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# Moderate-to-severe ARDS: COVID-19 patients compared to influenza patients for ventilator parameters and mortality

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Shareable abstract (@ERSpublications)

In COVID-19 and influenza patients with mild-to-moderate ARDS managed similarly for mechanical ventilation, dead space estimates were higher in COVID-19 patients than in influenza patients in the first days of ARDS but short-term mortality was similar <https://bit.ly/3ZYeXWG>

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## Abstract

**Background** This study aimed to compare ventilatory parameters recorded in the first days of acute respiratory distress syndrome (ARDS) and mortality at day 60 between coronavirus disease 2019 (COVID-19) and influenza ARDS patients with arterial oxygen tension ( $P_{aO_2}$ )/inspiratory oxygen fraction ( $F_{IO_2}$ )  $\leq 150$  mmHg.

**Methods** We compared 244 COVID-19 ARDS patients with 106 influenza ARDS patients. Driving pressure, respiratory system compliance ( $C_{rs}$ ), ventilator ratio, corrected minute ventilation ( $V'_{Ecorr}$ ) and surrogate of mechanical power (index=(4×driving pressure)+respiratory rate) were calculated from day 1 to day 5 of ARDS. A propensity score analysis and a principal component analysis (PCA) were performed.

**Results** On day 1 of ARDS, COVID-19 patients had significantly higher  $P_{aO_2}/F_{IO_2}$  (median (interquartile range) 97 (79–129.2) versus 83 (62.2–114) mmHg;  $p=0.001$ ), and lower driving pressure (13.0 (11.0–16.0) versus 14.0 (12.0–16.7) cmH<sub>2</sub>O;  $p=0.01$ ), ventilatory ratio (2.08 (1.73–2.49) versus 2.52 (1.97–3.03);  $p<0.001$ ),  $V'_{Ecorr}$  (12.7 (10.2–14.9) versus 14.9 (11.6–18.6) L·min<sup>-1</sup>;  $p<0.001$ ) and index (80 (70–89) versus 84 (75–94);  $p=0.004$ ). PCA demonstrated an important overlap of ventilatory parameters recorded on day 1 between the two groups. From day 1 to day 5, repeated values of  $P_{aO_2}/F_{IO_2}$ , arterial carbon dioxide tension, ventilatory ratio and  $V'_{Ecorr}$  differed significantly between influenza and COVID-19 patients in the unmatched and matched populations. Mortality at day 60 did not differ significantly after matching (29% versus 21.7%;  $p=0.43$ ).

**Conclusions** Ventilation was more impaired in influenza than in COVID-19 ARDS patients on the first day of ARDS with an important overlap of values. However, mortality at day 60 did not differ significantly in the matched population.

## Introduction

Influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses both may be involved in the development of acute respiratory distress syndrome (ARDS), and physicians may be confronted with co-circulation of influenza virus and SARS-CoV-2 [1]. Although sharing several similarities, the course of respiratory failure may differ between COVID-19- and influenza-associated ARDS because of differences in pathophysiology leading to different pathological processes in the lungs [2–5]. Mortality rates associated with these two viral infections appear to differ, although results are conflicting depending on whether outcomes are compared in inpatients or outpatients [6, 7]. Authors have challenged the fact that COVID-19-associated ARDS could have a particular phenotype leading to particular management in mechanical ventilation settings [8–12]. In our intensive care unit (ICU), patients with ARDS due to SARS-CoV-2 and ARDS due to influenza were managed similarly for mechanical



ventilation. This gave us the opportunity to assess and compare ventilator parameters associated with the prognosis of ARDS, including plateau pressure ( $P_{\text{plat}}$ ), driving pressure [13], ventilatory ratio [14] and the surrogate of mechanical power described by COSTA *et al.* [15], between COVID-19 ARDS patients and influenza ARDS patients. Comparing influenza-associated ARDS with COVID-19-associated ARDS in terms of ventilator parameters could provide the opportunity to determine whether these two viral-induced ARDS represent two subgroups of ARDS [16].

## Patients and methods

### Patients and setting

This is a retrospective study performed on data collected prospectively in a 24-bed ICU of a university hospital (CHU Rennes, Rennes, France). Patients were followed until day 60 after the diagnosis of ARDS. The study was approved by the hospital's ethics committee (number 20-39). We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology; [www.strobe-statement.org](http://www.strobe-statement.org)) recommendations for cohort studies. All consecutive patients aged over 18 years who were admitted between 1 October 2009 and 1 February 2022 for ARDS with arterial oxygen tension ( $P_{\text{aO}_2}$ )/inspiratory oxygen fraction ( $F_{\text{IO}_2}$ )  $\leq 150$  mmHg and a positive result on a real-time reverse transcriptase (RT)-PCR assay for influenza or COVID-19 on a respiratory specimen were included. ARDS was diagnosed in patients with  $P_{\text{aO}_2}/F_{\text{IO}_2} \leq 150$  mmHg after at least 12 h of lung-protective mechanical ventilation with  $F_{\text{IO}_2} \geq 50\%$  and positive end-expiratory pressure (PEEP)  $\geq 5$  cmH<sub>2</sub>O, and not explained by cardiac failure following echocardiographic exam and/or pulmonary arterial occlusion pressure measurement [17]. Since the 2009 A H1N1 pandemic, systematic detection of influenza virus in times of epidemics using RT-PCR is routine practice in our ICU, which was extensively described previously [18]. Screening for influenza was maintained during COVID-19 epidemic waves. Patients with influenza received double doses of oseltamivir treatment for a maximum duration of 10 days. The primary end-point was difference in respiratory parameters between COVID-19 and influenza patients; the secondary end-point was mortality at day 60 from the diagnosis of ARDS.

### Management of mechanical ventilation

During the study period, all patients received lung-protective ventilation using assist-control mode with initial tidal volume ( $V_T$ ) set at 6 mL·kg<sup>-1</sup> predicted body weight (PBW). PEEP level was selected from the PEEP- $F_{\text{IO}_2}$  table proposed by the ARDS Network [19], and the end-inspiratory  $P_{\text{plat}}$  was measured to be kept  $< 30$  cmH<sub>2</sub>O until  $P_{\text{aO}_2}/F_{\text{IO}_2}$  was  $> 150$  mmHg with a level of PEEP  $\leq 10$  cmH<sub>2</sub>O and  $F_{\text{IO}_2} \leq 60\%$ . All patients received neuromuscular blockade for at least the first 48 h of mechanical ventilation, maintained as long as  $P_{\text{aO}_2}/F_{\text{IO}_2}$  remained  $\leq 150$  mmHg [20]. All patients received midazolam and morphine for sedation. Since 2009, patients received early prone positioning according to the criteria and contraindications listed in the PROSEVA trial protocol [21], and a heated humidifier during the 5 days of mechanical ventilation was used. After 5 days of mechanical ventilation, the use of a heat and moisture exchanger was left to the discretion of the attending physician. Extracorporeal membrane oxygenation (ECMO) was available throughout the study period.

### Management of treatment with steroids

In cases of suspected or documented bacterial infection and septic shock, influenza patients received 50 mg hydrocortisone per 6 h plus 50  $\mu$ g fludrocortisone in association with norepinephrine [22]. From August 2020, COVID-19 patients received 6 mg intravenous dexamethasone once daily for up to 10 days [23].

### Data collection

Day 1 was defined as the day the patient first met the criteria for moderate-to-severe ARDS. Demographic characteristics and the Simplified Acute Physiology Score (SAPS) II score [24] were recorded on admission to the ICU. Duration of symptoms suggestive of viral infection before admission to the ICU, treatment with high-flow nasal oxygen before intubation and prior treatment with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker were recorded. The following data were also recorded: vaccination against influenza and complete vaccination against SARS-CoV-2, and comorbidities including arterial hypertension, obesity, diabetes mellitus, previous coronary artery and/or vascular disease with treatment, aplasia and/or recent chemotherapy for a solid tumour or haematological disease, and COPD. The diagnosis of COPD was considered based on American Thoracic Society/European Respiratory Society Task Force criteria [25]. The Sequential Organ Assessment Failure (SOFA) score [26] was calculated from day 1 to day 5 of ARDS. In addition, daily mechanical ventilation settings were recorded from day 1 to day 5 of ARDS: the highest arterial carbon dioxide tension ( $P_{\text{aCO}_2}$ ), the lowest values of the  $P_{\text{aO}_2}/F_{\text{IO}_2}$  ratio, the highest values of expiratory  $V_T$  and PEEP applied, and the highest  $P_{\text{plat}}$ . Duration of invasive mechanical ventilation and days free of mechanical ventilation at day 28 were calculated (deceased patients had 0 days free of mechanical

ventilation for calculation). We also recorded the need for renal replacement therapy, vasopressors (dobutamine, epinephrine and norepinephrine) at any dose and ECMO.

#### Definitions and calculated ventilatory parameters

Obesity was defined as body mass index  $>30 \text{ kg}\cdot\text{m}^{-2}$ . Patients were classified for acute kidney injury (AKI) according to the KDIGO (Kidney Disease Improving Global Outcomes) categories using serum creatinine only [27]. Stage 2 AKI was defined by an increase in the serum creatinine level to 2.0–2.9 times baseline and stage 3 AKI was defined by an increase in the serum creatinine level to 3 times baseline.

Respiratory system compliance ( $C_{rs}$  ( $\text{mL}\cdot\text{cmH}_2\text{O}^{-1}$ )) was defined as  $V_T$  divided by the difference between  $P_{\text{plat}}$  and PEEP, and the driving pressure as the difference between  $P_{\text{plat}}$  and the PEEP level. Two surrogates of the ratio of dead space to  $V_T$  were calculated: 1) ventilatory ratio was calculated as  $(V'_E (\text{mL}\cdot\text{min}^{-1})\times P_{\text{aCO}_2} (\text{mmHg})) / (\text{PBW}\times 100\times 37.5)$ , where  $V'_E$  is the minute ventilation, and 2) corrected  $V'_E$  ( $V'_{E\text{corr}}$ ) defined as  $(V'_E\times P_{\text{aCO}_2}) / 40 \text{ mmHg}$ , where 40 mmHg is the ideal value of  $P_{\text{aCO}_2}$  [14, 28, 29]. For ventilatory ratio, a value approximating 1 would represent normal ventilating lungs. The model compared to mechanical power for the prognosis of ARDS, described by COSTA *et al.* [15] according to the formula  $\text{index}=(4\times\text{driving pressure})+\text{respiratory rate}$ , was also calculated.  $C_{rs}$ , driving pressure, ventilatory ratio,  $V'_{E\text{corr}}$ , and the index combining respiratory rate and driving pressure were calculated on each day from day 1 to day 5.

The following causes of death were distinguished: primary infection-related organ failure, refractory hypoxaemia, mesenteric ischaemia, central nervous system disorder and end-of life decision [30].

#### Statistical analysis

Data are expressed as count and percentage for categorical variables. Continuous variables were initially assessed for normality and are presented as mean and standard deviation, and when not normally distributed as median and interquartile range. The Chi-squared test was used to compare categorical variables and the Mann–Whitney U-test was used to compare continuous variables. In a first step, we performed analyses on the whole population. We used a linear mixed model to analyse repeated values and assess longitudinal changes in respiratory parameters and SOFA scores from day 1 to day 5 of ARDS. COVID-19 and influenza were included as fixed effects and we used a random intercept to take into account the heterogeneity across subjects. We used Bonferroni's correction for *post hoc* analysis of repeated values. In a second step, we performed an exploratory analysis to determine whether COVID-19 patients can be reliably distinguished from influenza patients based on respiratory parameters recorded on day 1 of ARDS. Principal component analysis (PCA) was performed using day 1 respiratory parameters. PCA is a dimensionality reduction method used to reduce the dimensionality of large datasets [31]. Its goal is to extract the important information from the dataset. After transformation the number of variables is reduced and still contains most of the information of the initial dataset (the principal components, which are the linear combination of the original variables). Databases are then easier to explore and visualise. In a third step and in order to compare outcomes of patients, a propensity score near-neighbour with 0.25 caliper matching (1:1 ratio) method was applied in order to mitigate confounding bias. The following baseline characteristics and coexisting conditions were used for the calculation of the propensity score: age, SAPS II score, SOFA score, age-adjusted Charlson Comorbidity Index, high-flow oxygen therapy (HFOT) before intubation, arterial hypertension, valvular and/or coronary disease with treatment, severity according to the Berlin criteria, and AKI stage 2–3. We used a logistic regression analysis to determine the variables independently associated with mortality at day 60. Variables entered in the model were those achieving  $p\leq 0.1$  in the univariate analysis. Tests were two-sided and we considered  $p<0.05$  as significant. Statistical analyses were performed using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Baseline characteristics of the patients assessed on the whole population

From October 2009 to October 2020, 106 patients (30%) were admitted to the ICU with influenza-associated ARDS with  $P_{\text{aO}_2}/F_{\text{IO}_2}\leq 150 \text{ mmHg}$ . From 10 March 2020 to February 2022, 350 patients (70%) were admitted to the ICU with COVID-19-associated ARDS with  $P_{\text{aO}_2}/F_{\text{IO}_2}\leq 150 \text{ mmHg}$ . Of note, there was no influenza and SARS-CoV-2 co-infection. The characteristics of the patients before the matching process are presented in table 1 (population before matching). After comparisons, patients with COVID-19 differed significantly from patients with influenza for almost all baseline characteristics, coexisting conditions and treatments used during the ICU stay. Compared to patients with influenza, COVID-19 patients were older, their aged-adjusted Charlson Comorbidity Index was higher, they were more frequently obese and suffered more frequently from arterial hypertension with treatment, but had lower severity scores, less frequently ARDS with  $P_{\text{aO}_2}/F_{\text{IO}_2}<100 \text{ mmHg}$  and less severe AKI. Only 18

TABLE 1 Characteristics of COVID-19 and influenza acute respiratory distress syndrome (ARDS) patients

	Population before matching (n=350)			Population after matching (n=138)		
	COVID-19 ARDS (n=244)	Influenza ARDS (n=106)	p-value	COVID-19 ARDS (n=69)	Influenza ARDS (n=69)	p-value
<b>Baseline characteristics</b>						
Age (years)	63.5 (54.0–71.2)	59.0 (49.0–65.7)	0.001	58.0 (49.0–69.0)	60.0 (50.0–67.0)	0.92
Male	163 (66.8)	65 (61.3)	0.39	43 (62.3)	42 (60.9)	1
Aged-adjusted CCI	3.0 (1.0–4.0)	2.0 (1.0–3.0)	0.01	2 (1.0–4.0)	2.0 (1.0–3.0)	0.056
Previous treatment with ACEI	49 (20.1)	9 (8.5)	0.01	9 (13.0)	6 (8.7)	0.58
Previous treatment with ARB	33 (13.5)	4 (3.8)	0.003	6 (8.7)	4 (5.8)	0.74
Symptom duration (days) <sup>#</sup>	7 (5–10)	6 (4–9)	0.006	7 (4–10)	5 (3–9)	0.11
HFOT before intubation	92 (37.7)	20 (18.9)	0.001	13 (18.8)	16 (23.2)	0.68
SAPS II score	34 (26–44)	47 (35–60.8)	<0.001	40 (31–58)	43 (35–55)	0.59
AKI stage 2–3	19 (7.8)	27 (25.5)	<0.001	8 (11.6)	12 (17.4)	0.59
Lymphocyte count ( $\times 10^9 \text{ L}^{-1}$ )	0.64 (0.41–0.94)	0.48 (0.32–0.81)	0.0009	0.69 (0.39–0.93)	0.52 (0.34–0.82)	0.23
Pulmonary bacterial co-infection	13 (5.3)	27 (25.4)	<0.001	7 (10.1)	13 (18.8)	0.15
<b>Coexisting condition</b>						
Arterial hypertension	106 (43.4)	26 (24.5)	0.001	18 (26.1)	21 (30.4)	0.70
Obesity	115 (47.1)	36 (34.0)	0.03	29 (42)	30 (43.5)	1
Diabetes mellitus	45 (18.4)	15 (14.2)	0.41	13 (18.8)	10 (14.5)	0.65
Coronary artery and/or vascular disease with treatment	54 (22.1)	13 (12.3)	0.18	11 (15.9)	10 (14.5)	1
Aplasia and/or recent chemotherapy for solid tumour or haematological disease	27 (11.1)	18 (17.0)	0.02	9 (13)	12 (17.4)	0.64
COPD	39 (16.0)	26 (24.5)	0.082	10 (14.5)	18 (26.1)	0.14
Severe ARDS ( $P_{aO_2}/F_{iO_2} < 100 \text{ mmHg}$ )	129 (52.9)	69 (65.1)	0.045	37 (53.6)	44 (63.8)	0.30
SOFA score on day 1 of ARDS	5 (5–6)	9 (7–11)	<0.001	6 (5–8)	8 (6–9)	0.23
<b>Interventions</b>						
Treatment with steroids within 7 days of ARDS diagnosis	219 (90)	44 (41)	<0.001	55 (80)	24 (35)	<0.001
Prone positioning	181 (74.2)	55 (51.9)	<0.001	52 (75.4)	38 (55.1)	0.02
ECMO	14 (5.7)	14 (13.2)	0.03	7 (10.1)	8 (11.6)	1
Renal replacement therapy	24 (9.8)	32 (30.2)	<0.001	14 (20.3)	13 (18.8)	1
Vasopressors	194 (79.5)	85 (80.2)	0.99	57 (82.6)	51 (73.9)	0.30
<b>Outcomes</b>						
Ventilator-free days at day 28	13.5 (0.25–19.75)	4.5 (0.0–15.7)	0.001	10 (0–18)	6 (0–16)	0.32
Mortality in the ICU	27 (12.4)	30 (28.3)	<0.001	15 (21.7)	19 (27.5)	0.55
Mortality at day 28	25 (10.2)	25 (23.6)	<0.001	12 (17.4)	15 (21.7)	0.66
Mortality at day 60	37 (15.1)	32 (30.1)	<0.001	15 (21.7)	20 (29.0)	0.43

Data are presented as median (interquartile range) or n (%), unless otherwise stated. CCI: Charlson Comorbidity Index; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; HFOT: high-flow oxygen therapy; SAPS: Simplified Acute Physiology Score; AKI: acute kidney injury;  $P_{aO_2}$ : arterial oxygen tension;  $F_{iO_2}$ : inspiratory oxygen fraction; SOFA: Sequential Organ Failure Assessment; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit. <sup>#</sup>: duration of symptoms suggestive of infection due to influenza virus or severe acute respiratory syndrome coronavirus 2.

patients received noninvasive ventilation before intubation (seven patients with COVID-19 and 11 patients with influenza). The proportion of patients intubated after failure of treatment with HFOT was significantly higher in COVID-19 patients than in influenza patients. All patients received neuromuscular blockade, and the proportion of patients who received steroids and prone positioning was higher in COVID-19 than in influenza patients. Fewer patients with COVID-19 received ECMO compared to influenza patients. The ventilators brands used in our ICU were the same during the study period.

#### Ventilatory parameters assessed on day 1 of ARDS on the whole population

Results for recorded and calculated respiratory parameters on day 1 of ARDS are listed in table 2 (population before matching). After comparisons between influenza and COVID-19 patients, almost all of the parameters assessed differed significantly between the two groups of patients: driving pressure, ventilatory ratio,  $V'_{Ecorr}$  and index ((4×driving pressure)+respiratory rate) were all significantly higher in influenza patients than in COVID-19 patients. The level of PEEP applied did not differ significantly between the two groups of patients.

TABLE 2 Ventilatory parameters at day 1 of acute respiratory disease syndrome (ARDS) in patients with influenza and COVID-19 before and after matching

	Population before matching (n=350)			Population after matching (n=138)		
	COVID-19 ARDS (n=244)	Influenza ARDS (n=106)	p-value	COVID-19 ARDS (n=69)	Influenza ARDS (n=69)	p-value
$P_{aO_2}/F_{IO_2}$ (mmHg)	97 (79–129.2)	83 (62.2–114)	0.001	97 (78–127)	86 (65–114)	0.09
$P_{aCO_2}$ (mmHg)	47.5 (42–55)	55 (46–64.8)	<0.001	47 (42–58)	55 (46–62)	0.014
$V_T$ (mL·kg <sup>-1</sup> PBW)	6.22 (5.98–6.49)	6.43 (6–6.84)	0.014	6.18 (5.91–6.41)	6.44 (6.06–6.88)	0.005
Respiratory rate (breaths·min <sup>-1</sup> )	26 (24–28)	28 (25–30)	0.02	27 (25–30)	28 (24–30)	0.87
PEEP set (cmH <sub>2</sub> O)	12 (10–12)	12 (10–14)	0.19	12 (10–12)	12 (9–14)	0.65
$P_{plat}$ (cmH <sub>2</sub> O)	24.5 (22–27)	26.5 (24.0–29)	<0.001	25 (23–28)	26 (24–28)	0.55
$C_{rs}$ (mL·cmH <sub>2</sub> O <sup>-1</sup> )	30.3 (24.8–37.4)	28.6 (23.6–35)	0.11	28.3 (22.9–36.9)	28.6 (23.8–35.2)	0.57
Driving pressure (cmH <sub>2</sub> O)	13.0 (11.0–16.0)	14 (12.0–16.7)	0.01	15.0 (11.0–16.0)	14.0 (12.0–16.0)	0.83
Ventilatory ratio	2.08 (1.73–2.49)	2.52 (1.97–3.03)	<0.001	2.17 (1.74–2.64)	2.49 (1.89–3.02)	0.009
$V_{Ecorr}$ (L·min <sup>-1</sup> )	12.7 (10.2–14.9)	14.9 (11.6–18.6)	<0.001	12.7 (10.4–15.2)	14.1 (11.4–17.7)	0.048
Index <sup>#</sup>	80 (70–89)	84 (75–94)	0.004	85 (70–93)	84 (75–94)	0.67

Data are presented as median (interquartile range), unless otherwise stated.  $P_{aO_2}$ : arterial oxygen tension;  $F_{IO_2}$ : inspiratory oxygen fraction;  $P_{aCO_2}$ : arterial carbon dioxide tension;  $V_T$ : tidal volume; PBW: predicted body weight; PEEP: positive end-expiratory pressure;  $P_{plat}$ : plateau pressure;  $C_{rs}$ : respiratory system compliance;  $V_{Ecorr}$ : corrected minute ventilation. <sup>#</sup>: (4×driving pressure)+respiratory rate [15].

### Changes in ventilatory parameters from day 1 to day 5 of ARDS according to the virus involved

Results for analysis of ventilatory parameter changes in unmatched and matched COVID-19-associated ARDS and influenza-associated ARDS, with the linear mixed model, are presented in table 3. Values recorded from day 1 to day 5 for  $P_{aO_2}/F_{IO_2}$ ,  $P_{aCO_2}$ , ventilatory ratio and  $V_{Ecorr}$  were significantly different between COVID-19 and influenza patients, both in unmatched and matched populations (table 3 and figure 1). The surrogate of mechanical power differed significantly between the two groups of patients in the unmatched population and tended to be different in the matched population. Ventilatory ratio and  $V_{Ecorr}$  were lower in COVID-19 ARDS patients than in influenza ARDS patients except on day 5 (figure 1).

### Results of exploratory analysis using PCA

The relationship between ventilator variables recorded on day 1 of ARDS and influenza and COVID-19 pneumonia as the cause of ARDS is presented in figure 2.

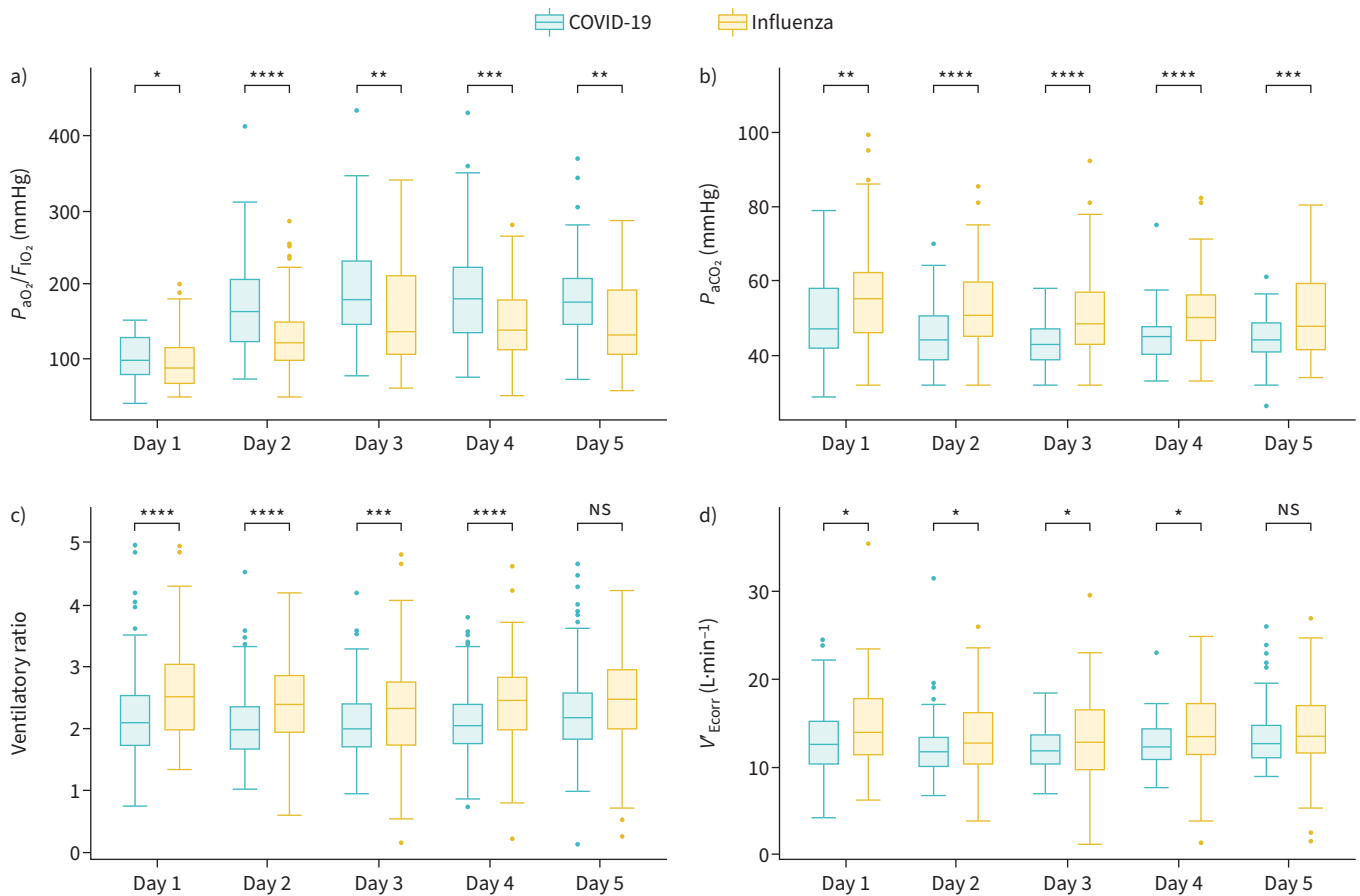
### Baseline characteristics of the patients assessed on the matched population

After matching, 69 COVID-19 ARDS patients were compared to 69 influenza ARDS patients, and did not differ significantly for baseline characteristics, comorbid conditions and interventions except for prone

TABLE 3 Association between virus involved (COVID-19 or influenza) and repeated values of ventilatory parameters

Model term (repeated values from day 1 to day 5 of ARDS)	Population before matching (n=340)		Population after matching (n=138)	
	Estimate (95% CI) <sup>#</sup>	p-value	Estimate (95% CI) <sup>#</sup>	p-value
$P_{aO_2}/F_{IO_2}$ (mmHg)	-36.17 (-26.64–-17.11)	<0.0001	-31.49 (-44.97–-18.00)	<0.0001
$P_{aCO_2}$ (mmHg)	5.14 (3.56–6.76)	<0.0001	6.96 (4.22–9.69)	<0.0001
$V_T$ (mL·kg <sup>-1</sup> PBW)	0.02 (-0.13–0.19)	0.72	0.03 (-0.12–0.18)	0.71
Respiratory rate (breaths·min <sup>-1</sup> )	0.78 (0.13–1.42)	0.02	0.23 (-0.81–1.29)	0.65
PEEP set (cmH <sub>2</sub> O)	-0.14 (-0.64–0.35)	0.56	-0.22 (-1.07–0.62)	0.62
$P_{plat}$ (cmH <sub>2</sub> O)	0.94 (0.20–1.68)	0.01	0.94 (0.20–1.68)	0.10
$C_{rs}$ (mL·cmH <sub>2</sub> O <sup>-1</sup> )	-0.92 (-3.08–1.24)	0.40	-2.01 (-5.42–1.38)	0.25
Driving pressure (cmH <sub>2</sub> O)	0.77 (0.06–1.50)	0.03	1.11 (-0.14–2.37)	0.08
Ventilatory ratio	0.30 (0.19–0.41)	<0.0001	0.35 (0.16–0.52)	<0.0001
$V_{Ecorr}$ (L·min <sup>-1</sup> )	1.88 (1.17–2.58)	<0.0001	1.68 (0.54–2.83)	0.004
Index <sup>¶</sup>	4.05 (1.04–7.06)	0.008	5.29 (0.10–10.48)	0.06

ARDS: acute respiratory distress syndrome;  $P_{aO_2}$ : arterial oxygen tension;  $F_{IO_2}$ : inspiratory oxygen fraction;  $P_{aCO_2}$ : arterial carbon dioxide tension;  $V_T$ : tidal volume; PBW: predicted body weight; PEEP: positive end-expiratory pressure;  $P_{plat}$ : plateau pressure;  $C_{rs}$ : respiratory system compliance;  $V_{Ecorr}$ : corrected minute ventilation. <sup>#</sup>: coefficient estimates from a linear mixed effects model on the repeated values. A random intercept was modelled per patient. <sup>¶</sup>: (4×driving pressure)+respiratory rate [15].



**FIGURE 1** a) Arterial oxygen tension ( $P_{aO_2}$ )/inspiratory oxygen fraction ( $F_{IO_2}$ ), b) arterial carbon dioxide tension ( $P_{aCO_2}$ ), c) ventilatory ratio and d) corrected minute ventilation ( $V_{Ecorr}$ ) in matched patients with COVID-19 and influenza from day 1 to day 5 of moderate-to-severe acute respiratory distress syndrome. Box-and-whisker plots display median, 10th, 25th, 75th and 90th percentiles, as well as outliers. \*:  $p<0.05$ ; \*\*:  $p<0.01$ ; \*\*\*:  $p<0.001$ ; \*\*\*\*:  $p<0.0001$ ; NS: nonsignificant.

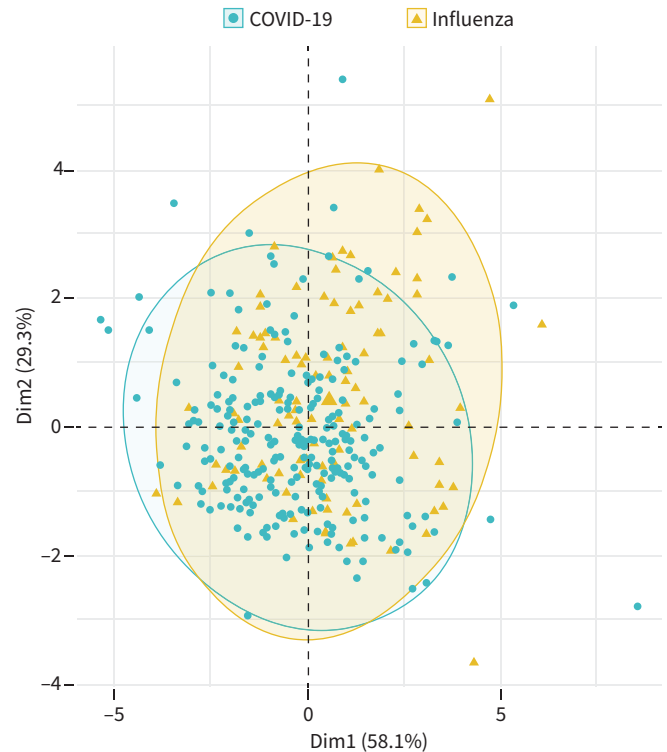
positioning and treatment with steroids in the first week of ARDS, both being more frequently used in patients with COVID-19 (table 1). We ensured that repeated values for SOFA scores did not differ or vary significantly with time in the matched population (estimate:  $-0.04$ , 95% coefficient estimate  $-0.97$ – $0.89$ ;  $p=0.90$ ) (supplementary figure S1). Mortality rates did not differ significantly between COVID-19 and influenza patients.

### Short-term mortality

Mortality rates in the ICU, at day 28 and at day 60 were significantly lower in patients with COVID-19 than in patients with influenza after comparisons on the whole population but not after comparisons on the matched population. Interestingly, the causes of death differed significantly between COVID-19 and influenza patients ( $p=0.04$ ) when assessed on the whole population and were distributed as: primary infection-related multiple-organ failure (23% versus 57%), refractory hypoxaemia (50% versus 17%), mesenteric ischaemia (10% versus 7%), central nervous system disorder (7% versus 10%) and end-of-life decision (7% versus 10%).

### Discussion

In this retrospective clinical study, we compared the clinical characteristics, ventilatory parameters and mortality rates at day 60 of moderate-to-severe ARDS between COVID-19 and influenza patients managed similarly for mechanical ventilation. After matching the patients on comorbidities and severity scores, and among the ventilator parameters assessed, no differences in mortality were found between the two groups, although significant differences in ventilator parameters were noted.



**FIGURE 2** Principal component analysis of COVID-19 and influenza acute respiratory distress syndrome with arterial oxygen tension ( $P_{aO_2}$ )/inspiratory oxygen fraction ( $F_{iO_2}$ )  $\leq 150$  mmHg. Two dimensions (Dim1 and Dim2) are represented on the  $x$ - and  $y$ -axis, respectively. Ventilatory variables entered into the analysis correspond to those listed in table 2.

Since the management of ARDS patients did not change in our ICU during the study period we aimed to compare ventilator parameters between influenza and COVID-19 patients matched for baseline comorbidities and severity scores. We found that surrogate markers of increased dead space such as ventilatory ratio and  $V_{E\text{CORR}}$  were higher during the first 4 days of ARDS in influenza patients than in COVID-19 patients. Other authors have suggested that a high dead space fraction, related to the conjunction of alveolar oedema and widespread thrombosis in the pulmonary circulation, is characteristic of COVID-19-associated ARDS [1]. BELONCLE *et al.* [32] found that, in a population of matched COVID-19 and non-COVID-19 ARDS, ventilatory ratio, a surrogate marker of dead space, was significantly lower in COVID-19 ARDS patients. Elevated pulmonary dead space fraction is a strong indicator of mortality risk. In addition, compared to oxygenation indices, the pulmonary dead space fraction is a more sensitive marker of changes in pulmonary function in response to therapies aimed at alveolar recruitment. The highest dead space estimation noted in influenza patients in the initial phase of ARDS may be explained by the obstruction of the airway reported with influenza virus infection and/or the largest areas of diffuse alveolar damage and increased vascular inflammation [3]. Furthermore, values for the surrogate of mechanical power described by COSTA *et al.* [15] were higher in ARDS patients with infection due to influenza. However, driving pressure, which is a surrogate for cyclic lung strain during mechanical ventilation and predicts lung injury, did not differ between influenza and COVID-19 patients, and we did not find that  $C_{rs}$  values were different between the two groups.  $C_{rs}$  is related to the volume of aerated lung available for tidal ventilation during viral pneumonia [17, 18]. Taken together, our results for driving pressure and  $C_{rs}$  do not suggest that the proportion of lung available for ventilation differs significantly between influenza and COVID-19 patients with moderate-to-severe ARDS. Overall, the overlap across COVID-19 and influenza patients noted after exploratory analysis does not allow the physician to distinguish and consequently manage these two groups of patients differently at initiation of mechanical ventilation.

In accordance with previous studies [6, 7, 33], patients with COVID-19 were more often obese and hypertensive, whereas patients with influenza were more often immunocompromised. It is noteworthy that the occurrence of AKI among patients with COVID-19 was significantly lower compared to influenza



patients, although previous studies have reported that AKI stage 2–3 could be a major concern in critically ill COVID-19 patients [34].

After comparisons on the whole population, we found that 60-day mortality was higher in patients with influenza pneumonia than in patients with COVID-19. Importantly, when matching the two populations, there was no difference in mortality rate. Studies comparing outcomes of influenza and COVID-19 infections reported conflicting results. Although the mortality rates reported in our study were lower than usually published mortality [12, 30–37], our results are in accordance with the results reported by TANG *et al.* [6]. Conversely, in a recent French study, DE MARIGNAN *et al.* [38] reported that COVID-19 patients had higher 90-day adjusted mortality in the ICU than influenza patients. However, the authors did not include patients hospitalised during the 2009 A H1N1 pandemic, a particularly severe form of ARDS.

Our study has several limitations. The study covers a long period and a possible historical bias must be taken into account when interpreting the results. We noted differences in organ supports and treatments used between influenza and COVID-19 patients, with a possible impact on outcomes. However, mortality rates did not differ significantly between the two viral diseases after the matching process. The study was observational and performed on consecutive patients, but we cannot exclude uncontrolled confounders. However, we tried to minimise bias by performing comparisons in a matched population. The study was conducted at a single site, 250 patients only were studied and consequently the results may not be applicable to other ICUs.

### Conclusions

Our results suggest that ventilatory parameters recorded on the first day of ARDS in COVID-19 patients are largely shared with those recorded in influenza patients. Dead space appeared more increased in influenza patients than in COVID-19 patients during the first 4 days of ARDS. In contrast, driving pressure, a surrogate of cyclic strain, did not differ between influenza and COVID-19 patients. We believe that these results do not support that protective ventilation should be managed differently during the first days whether ARDS was due to influenza pneumonia or COVID-19 pneumonia. Short-term mortality did not differ significantly between matched COVID-19 and influenza patients.

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