Differences of respiratory mechanics in mechanical ventilation of acute respiratory distress syndrome between patients with COVID-19 and Influenza A

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Abstract

Background Whether COVID-19-induced acute respiratory distress syndrome (ARDS) should be approached differently in terms of mechanical ventilation therapy compared to other virus-induced ARDS is debatable. Therefore, we aimed to ascertain whether the respiratory mechanical characteristics of COVID-19-induced ARDS differ from those of influenza A induced ARDS, in order to establish a rationale for mechanical ventilation therapy in COVID-19-induced ARDS.

Methods This was a retrospective cohort study comparing patients with COVID-19-induced ARDS and influenza A induced ARDS. We included intensive care unit (ICU) patients with COVID-19 or Influenza A aged ≥ 19, who were diagnosed with ARDS according to the Berlin definition between January 2015 and July 2021. Ventilation parameters for respiratory mechanics were collected at specific times on days one, three, and seven after intubation.

Results The median age of the 87 participants was 71.0 (62.0–78.0) years old, and 63.2% were male. The ratio of partial pressure of oxygen in arterial blood to the fractional of inspiratory oxygen concentration in COVID-19-induced ARDS was lower than that in influenza A induced ARDS during the initial stages of mechanical ventilation (influenza A induced ARDS 216.1 vs. COVID-19-induced ARDS 167.9, $p = 0.009$, day 1). The positive end expiratory pressure remained consistently higher in the COVID-19 group throughout the follow-up period (7.0 vs. 10.0, $p < 0.001$, day 1). COVID-19 and influenza A initially showed different directions for peak inspiratory pressure and dynamic compliance; however, after day 3, both groups exhibited similar directions. Dynamic driving pressure exhibited opposite trends between the two groups during mechanical ventilation.

Conclusions Respiratory mechanics show clear differences between COVID-19-induced ARDS and influenza A induced ARDS. Based on these findings, we can consider future treatment strategies for COVID-19-induced ARDS.

Keywords Acute respiratory distress syndrome, COVID-19, Influenza A, Mechanical ventilation

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Background

Acute respiratory distress syndrome (ARDS) is characterized by bilateral pulmonary edema caused by increased permeability of the alveolar capillary membrane, severe hypoxemia, and reduced lung compliance [1, 2]. During the recent COVID-19 pandemic, COVID-19-induced ARDS emerged as a significant cause of death among patients, and its mortality rate is comparable to that of conventional ARDS [3, 4].

Moreover, comparative studies found histopathological and clinical differences between influenza A induced ARDS and COVID-19-induced ARDS, both of which share common features of virus-induced ARDS [5–8]. However, research on whether there are differences in respiratory mechanics during mechanical ventilation between the two diseases is lacking. Furthermore, while the adjustment of mechanical ventilation is a crucial factor in the treatment of ARDS, additional research is necessary to determine whether there are differences in the methods of mechanical ventilation adjustment between the two diseases.

Various perspectives have emerged regarding the treatment of COVID-19-induced ARDS. Given that the respiratory biomechanical characteristics of COVID-19-induced ARDS closely resemble those of other forms of ARDS, some stances advocate for the application of traditional ARDS treatment protocols [9]. Conversely, others argue that the distinctive respiratory dynamics evident at different stages of COVID-19-induced ARDS should be acknowledged, urging consideration of alternative approaches to treatment for each stage [10].

Therefore, this study aimed to ascertain whether there is a difference in respiratory mechanics during mechanical ventilation over time between COVID-19-induced ARDS and influenza A induced ARDS, and to determine whether a different approach for controlling mechanical ventilation is necessary in the future for these diseases.

Methods

Study design and population

This single-center, retrospective, observational cohort study was conducted at a tertiary referral hospital in the Republic of Korea. The study included intensive care unit (ICU) patients aged≥19 years old who were diagnosed with ARDS according to the Berlin definition among patients with COVID-19 or Influenza A between January 2015 and July 2021. Of the 92 patients registered in the cohort, five who underwent extracorporeal membrane oxygenation (ECMO), which could potentially impact mechanical ventilation settings, were excluded. Finally, 42 and 45 patients with COVID-19-induced ARDS and Influenza A induced ARDS, respectively, were included.

Collection and definition of variables

Demographic data and Charlson comorbidity index (CCI) scores were collected upon ICU admission. The predicted body weight (PBW) was calculated based on sex, with the formula $50+0.91 \times$ (height (cm)−152.4) for males, and $45.5+0.91 \times$ (height (cm)−152.4) for females [11]. The Sequential Organ Failure Assessment (SOFA) score was determined based on the patient's condition at the time of intubation. The use of vasopressors and renal replacement therapy (RRT) was indicated if they occurred within seven days after intubation and lasted for at least one day. Weaning success was defined as successful extubation and absence of ventilator support within 48 h.

The diagnosis of COVID-19 and Influenza A was confirmed when the first positive result was obtained during hospitalization using a reverse transcription-polymerase chain reaction assay of respiratory samples. The diagnosis of ARDS was confirmed if the criteria outlined in the 2012 Berlin definition for timing, chest imaging, and origin of edema were met, and if the ratio of partial pressure of oxygen in arterial blood to the fractional of inspiratory oxygen concentration (P/F ratio) on the day of intubation (Day 0) indicated at least mild oxygenation impairment (P/F ratio≤300 mmHg with positive end expiratory pressure [PEEP] or continuous positive airway pressure [CPAP]≥5 cmH$_2$O) as per the oxygenation category [1].

Collection and definition of ventilatory parameters

Ventilation parameters for respiratory mechanics were collected at specific times on days one, three, and seven after intubation. The collected variables were exhaled minute volume (Mve), respiratory rate, tidal volume (TV), peak inspiratory pressure (PIP), PEEP, fraction of inspired oxygen (FiO2), and in the case of the pressure support mode, it was the pressure support pressure. The dynamic driving pressure (DP) and dynamic compliance (Cdyn) were estimated using the following equations: DP=PIP−PEEP, and Cdyn=TV/(PIP−PEEP), respectively.

Treatment and management of ARDS

To maximize the implementation of a protective ventilation approach, TV was set to ≤7 ml/kg of PBW and PIP was set to ≤30 cm H2O immediately after intubation. A minimal level of sedation and analgesia necessary to achieve synchronization with the mechanical ventilator was administered, and stress ulcer prophylaxis and deep venous thrombosis prophylaxis were applied unless contraindicated [2]. During hospitalization, if additional bacterial infections occurred in both disease groups, appropriate antibiotics were administered based on the culture results, and the recommended nutrition was provided to both disease groups via consultation with a

Chung *et al. Respiratory Research*   (2024) 25:112

Page 3 of 9

nutrition specialist. A spontaneous breathing trial was conducted when the ventilator parameters allowed for $FiO_2 \leq 0.35$ and $PEEP \leq 5$ cmH2O, as part of the weaning process. Patients with ARDS diagnosed with influenza A received antiviral drugs such as oseltamivir or peramivir without steroid treatment, whereas those diagnosed with COVID-19 were administered steroids [4, 7].

Statistical analysis

The normality of the data was assessed using the Shapiro–Wilk test. Pearson's chi-squared test or Fisher's exact test was applied for categorical variables and Mann–Whitney U test was used for continuous variables. Continuous variables were presented as medians (interquartile range) because most variable distributions were non-normal distribution. Statistical significance was set at $p < 0.05$. R software (v.4.2.1, Vienna, Austria) and SPSS (v.26.0, New York, USA) were used for all statistical analyses.

Results

Baseline characteristics

The baseline characteristics of the 87 patients are presented in Table 1. Among the total patients, 63.2% were male, and the median age was 71.0 (62.0–78.0) years old. The influenza A induced ARDS group had higher CCI and SOFA scores at intubation, along with higher rates of vasopressor and RRT use, and mortality than the COVID-19-induced ARDS group. Tracheostomy and weaning success rates did not differ significantly between the groups; however, the influenza A induced ARDS group had a shorter ICU stay than the COVID-19-induced ARDS group (Influenza A induced ARDS 10.0 days vs. COVID-19-induced ARDS 24.5 days, $p < 0.001$).

Differences in respiratory mechanics during mechanical ventilation

Table 2 presents the respiratory mechanics differences over time after intubation between COVID-19-induced ARDS and Influenza A induced ARDS. On day 1, the Influenza A group had a higher P/F ratio (216.1 vs. 167.9, $p = 0.009$) and lower PEEP (8.0 cm H_2O vs. 10.0 cm H_2O, $p < 0.001$) than the COVID-19 group, however, they showed lower Cdyn (25.7 cm H_2O vs. 35.8 cm H_2O, $p = 0.001$). Starting from day 3, the P/F ratio showed a statistically significant difference like the 1st day (279.5 vs. 181.1, $p = 0.009$), but there were no statistical differences in Cdyn and DP between the two groups. PEEP remained consistently higher in the COVID-19 group throughout the follow-up period. A schematic diagram of this is illustrated in Fig. 1. The overall trend is that the COVID-19 and Influenza A groups exhibit similar increasing patterns in P/F ratio over time. In the case of pip and Cdyn, the directions of COVID and influenza A were initially different. However, after day 3, both groups exhibited a decrease in PIP and an increase in Cdyn. Unlike other indicators, DP exhibited opposite trends, increasing consistently in the COVID-19 group and decreasing consistently in the Influenza A group.

Differences in respiratory mechanics during mechanical ventilation between COVID-19-induced ARDS and Influenza A induced ARDS survivors

Table 3 compares the baseline characteristics of COVID-19-induced ARDS and influenza A induced ARDS in survivors. Influenza A induced ARDS survivors had lower BMI (19.9 kg/m² vs. 24.1 kg/m², $p < 0.001$) and higher CCI (3.0 vs. 0.0, $p < 0.001$) and SOFA scores (10.0 vs. 5.0, $p < 0.001$) compared to COVID-19-induced ARDS survivors. However, tracheostomy and weaning success rates

Table 1 Baseline characteristics between influenza A induced ARDS and COVID-19-induced ARDS.

Characteristics	Total participants (N=87)	Influenza A induced ARDS (N=45)	COVID-19-induced ARDS (N=42)	p-value
Age (year)	71.0 (62.0–78.0)	73.0 (62.5–79.5)	69.5 (62.0–76.0)	0.322
Male, no. (%)	55 (63.2)	29 (64.4)	26 (61.9)	0.806
Smoking status (Current or former), no. (%)	25 (28.7)	14 (31.1)	11 (26.2)	0.612
BMI (kg/m²)	22.8 (19.9–25.1)	20.3 (17.7–24.1)	24.3 (22.2–25.9)	< 0.001
CCI	1.0 (0.0–4.0)	3.0 (1.0–5.0)	1.0 (0.0–1.3)	< 0.001
SOFA	9.0 (5.0–13.0)	11.0 (7.5–14.5)	6.5 (4.0–11.0)	< 0.001
Use of vasopressor, no (%)	71 (81.6)	42 (93.3)	29 (69.0)	0.005
RRT, no (%)	13 (14.9)	12 (26.7)	1 (2.4)	0.002
ICU hospitalization period (day)	20.0 (9.0–32.0)	10.0 (7.0–23.5)	24.5 (19.0–51.5)	< 0.001
28-day mortality, no (%)	20 (23.0)	16 (35.6)	4 (9.5)	0.005
Final mortality, no (%)	32 (36.8)	22 (48.9)	10 (23.8)	0.015
Tracheostomy, no (%)	20 (23.0)	8 (17.8)	12 (28.6)	0.232
Weaning success, no (%)	49 (56.3)	25 (55.6)	24 (57.1)	0.881

Data are presented as no. (%) or median (IQR)

ARDS, acute respiratory distress syndrome; BMI, body mass index; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment score; RRT, Renal replacement therapy; ICU, intensive care unit

Chung *et al. Respiratory Research*   (2024) 25:112

Page 4 of 9

Table 2 Differences in respiratory mechanics during mechanical ventilation between influenza A- and COVID-19-induced ARDS.

Day 1

Characteristics	Total participants (N=87)	Influenza A induced ARDS (N=45)	COVID-19-induced ARDS (N=42)	p-value
Pco_2	38.9 (33.5–43.6)	37.5 (33.8–44.3)	40.0 (33.0–43.3)	0.584
$Pa_{O_2}:Fi_{O_2}$	184.7 (135.7–243.6)	216.1 (134.2–271.3)	167.9 (137.5–212.7)	0.009
Mve (L/min)	8.9 (7.6–10.3)	8.5 (7.2–10.2)	9.0 (8.0–10.3)	0.707
TV/PBW (ml/kg)	7.2 (6.3–8.4)	7.0 (6.3–8.3)	7.2 (6.3–8.5)	0.763
PIP (cm H_2O)	23.0 (20.0–26.0)	23.0 (20.5–27.0)	22.0 (19.0–25.0)	<0.001
PEEP (cm H_2O)	8.0 (7.0–10.0)	8.0 (5.0–8.0)	10.0 (8.0–12.0)	<0.001
Cdyn (cm H_2O) [a]	30.0 (23.7–37.9)	25.7 (21.3–34.4)	35.8 (28.9–41.6)	0.001
DP (cm H_2O) [b]	14.0 (12.0–17.0)	15.0 (13.5–19.0)	13.0 (9.8–16.0)	0.369

Day 3

Characteristics	Total participants (N=80)	Influenza A induced ARDS (N=39)	COVID-19-induced ARDS (N=41)	p-value
Pco_2	38.8 (33.3–44.2)	37.7 (30.3–47.1)	39.8 (35.0–42.8)	0.763
$Pa_{O_2}:Fi_{O_2}$	215.2 (158.2–309.0)	279.5 (172.0–333.0)	181.0 (141.0–252.0)	0.005
Mve (L/min)	8.4 (7.3–9.8)	7.9 (6.1–9.3)	8.4 (7.7–9.9)	0.072
TV/PBW (ml/kg)	7.3 (6.5–7.8)	7.2 (6.4–8.0)	7.3 (6.6–7.8)	0.969
PIP (cm H_2O)	23.0 (18.3–25.8)	22.0 (16.0–25.0)	24.0 (20.0–26.5)	0.051
PEEP (cm H_2O)	8.0 (6.0–10.0)	6.0 (5.0–8.0)	10.0 (8.0–11.0)	<0.001
Cdyn (cm H_2O) [a]	28.4 (22.7–39.0)	28.2 (21.4–47.9)	28.6 (23.1–37.9)	0.935
DP (cm H_2O) [b]	14.0 (11.0–17.0)	14.0 (9.0–18.0)	14.0 (12.0–17.0)	0.817

Day 7

Characteristics	Total participants (N=64)	Influenza A induced ARDS (N=27)	COVID-19-induced ARDS (N=37)	p-value
Pco_2	38.2 (34.0–42.5)	36.9 (31.6–42.6)	39.1 (35.1–42.6)	0.799
P/F ratio	215.0 (146.4–310.7)	279.1 (143.6–353.3)	204.2 (147.6–282.5)	0.170
Mve (L/min)	8.8 (7.5–10.6)	8.6 (6.4–10.1)	8.9 (8.1–10.9)	0.123
TV/PBW (ml/kg)	7.4 (6.5–8.5)	7.4 (6.0–8.7)	7.4 (6.6–8.4)	0.838
PIP (cm H_2O)	21.0 (16.3–25.0)	18.0 (13.0–25.0)	22.0 (19.0–25.5)	0.108
PEEP (cm H_2O)	8.0 (5.0–10.0)	6.0 (5.0–7.0)	8.0 (8.0–10.0)	<0.001
Cdyn (cm H_2O) [a]	31.3 (23.7–45.3)	32.5 (20.5–62.2)	31.3 (24.5–37.8)	0.951
DP (cm H_2O) [b]	13.5 (9.3–16.8)	12.0 (8.0–18.0)	15.0 (11.0–16.0)	0.643

Data are presented as no. (%) or median (IQR)

Pco2, partial pressure of carbon dioxide; P/F ratio, the arterial partial pressure of oxygen (PaO2) divided by the inspired oxygen concentration (FiO2); Mve, Exhaled minute volume; TV, tidal volume; PBW, predicted body weight, PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; Cdyn, dynamic compliance; DP, dynamic driving pressure

[a] Cdyn=TV/(PIP-PEEP)

[b] DP=PIP-PEEP

were similar between the two groups, and the ICU hospitalization period was shorter in influenza A induced ARDS survivors (9.0 days vs. 22.0 days, $p<0.001$). Additionally, there were no statistically significant differences in the use of vasopressors or RRT in the survivor group, unlike in overall participants.

Table 4 presents changes in respiratory mechanics over time during mechanical ventilation in survivors. On Day 1, COVID-19-induced ARDS survivors had a lower P/F ratio (268.0 vs. 162.5, $p<0.001$) and higher PEEP (7.0 cm H_2O vs. 10.0 cm H_2O, $p<0.001$) compared to Influenza A induced ARDS survivors, which was consistent with the results in the overall participants. However, there were no significant differences in PIP and Cdyn, unlike the entire patient population, among the survivor groups. On

Day 3 and Day 7, COVID-19-induced ARDS survivors had higher PIP (18.5 cm H_2O vs. 23.0 cm H_2O, $p=0.001$), and DP (11.0 cm H_2O vs. 13.1 cm H_2O, $p=0.044$). Throughout the study, differences in P/F ratio, Mve, and PEEP between Influenza A induced ARDS survivors and COVID-19-induced ARDS survivors persisted. The graphical representation of respiratory mechanics over time in Fig. 2 closely paralleled the results of Fig. 1 for the entire patient group.

Discussion

We compared COVID-19-induced ARDS and influenza A induced ARDS, a representative condition of virus-induced ARDS, to investigate whether there were differences in respiratory mechanics during mechanical
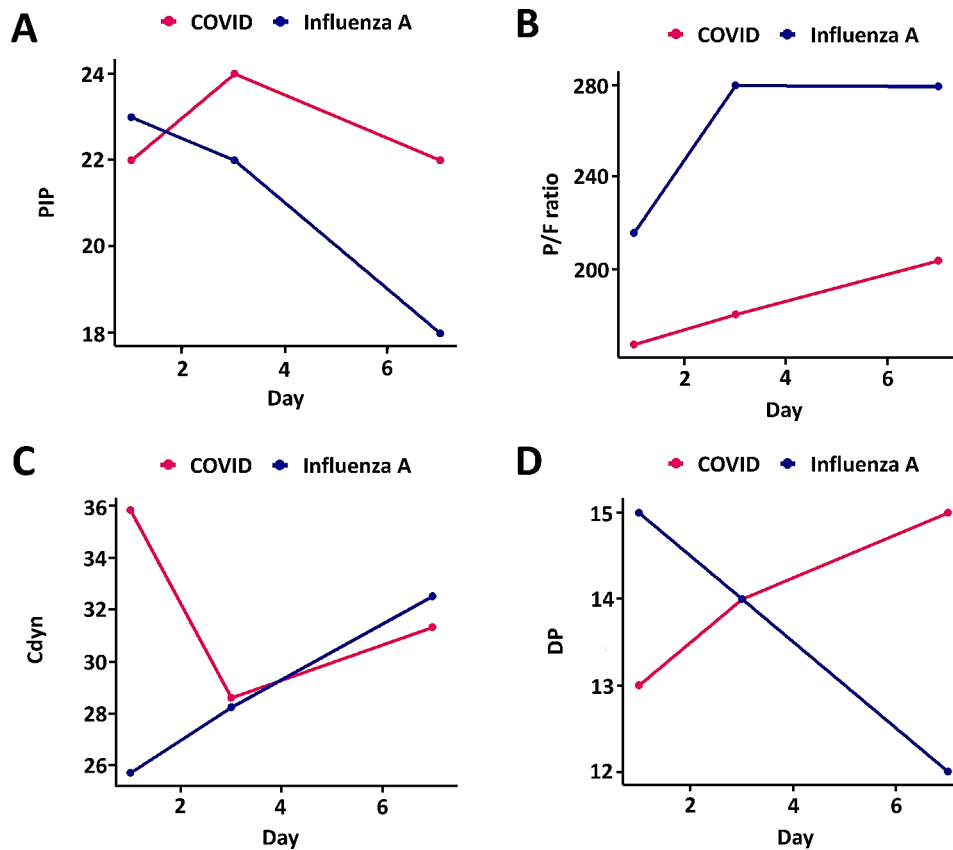
Chung *et al. Respiratory Research* (2024) 25:112

Page 5 of 9

Fig. 1 Changes in respiratory mechanics between COVID-19-induced ARDS and influenza A induced ARDS. Median values of each parameter, including PIP (A), P/F ratio (B), Cdyn (C), and DP (D), are displayed according to the number of days after intubation. PIP, peak inspiratory pressure; P/F ratio, arterial partial pressure of oxygen (PaO_2) divided by inspired oxygen concentration (FiO_2); Cdyn, dynamic compliance; DP, dynamic driving pressure

Table 3 Baseline characteristics between influenza A induced ARDS and COVID-19-induced ARDS survivors

Characteristics	Total participants (*N*=55)	Influenza A induced ARDS (*N*=23)	COVID-19-induced ARDS (*N*=32)	p-value
Age (year)	70.0 (59.0–75.0)	70.0 (59.0–78.0)	69.0 (59.8–74.8)	0.322
Male, no. (%)	30 (54.5)	12 (52.2)	18 (56.3)	0.765
Smoking status (Current or former), no. (%)	12 (21.8)	4 (17.4)	8 (25.0)	0.742
BMI (kg/m^2)	22.6 (19.7–25.1)	19.9 (16.9–22.5)	24.1 (22.2–25.5)	<0.001
CCI	1.0 (0.0–3.0)	3.0 (1.0–5.0)	0.0 (0.0–1.0)	<0.001
SOFA	7.0 (4.0–12.0)	10.0 (5.0–12.0)	5.0 (3.3–9.0)	<0.001
Use of vasopressor, no (%)	40 (72.7)	20 (87.0)	20 (62.5)	0.066
RRT, no (%)	3 (5.5)	3 (13.0)	0 (0.0)	0.068
ICU hospitalization period (day)	19.0 (10.0–29.0)	9.0 (7.0–16.0)	22.0 (19.0–42.3)	<0.001
Tracheostomy, no (%)	12 (21.8)	6 (26.1)	6 (18.8)	0.516
Weaning success, no (%)	46 (83.6)	22 (95.7)	24 (75.0)	0.064

Data are presented as no. (%) or median (IQR)

ARDS, acute respiratory distress syndrome; BMI, body mass index; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment score; RRT, Renal replacement therapy; ICU, intensive care unit

ventilation. In the initial phases of mechanical ventilation, disparities in respiratory mechanics were observed between the two groups, persisting in some variables over time and diminishing in others.

This difference was maintained with respect to hypoxemia. Our results revealed that the P/F ratio in patients with COVID-19-induced ARDS was significantly lower than that in patients with influenza A induced ARDS during the early stages of mechanical ventilation in all participants. Nevertheless, contradictory results have been observed in previous studies with respect to the P/F ratio. Cobb et al. reported no significant difference between the

Table 4 Differences in respiratory mechanics during mechanical ventilation between influenza A- and COVID-19-induced ARDS survivors

Day 1				
Characteristics	Total participants (N = 55)	Influenza A induced ARDS (N = 23)	COVID-19-induced ARDS (N = 32)	p-value
Pco_2	38.0 (35.1–43.6)	37.1 (34.4–40.5)	40.3 (36.8–44.3)	0.096
$Pa_{O_2}:Fi_{O_2}$	194.4 (149.4–268.3)	268.0 (196.4–304.3)	162.5 (139.4–208.3)	< 0.001
Mve (L/min)	8.7 (7.2–10.3)	7.8 (6.1–8.5)	9.4 (8.0–10.4)	0.005
TV/PBW (ml/kg)	7.2 (6.6–7.8)	7.0 (6.6–8.0)	7.2 (6.4–7.8)	0.824
PIP (cm H_2O)	22.0 (19.0–25.0)	22.0 (19.0–25.0)	22.0 (19.0–25.0)	0.537
PEEP (cm H_2O)	8.0 (7.0–10.0)	7.0 (5.0–8.0)	10.0 (8.0–11.8)	< 0.001
Cdyn (cm H_2O) [a]	33.4 (25.6–40.0)	27.0 (23.5–36.8)	35.7 (28.7–42.9)	0.056
DP (cm H_2O) [b]	14.0 (11.0–16.0)	14.0 (12.0–17.0)	12.5 (9.3–15.8)	0.072
Day 3				
Characteristics	Total participants (N = 53)	Influenza A induced ARDS (N = 22)	COVID-19-induced ARDS (N = 31)	p-value
Pco_2	38.9 (33.7–42.6)	36.4 (32.3–41.8)	40.0 (35.1–42.6)	0.136
$Pa_{O_2}:Fi_{O_2}$	269.3 (171.3–333.0)	308.9 (276.9–379.1)	185.0 (157.0–275.6)	< 0.001
Mve (L/min)	8.3 (7.2–9.8)	7.2 (5.5–9.2)	8.7 (7.7–9.9)	0.012
TV/PBW (ml/kg)	7.3 (6.5–7.8)	7.4 (6.3–8.0)	7.3 (6.5–7.8)	0.691
PIP (cm H_2O)	21.0 (17.5–24.5)	18.5 (14.5–22.0)	23.0 (20.0–25.0)	0.001
PEEP (cm H_2O)	8.0 (6.0–10.0)	6.0 (5.0–8.0)	10.0 (8.0–10.0)	< 0.001
Cdyn (cm H_2O) [a]	30.2 (25.0–41.6)	32.9 (27.3–56.1)	28.6 (22.7–38.9)	0.108
DP (cm H_2O) [b]	13.0 (10.5–16.0)	11.0 (8.0–15.3)	13.1 (12.0–17.0)	0.044
Day 7				
Characteristics	Total participants (N = 42)	Influenza A induced ARDS (N = 14)	COVID-19-induced ARDS (N = 28)	p-value
Pco_2	36.7 (33.5–41.6)	35.5 (29.1–39.1)	37.3 (34.0–42.2)	0.196
P/F ratio	260.3 (182.2–336.9)	314.6 (267.9–366.8)	212.9 (174.2–283.9)	0.014
Mve (L/min)	8.6 (6.9–10.7)	6.7 (5.7–8.8)	9.3 (8.3–11.1)	0.001
TV/PBW (ml/kg)	7.6 (6.6–8.6)	7.5 (6.0–9.1)	7.6 (6.8–8.6)	0.626
PIP (cm H_2O)	20.0 (14.8–24.0)	16.5 (12.8–20.0)	21.5 (17.3–24.8)	0.007
PEEP (cm H_2O)	8.0 (5.0–8.3)	6.0 (5.0–7.0)	8.0 (7.0–10.0)	0.005
Cdyn (cm H_2O) [a]	32.1 (27.3–55.3)	35.0 (28.0–81.6)	31.5 (26.1–38.6)	0.348
DP (cm H_2O) [b]	13.0 (8.0–16.0)	10.0 (7.0–13.3)	15.0 (10.3–16.0)	0.048

Data are presented as no. (%) or median (IQR)

Pco_2, partial pressure of carbon dioxide; P/F ratio, the arterial partial pressure of oxygen (PaO2) divided by the inspired oxygen concentration (FiO2); Mve, Exhaled minute volume; TV, tidal volume; PBW, predicted body weight, PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; Cdyn, dynamic compliance; DP, dynamic driving pressure

[a] Cdyn = TV/(PIP-PEEP)

[b] DP = PIP-PEEP

two disease groups on mechanical ventilation day 1; however, from day 2 onwards, the P/F ratio in the COVID-19 group was significantly lower [12]. In contrast, Tang et al. and Ding et al. showed that the P/F ratio in COVID-19-induced ARDS was higher than that in influenza A induced ARDS [13, 14]. Considering ECMO was provided to patients in the studies by Tang et al. and Ding et al., it is possible that differences in disease severity led to variations in the reduction of the P/F ratio in each condition. In our study, we analyzed data after excluding patients receiving ECMO; therefore, we speculate that a relatively higher proportion of mild ARDS cases may have resulted in findings similar to those of Cobb et al. Furthermore, PEEP exhibited higher values in both the entire group and the group of survivors among COVID-19 patients, which is surmised to be a clinical response aimed at compensating for the low P/F ratio. The lower P/F ratio in COVID-19-induced ARDS may be attributed to relatively increased microthrombosis and endothelialitis compared with influenza A patients, potentially leading to a ventilation-perfusion mismatch and disruption of pulmonary vasoregulation [10, 15]. Additionally, histopathological studies showing a higher incidence of microthrombosis in COVID-19 patients than in influenza A patients, along with spatial transcriptomic studies demonstrating greater expression of coagulation-related genes in COVID-19 than in influenza A, support this finding [5, 6].
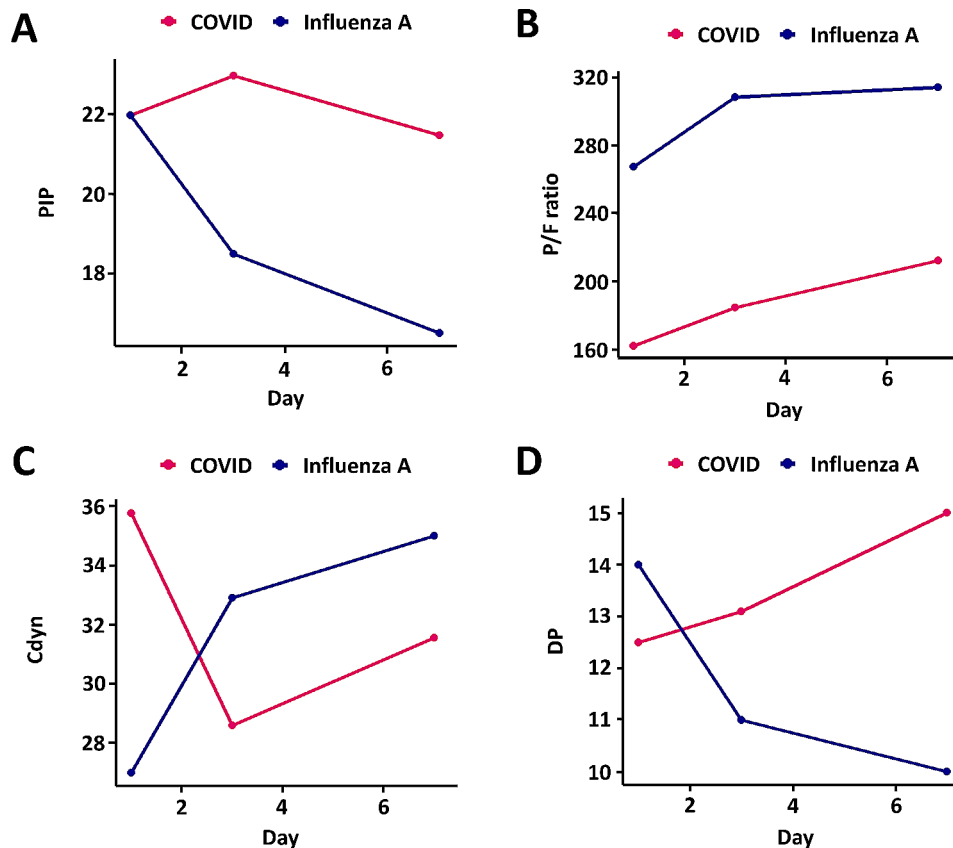
Fig. 2 Changes in respiratory mechanics between COVID-19-induced ARDS and influenza A induced ARDS survivors. Median values of each parameter, including PIP (A), P/F ratio (B), Cdyn (C), and DP (D), are displayed according to the number of days after intubation. PIP, peak inspiratory pressure; P/F ratio, arterial partial pressure of oxygen (PaO_2) divided by inspired oxygen concentration (FiO_2); Cdyn, dynamic compliance; DP, dynamic driving pressure

In our results, the difference in lung compliance between the two diseases diminished. In the case of COVID-19-induced ARDS, initial compliance was significantly higher than that of influenza A induced ARDS. However, over time, Cdyn in COVID-19 decreased relatively quickly, and showed no statistical difference compared with the influenza A group after day 3. Previous studies have reported that lung compliance is higher in COVID-19-induced ARDS than in classic ARDS [15, 16]. In a study by Kronibus et al., which examined changes in compliance over time, initial compliance did not show a statistically significant difference between the two groups. However, the absolute value of median compliance in COVID-19 patients was higher, and over time, a trend was observed where the difference in median values between the two groups decreased, similar to the results of our study [17]. Therefore, in the case of COVID-19-induced ARDS, compliance is higher in the early stages than that in influenza A induced ARDS; however, over time, it becomes similar to that of influenza A induced ARDS. Moreover, Influenza A showed a time-dependent decrease in the DP, which was inversely related to Cdyn (Fig. 1D), while COVID-19 did not exhibit a complete inverse correlation with Cdyn. This is presumed to be because the increase in TV due to recovery between Days 3 and 7 was reflected in Cdyn but not in DP, and this trend was more pronounced in the analysis of survivors (Fig. 2D).

Based on our findings regarding the respiratory mechanics of COVID-19-induced ARDS, we propose the following treatment strategies. First, COVID-19-induced ARDS exhibited a relatively low P/F ratio in the early stages of endotracheal intubation. Therefore, early implementation of the prone position, a method validated in previous studies, is necessary along with simultaneously efforts to reduce hypoperfusion of well-ventilated lung areas and improve ventilation-perfusion mismatch through personalized PEEP ventilation adjustments to improve early hypoxemia [18–21]. However, the relatively high lung compliance in COVID-19-induced ARDS may lead to an overestimation of the patient's condition, posing a risk of delayed introduction of the prone position. Thus, when assessing the severity of COVID-19-induced ARDS, clinical decision-making should primarily consider the P/F ratio. Furthermore, recent clinical practice guidelines for ARDS recommend considering the application of venovenous ECMO in cases of severe ARDS with a low P/F ratio [22, 23]. Positive impacts of ECMO

on short-term survival have been also noted in observational studies of respiratory failure induced by COVID-19 [24, 25]. Therefore, early implementation of the prone position and the consideration of ECMO should also be prioritized in COVID-19-induced ARDS. Second, as time elapses following the abrupt decrease in lung compliance in the early stages, the respiratory mechanic pattern of COVID-19-induced ARDS becomes similar to influenza A induced ARDS. This emphasizes the importance of a lung protective strategy in COVID-19-induced ARDS. Influenza A induced ARDS with initially low lung compliance tends to improve over time and has a relatively low risk of barotrauma even with delayed adjustments to the ventilator. However, in case of COVID-19, which exhibits a rapid decrease in lung compliance in the initial stage, there is a higher likelihood of ventilator-induced lung injury occurring if real-time ventilator setting adjustments are insufficient due to limitations in medical resources. Therefore, the importance of low tidal volume becomes even more marked in the case of COVID-19-induced ARDS compared to that in other forms of ARDS.

According to a previous study, the median duration from the onset of symptoms to the development of ARDS was 9.5 days in the case of COVID-19, whereas it was relatively shorter at 7.0 days for influenza A [14]. The onset of ARDS appears to be more influenced by cytokine levels than by viral load, and the peak cytokine level is known to occur earlier in influenza A than in COVID-19. This may explain the difference in the ARDS onset period, as previously described [26, 27]. Owing to the difference in the timing of the cytokine peak, it is possible that in COVID-19-induced ARDS, there was a relatively high Cdyn on day 1, followed by a sharp decrease on day 3 and an increase in PIP. However, in the case of COVID-19, although the cytokines reach their peak later, they remain at elevated levels for a much longer duration. As a result, overall cumulative cytokine exposure is greater in patients with COVID-19 patients than with influenza A [27]. Hence, persistent inflammation could contribute to increased DP and elevated PIP in COVID-19-induced ARDS, leading to delays in weaning and a prolonged ICU hospitalization period. In our study, despite the relatively unfavorable clinical indicators of influenza A patients at the time of ICU admission, as predicted by a previous study, we found that the weaning outcomes between survivors were similar between the two groups, with influenza A patients showing a relatively shorter ICU hospitalization period.

This study had some limitations. First, this was a single-center study, which may have been influenced by regional variations in COVID-19 incidence rates. However, involvement of the same institution provided simultaneous benefits because it was possible to reduce the impact of time frame differences on data quality, specifically in terms of equipment, healthcare providers, and adherence to the protocol. Second, at the end of the research period in July 2021, the vaccination rate for COVID-19 was significantly different from that for influenza A. Approximately only 10% of the population in South Korea achieved full COVID-19 vaccination in July 2021 [28]. On the other hand, approximately 30–40% of South Korea's entire population had been vaccinated against Influenza A, with an 80% vaccination rate among those aged ≥65 [29]. Therefore, it cannot be ruled out that patients with influenza A induced ARDS with worse clinical indicators were included, as patients who developed ARDS despite vaccination tended to have an unfavorable clinical status.

Conclusions
The respiratory mechanics of COVID-19-induced ARDS and influenza A induced ARDS have been proven to differ significantly. The findings of this study are anticipated to form the basis for devising future treatment strategies that contemplate the optimal adjustment of ventilators at distinct stages of mechanical ventilation in patients with COVID-19-induced ARDS.

Abbreviations
ARDS	Acute respiratory distress syndrome
CCI	Charlson comorbidity index
Cdyn	Dynamic compliance
CPAP	Continuous positive airway pressure
DP	Dynamic driving pressure
ECMO	Extracorporeal membrane oxygenation
FiO2	Fraction of inspired oxygen
ICU	Intensive care unit
Mve	Exhaled minute volume
P/F ratio	The ratio of partial pressure of oxygen in arterial blood to the fractional of inspiratory oxygen concentration
PBW	Predicted body weight
PEEP	Positive end expiratory pressure
PIP	Peak inspiratory pressure
RRT	Renal replacement therapy
SOFA	The sequential organ failure assessment
TV	Tidal volume

Data availability
The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was reviewed and approved by the Institutional Review Board of the Severance Hospital Ethics Committee (IRB number: 4-2023-0504). The requirement for informed consent was waived by the Institutional Review Board due to the use of de-identified public data and the retrospective nature of the study. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References
1. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33.
2. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet. 2021;398:622–37.
3. Macedo A, Goncalves N, Febra C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Ann Epidemiol. 2021;57:14–21.
4. Hasan SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant HA, Zaidi STR. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. Expert Rev Respir Med. 2020;14:1149–63.
5. Hariri LP, North CM, Shih AR, Israel RA, Maley JH, Villalba JA, Vinarsky V, Rubin J, Okin DA, Sclafani A, et al. Lung histopathology in Coronavirus Disease 2019 as compared with severe Acute Respiratory Sydrome and H1N1 Influenza: a systematic review. Chest. 2021;159:73–84.
6. Margaroli C, Benson P, Sharma NS, Madison MC, Robison SW, Arora N, Ton K, Liang Y, Zhang L, Patel RP, Gaggar A. Spatial mapping of SARS-CoV-2 and H1N1 lung injury identifies differential transcriptional signatures. Cell Rep Med. 2021;2:100242.
7. Zhou Y, Fu X, Liu X, Huang C, Tian G, Ding C, Wu J, Lan L, Yang S. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. Sci Rep. 2020;10:3044.
8. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain Randomized Clinical Trial. JAMA. 2020;324:1317–29.
9. Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, Brodie D. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med. 2020;8:816–21.
10. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA. 2020;323:2329–30.
11. Acute Respiratory Distress, Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
12. Cobb NL, Sathe NA, Duan KI, Seitz KP, Thau MR, Sung CC, Morrell ED, Mikacenic C, Kim HN, Liles WC, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus Influenza. Ann Am Thorac Soc. 2021;18:632–40.
13. Tang X, Du RH, Wang R, Cao TZ, Guan LL, Yang CQ, Zhu Q, Hu M, Li XY, Li Y, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. Chest. 2020;158:195–205.
14. Ding L, Chen Y, Su N, Xu X, Yin J, Qiu J, Wang J, Zheng D. Comparison of acute respiratory distress syndrome in patients with COVID-19 and influenza A (H7N9) virus infection. Int J Infect Dis. 2022;122:593–8.
15. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, Laffey J, Carrafiello G, Carsana L, Rizzuto C, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8:1201–8.
16. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a typical Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;201:1299–300.
17. Kronibus N, Seiler F, Danziger G, Muellenbach RM, Reyher C, Becker AP, Kamphorst M, Rixecker TM, Metz C, Bals R et al. Respiratory physiology of COVID-19 and Influenza Associated Acute Respiratory Distress Syndrome. J Clin Med 2022, 11.
18. Gierhardt M, Pak O, Walmrath D, Seeger W, Grimminger F, Ghofrani HA, Weissmann N, Hecker M, Sommer N. Impairment of hypoxic pulmonary vasoconstriction in acute respiratory distress syndrome. Eur Respir Rev 2021, 30.
19. Bachmann MC, Basoalto R, Diaz O, Bruhn A, Bugedo G, Retamal J. Prone position improves ventilation-perfusion mismatch in patients with severe acute respiratory distress syndrome. Med Intensiva (Engl Ed). 2023;47:175–8.
20. Mittermaier M, Pickerodt P, Kurth F, de Jarcy LB, Uhrig A, Garcia C, Machleidt F, Pergantis P, Weber S, Li Y, et al. Evaluation of PEEP and prone positioning in early COVID-19 ARDS. EClinicalMedicine. 2020;28:100579.
21. Boesing C, Graf PT, Schmitt F, Thiel M, Pelosi P, Rocco PRM, Luecke T, Krebs J. Effects of different positive end-expiratory pressure titration strategies during prone positioning in patients with acute respiratory distress syndrome: a prospective interventional study. Crit Care. 2022;26:82.
22. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, Arabi YM, Baroncelli F, Beitler JR, Bellani G, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023;49:727–59.
23. Qadir N, Sahetya S, Munshi L, Summers C, Abrams D, Beitler J, Bellani G, Brower RG, Burry L, Chen JT, et al. An update on management of adult patients with Acute Respiratory Distress Syndrome: an official American thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2024;209:24–36.
24. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, Chaudhry S, Mirza SH, Peev V, Anderson M, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. Intensive Care Med. 2021;47:208–21.
25. Urner M, Barnett AG, Bassi GL, Brodie D, Dalton HJ, Ferguson ND, Heinsar S, Hodgson CL, Peek G, Shekar K, et al. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. BMJ. 2022;377:e068723.
26. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, Tarhriz V, Farjami A, Ghasemian Sorbeni F, Farahzadi R, Ghasemnejad T. COVID-19 infection: an overview on cytokine storm and related interventions. Virol J. 2022;19:92.
27. Budinger GRS, Misharin AV, Ridge KM, Singer BD, Wunderink RG. Distinctive features of severe SARS-CoV-2 pneumonia. J Clin Invest 2021, 131.
28. Kwon SL, Oh J. COVID-19 vaccination program in South Korea: a long journey toward a new normal. Health Policy Technol. 2022;11:100601.
29. Seo J, Lim J. The impact of free vaccination policies under the Korean Influenza National Immunization Program: Trends in influenza vaccination rates in South Korea from 2010 to 2019. PLoS ONE. 2022;17:e0262594.

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