQR], 14–75 days). Three patients (21.43%) required extracorporeal membrane oxygenation (ECMO), with a treatment duration of 7 to 12 days, and one patient (7.14%) underwent prone position ventilation. The average length of ICU stay was 26.50 days (IQR, 15–75 days), and the median length of hospital stay was 37.5 days (IQR, 29.75–81.00 days). Among the 14 patients in this study, there were two deaths, with a mortality rate of 14.29% during the study period (Table 4).

Table 4
Complications, treatments, and clinical outcomes in patients with adenovirus-associated ARDS

Characteristic	No(%)/Median(Interquartile range)
Complications	
AKI	10(71.43%)
Sepsis shock	4(28.57%)
Pneumothorax	2(14.29%)
Treatments	
CRRT	6(42.86%)
ECMO	3(21.43%)
Prone position ventilation	1(7.14%)
Vasoactive	11(78.57%)
Muscle relaxants	11(78.57%)
Intravenous immune globulin	6(42.86%)
anti-viral agents	
Oseltamivir	7(50.00%)
Ganciclovir	11(78.57%)
Clinical outcomes	
Duration of dyspnea to IMV	1.00(1.00–2.00)
Duration of IMV(days)	22.00(14.00-75.25)
Length of ICU stay(days)	26.50(15.75–75.25)
Length of hospital stay(days)	37.50(29.75-81.00)
Death	2(14.29%)

Discussion

The number of ARDS cases caused by viral pneumonia is increasing, resulting in a high mortality rate [14]. Previous studies have mostly focused on influenza viruses, such as H1N1 and H7N9 [15, 16]. Cases of adenovirus-associated ARDS have gradually been increasing, which may be due to recent developments in molecular diagnostic technology [17]. However, there is limited data about the viral etiology of ARDS in patients who required mechanical ventilation. Zhou et al. reported that the incidence of adenovirus pneumonia ranks third among viral pneumonia in adults in China [6]. They have also found that among virus-related ARDS patients with PO_2/FiO_2 ratio < 200 mmHg, HAdV infection was the most frequently detected virus [6]. Our study showed that in all ARDS patients, virus-related ARDS accounted for 32.87% of infections. Among these infections, adenovirus-associated ARDS accounted for 9.79% of all ARDS patients and 29.79% of virus-related ARDS patients. The prevalence of respiratory viruses varies in different countries and different populations [4–6, 13]. To the best of our knowledge, this is the first study about the viral etiology in ARDS patients who required mechanical ventilation in China.

There are few studies on adenovirus-associated ARDS in adults who required mechanical ventilation [4–6, 13]. In 2000, two non-immunocompromised soldiers became infected with adenovirus, which resulted in ARDS [4–6, 13]. In 2006, there was an outbreak of adenovirus pneumonia caused by HAdV-B11 in the USA; 140 people were diagnosed with HAdV infection, and 24 patients who were diagnosed with ARDS were admitted to the ICU [22]. Some studies have proposed that severe adenovirus infection is likely to occur in children and immunocompromised adults, such as HIV patients, and patients after transplantation [23, 24]. In this study, most of the adenovirus-associated ARDS patients, with a mean age of 54 years, had no underlying diseases. Among these patients, 78.57% of them were men, and 50% of the patients were smokers, suggesting that severe adenovirus pneumonia in non-immunocompromised adults was likely to occur in middle-aged men. Additionally, 85.71% of the patients had a significant decrease in the number of CD3 + CD4 + T cells during the early stage, which suggests that adenovirus infection may cause immune system dysregulation.

Delayed clearance of respiratory adenovirus infection leads to a worse prognosis in these patients, and monitoring the viral load may help to predict the disease severity and the patients' prognosis [25, 26]. Rapid identification of adenovirus viral infection is critical to reduce the overall costs of patient management. Multiplex Q-PCR is of great value in the early diagnosis of virus infection because of its high sensitivity [27, 28]. However, viral testing of URT and LRT samples may yield different results [27, 28]. Currently, few studies have been published that compare the diagnostic yields of URT and LRT samples to detect adenovirus. In our study, the detection rates of adenovirus from LRT and URT samples were 100% and 64.29%, respectively. Similarly, a European study in 2016 reported that the overall virus positivity rate of URT was lower than that of the LRT specimens (24.5% vs. 44.2%) [30]. In this study, the percentage of positive specimens was higher in LRT than in URT specimens. On average, URT specimens cleared faster than LRT specimens, suggesting that traditional nasopharyngeal diagnostic techniques can miss cases of severe adenovirus infection. This suggests that LRT specimens are more reliable for

diagnosing severe adenovirus infection, especially in patients with pneumonia that occurs several days after the infection onset when the frequency of virus detection in the URT has already decreased.

Several studies have shown that the mortality of severe adenovirus-associated ARDS can be as high as 26.7–80% in adults [10]. In our study, among the 14 patients with adenovirus-associated ARDS, there were only two deaths, and the mortality rate was 14.29%. Compared with previous studies, the mortality rate of adenovirus-associated ARDS in this study was relatively low, and this may have several explanations. First, rapid identification of adenovirus viral infection and early intervention are important to reduce the overall mortality rate. In this study, the time from onset to intubation was relatively short. In addition, the PO_2/FiO_2 ratio for most adenovirus-associated ARDS patients was > 150 in this study, while most other studies showed that the PO_2/FiO_2 ratio in patients with severe pneumonia was < 150 [6, 23, 31]. Considering that the condition of severe adenovirus pneumonia patients was more advanced, the above results suggested that early intervention in adenovirus pneumonia-related ARDS helped to improve the patients' prognosis. Second, establishing organ support, such as application of early renal replacement treatment and ECMO are important. Adenovirus-associated ARDS completely resolved in three patients who were supported by ECMO in this study, suggesting that early application of ECMO improved the prognosis of patients with adenovirus-associated ARDS. Finally, timely initiation of antiviral therapy is very important to improve patient outcome. Currently, antiviral therapies for adenovirus infection remain controversial. No specific and effective antiviral drug is available for adenovirus infection [32]. Some studies have shown that cidofovir antiviral therapy in severe adenovirus pneumonia improves the clinical prognosis [33]. However, clinical application of cidofovir is limited due to its toxic side effects and low-quality evidence. Other case reports have also shown that ribavirin can be used to treat adenovirus infection [34, 35]. Ganciclovir has been shown to be effective for treating adenovirus infection in animal experiments [36]. In our study, 11 patients (78.57%) received antiviral therapy with ganciclovir and immunoglobulin therapy after confirming adenovirus infection, which might be the reason for the lower mortality.

This study prospectively observed the viral etiology of ventilated ARDS patients, especially for patients where adenovirus was associated with ARDS. We compared the adenovirus detection rate and adenovirus load in different respiratory tract specimens, which were also a highlight of the study. This study also has several limitations. It was a single-center study with a relatively small number of patients enrolled. In addition, this study used multiplex Q-PCR to detect multiple respiratory viruses at the same time without genotyping the adenovirus.

Conclusions

Our findings indicated that adenovirus infection was an important cause of viral-related ARDS. The detection rate of adenovirus from the LRT was higher than that from the URT. However, mortality due to adenovirus-associated ARDS was high. Therefore, rapid identification of severe adenovirus infection, early effective intervention, and timely initiation of antiviral therapy are essential to reduce mortality and improve the prognosis in patients with adenovirus-associated ARDS.

Abbreviations

ARDS
Acute respiratory distress syndrome
ECMO
Extracorporeal membrane oxygenation
SARS
severe acute respiratory syndrome
SARS-CoV-2
Severe acute respiratory syndrome coronavirus2
MERS
Middle East Respiratory Syndrome
HAdVs
Human adenoviruses
AKI
Acute kidney injury
CRRT
Continuous renal replacement therapy
PEEP
Positive end-expiratory pressure
IMV
Invasive mechanical ventilation
BMI
Body mass index
APACHEII
Acute Physiology and Chronic Health Evaluation II
SOFA
Sequential Organ Failure Assessment
CPIS
Clinical pulmonary infection score
ETA
Endotracheal aspirates
PCR
Quantification polymerase chain reaction
Ct
Cycle threshold
URT
Upper respiratory tract
LRT
Lower respiratory tract

Declarations

Ethics approval and consent to participate

The study was approved by the local research ethics committee (2019-19), which waived the need for informed consent for the retrospective collection of demographic, physiological, and hospital outcome data, based on Chinese legislation.

Consent for publication

Not applicable.

Availability of data and material

All data generated and/or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study conception and design: XL, Data collection: ZW, RZ, DL, XL, SC, YX, JZ and ZZ. Analysis and interpretation: ZW, RZ, WH, XL and YL. Writing the manuscript: RZ and ZW. All authors read and approved the final manuscript.

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Figures

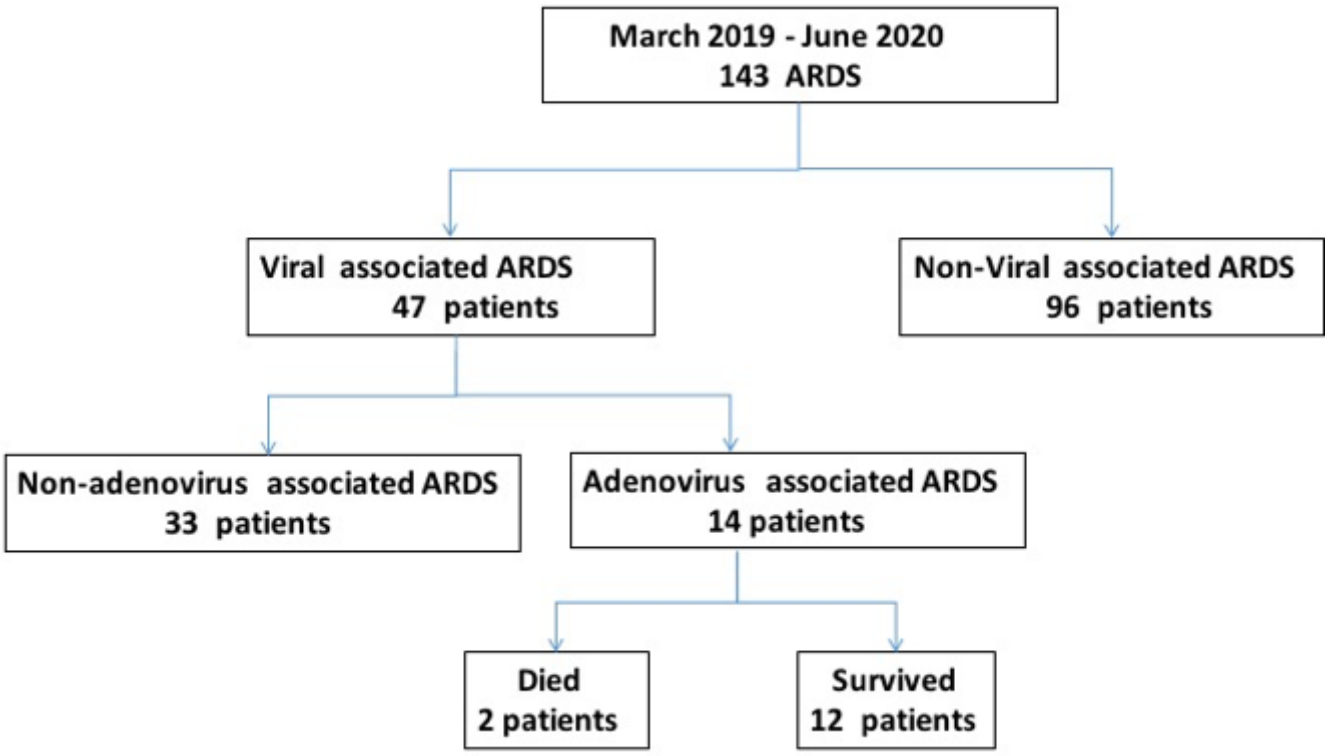

Figure 1

Flowchart of patient groups in the study. ARDS, acute respiratory distress syndrome

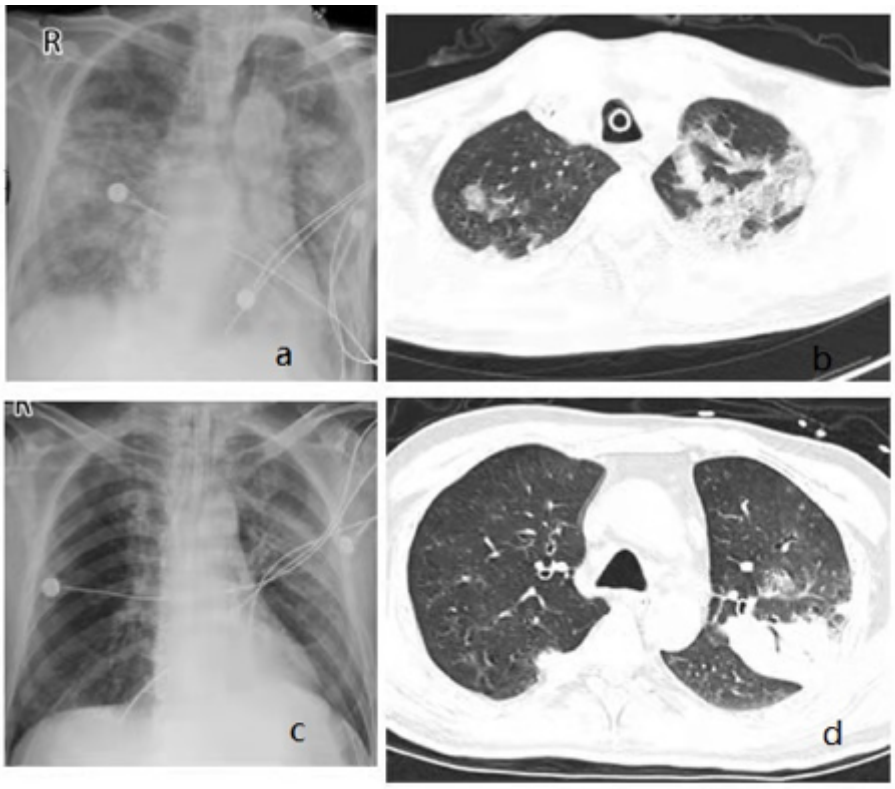

Figure 2

Imaging findings showing diffuse multifocal or diffuse opacity.

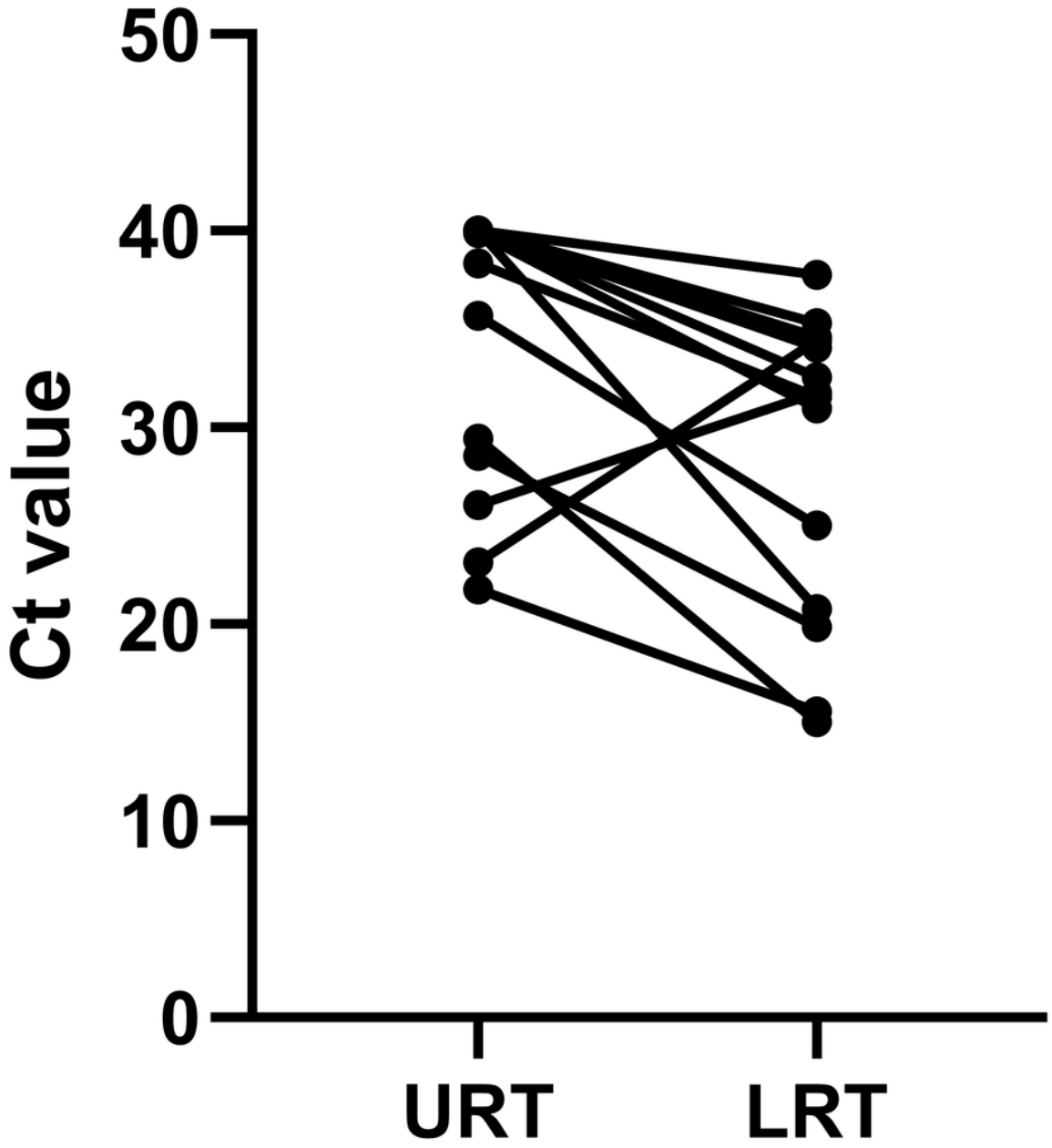

Figure 3

Comparison of the Ct value between URT and LRT samples upon admission to the ICU. URT, upper respiratory tract; LRT, lower respiratory tract; ICU, intensive care unit; Ct, cycle threshold

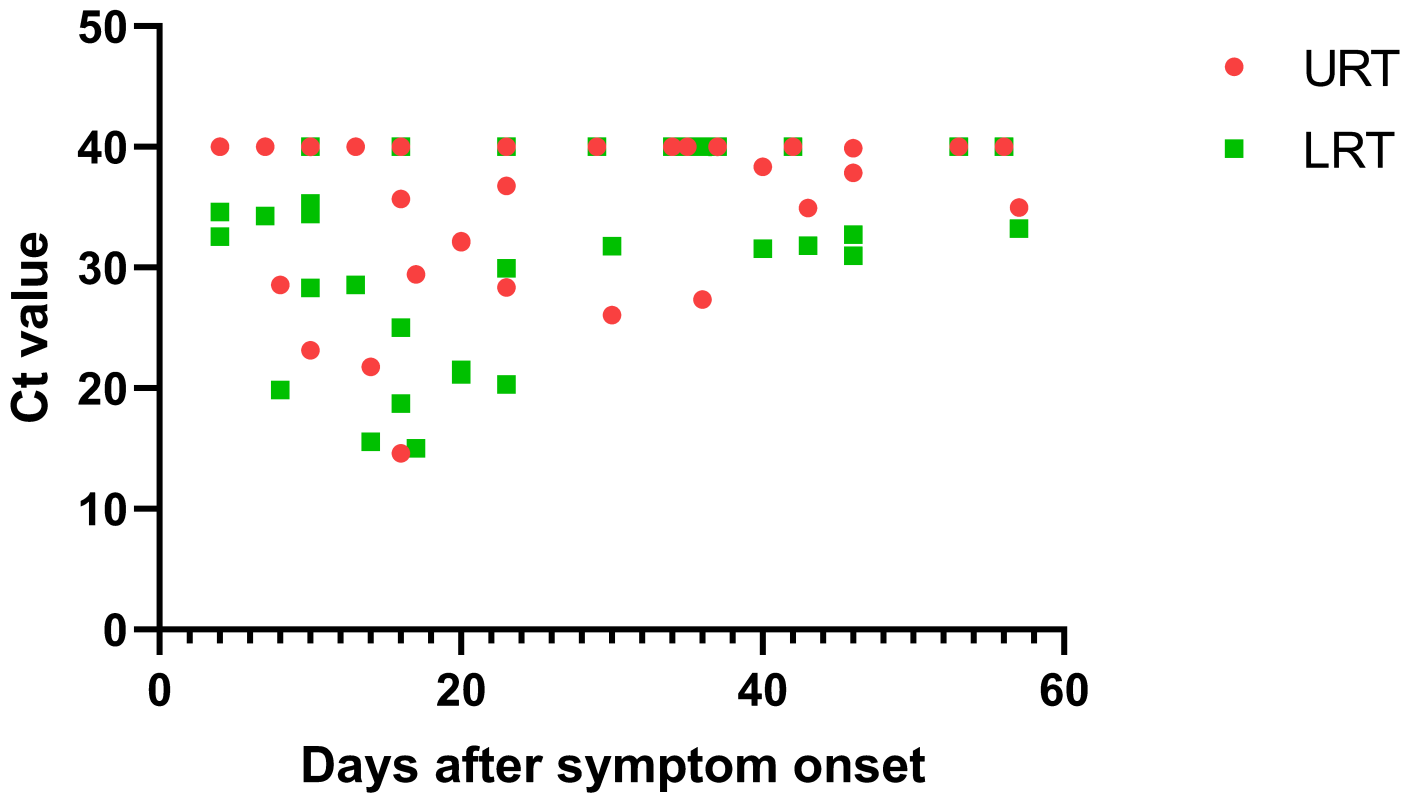

Figure 4

The relationship between Ct value and days after symptom onset in the URT and LRT samples. URT, upper respiratory tract; LRT, lower respiratory tract; ICU, intensive care unit; Ct, cycle threshold