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Early View

Original research article

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Please cite this article as: Maamar A, Guillot P, Joussellin V, *et al*. Moderate to severe ARDS: COVID-19 patients compared to influenza patients for ventilator parameters and mortality. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00554-2022).

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

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Declaration of interests: None.

Funding sources: This research receive any specific grant from funding agencies in the public, commercial, or not-for- profit sectors.

Key words: Influenza, COVID-19, ARDS, cohort study, mortality.

Take home message: 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 the first days of ARDS and short-term mortality similar.

ABSTRACT

Background: This study aimed to compare ventilatory parameters recorded the first days of ARDS, and mortality at day 60 between COVID-19 and influenza ARDS patients with $PaO_2/FiO_2 \leq 150$ mmHg.

Methods: We compared 244 COVID-19 ARDS patients with 106 influenza ARDS patients. Driving pressure (DP), respiratory system compliance (CRs), ventilator ratio (VR), corrected minute ventilation (VEcorr), and surrogate of mechanical power [index= (4 x DP) + respiratory rate] were calculated from day1 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 PaO_2/FiO_2 ratio (median [IQR], 97 mmHg [79-129] vs 83 [62.2-114]), p= 0.001), and lower DP (13 cmH20 [11-16.0] vs 14 [12.0-16.7], p= 0.01), VR (2.08 [1.73-2.49 vs 2.52 [1.97-3.03], p< 0.001), VEcorr (12.7 L/mn [10.2-14.9] vs 14.9 [11.6-18.6], p< 0.001), index (80 [70-89] vs 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 PaO_2/FiO_2 ratio, $PaCO_2$, VR and VEcorr 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% vs 21.7%, p= 0.43).

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

Introduction

Influenza and SARS-CoV-2 viruses both may be involved in the development of acute respiratory disease syndrome (ARDS) and physicians may be confronted to co-circulation of influenza virus and SARS-CoV-2 [1]. Although sharing several similitudes, the course of respiratory failure may differ between COVID-19 and influenza-associated ARDS because of differences in pathophysiology leading to different pathological process 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 challenged the fact that COVID-19-associated ARDS could have a particular phenotype leading to particular management in mechanical ventilation (MV) setting [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 MV. This gave us the opportunity to assess and compare ventilator parameters associated with the prognosis of ARDS, including plateau pressure (PP), driving pressure (DP) [13], ventilatory ratio (VR) [14] and the surrogate of mechanical power described by Costa ELV et al [15], between Covid-19 ARDS patients and influenza ARDS patients. Comparing influenza-associated ARDS to 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 intensive care unit (ICU) of a university hospital. Patients were followed until day 60 after the

diagnosis of ARDS. The study was approved by the hospital's ethics committee (N° 20-39). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies. All consecutive patients aged older than 18 years who were admitted between October 1st, 2009, and February 1st, 2022, for ARDS with PaO_2/FiO_2 ratio ≤ 150 mmHg and a positive result on a real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay for influenza or COVID-19 on a respiratory specimen were included. ARDS was diagnosed in patients with a PaO_2/FiO_2 ratio ≤ 150 mmHg after at least 12 hours of lung-protective mechanical ventilation (MV) with an FiO_2 ≥ 50% and a positive end-expiratory pressure (PEEP) level ≥ 5 cmH_2O, and not explained by cardiac failure following echocardiographic exam and/or pulmonary arterial occlusion pressure measurement [17]. Since the 2009 H1N1 pandemic, systematic detection of influenza virus in times of epidemics using RT-PCR is of routine practice to 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 Osletamivir treatment for a maximum duration of ten days. The primary endpoint was differences in respiratory parameters between COVID-19 and influenza patients, secondary end-point was mortality at day-60 from the diagnosis of ARDS.

Management of mechanical ventilation (MV)

During the study period, all patients received lung-protective ventilation using assist-control mode with initial tidal volume (Vt) set at 6 ml per kilogram of predicted body weight (PBW). PEEP level was selected from the PEEP-FiO_2 table proposed by the ARDS Network [19], and the end-inspiratory plateau pressure was measured to be kept below 30 cm of water until the PaO_2/FiO_2 ratio was higher than 150 mmHg with a level of PEEP ≤ 10 cmH_2O and FiO_2 ≤ 60%. All the patients received neuromuscular blockade for at least the first 48 hours of MV, maintained as long as the PaO_2/FiO_2 ratio remained below 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 protocol [21], and a heated humidifier during the first five days of MV was used. After five days of MV, the use of heat and moisture exchanger (HME) was left to the discretion of 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 per 6 hours of hydrocortisone plus 50 micrograms of 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 Simplified Acute Physiology Score (SAPS) II [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 (HFNO) before intubation, and prior treatment with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blocker (ARB) were recorded. The following data were also recorded: vaccination against Influenza and complete vaccination against Sars-CoV-2, comorbidities including arterial hypertension, obesity, diabetes mellitus, previous coronary artery and/or vascular disease with treatment, aplasia and/or recent chemotherapy for a solid tumor or hematological disease, and chronic obstructive pulmonary disease (COPD). The diagnosis of COPD was considered based on Task Force criteria [25]. Sequential Organ Assessment Failure (SOFA) [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 $PaCO_2$, the lowest values of the PaO_2/FiO_2 ratio, the highest values of expiratory Vt (Vte) and PEEP applied, and the highest plateau pressure. Duration of invasive MV and free days of MV at day 28 were calculated (deceased patients had zero free day of MV for calculation). We also recorded the need for renal replacement therapy (RRT), vasopressors (dobutamine, epinephrine and norepinephrine) at any dose, and ECMO.

Definitions and calculated ventilatory parameters

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

The respiratory system compliance (RSC, ml/cmH_2O) was defined as Vt divided by the difference between plateau pressure (Pplat) and PEEP, and the driving pressure (DP) as the difference between Pplat and the PEEP level. Two surrogates of the ratio of dead space to tidal volume were calculated: 1) Ventilatory ratio (VR) was calculated as [minute ventilation (mL/mn) x $PaCO_2$ (mmHg)] / (PBW x 100 x 37.5)] and 2) corrected minute ventilation (V_{Ecorr}) defined as [(minute ventilation x $PaCO_2$)/40 mmHg] where 40 mmHg is the ideal value of $PaCO_2$ [14, 28, 29]. For VR, a value approximating 1 would represent normal ventilating lungs. The model compared to mechanical power for the prognosis of ARDS, described by Costa ELV et al [15] according to the formula [(4 x DP) + respiratory rate] was also calculated. RSC, DP, VR, V_{Ecorr}, and the index combining respiratory rate and DP were calculated on each day from day 1 to day 5.

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

Statistical analysis

Data are expressed as counts and percentages for categorical variables. Continuous variables were initially assessed for normality and are presented as means and standard deviation (SD) and when not normally distributed as medians and interquartile ranges (IQRs, 25-75%). The chi-square 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 linear mixed model to analyze 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 distinguish from influenza patients based on respiratory parameters recorded on day 1 of ARDS. Proportional components analysis (PCA) was the performed using day 1 respiratory parameters. PCA is a dimensionality-reduction method used to reduce the dimensionality of large data sets [31]. Its goal is to extract the important information from the data set. After transformation the number of variables is reduced and still contains most of the information of the initial data set (the principal components, which are the linear combination of the original variables). Databases are then easier to explore and visualize. In a third step and in order to compare outcomes of patients, a propensity score (PS) near neighbor 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 PS: age,

SAPS II, SOFA score, age-adjusted Charlson comorbidity index, high flow oxygen therapy before intubation, arterial hypertension, valvular and/or coronary disease with treatment, severity according to the Berlin criteria, and AKI stage 2 or 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 a p value less or equal to 0.1 in the univariate analysis. Tests were two sided and, we considered $p < 0.05$ as significant. Statistical analyses were performed using R 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 a PaO_2/FiO_2 ratio ≤ 150 mmHg. From March 10, 2020, to February 2022, 350 patients (70%) were admitted to the ICU with COVID-19 associated-ARDS with a PaO_2/FiO_2 ratio ≤ 150 mmHg. Of note, there was no influenza and SARS-CoV-2 co-infection. The characteristics of the patients before matching process are represented in the **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, were more frequently obese and suffered more frequently from arterial hypertension with treatment, but had lower severity scores, less frequently ARDS with PaO_2/FiO_2 ratio <100 mmHg, and less severe AKI. Only 18 patients received non-invasive ventilation before intubation, 7 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. Less patients with COVID-19 received ECMO compared to influenza patients. The brands of ventilators 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 x Driving Pressure) + respiratory rate] were all significantly higher in Influenza patients than in COVID-19 patients. Level of PEEP applied did not differ significantly between the two groups of patients.

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

Results for analysis of ventilatory parameters changes in unmatched and matched COVID-19 associated ARDS and Influenza associated ARDS, with mixed linear model, are listed in **Table 3**. Values recorded from day 1 to day 5 for PaO_2/FiO_2 ratio, $PaCO_2$, ventilatory ratio, corrected minute ventilation 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. VR and

V_{Ecorr} were lower in the COVID-19 ARDS patients than in the 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 cause of ARDS is represented in **Figure 2**.

Baseline characteristics of the patients assessed on the matched population

After matching, 69 COVID-19 ARDS patients were compared with 69 Influenza ARDS patients and did not differ significantly for baseline characteristics, comorbid conditions, and interventions except for prone positioning and treatment with steroids the first week of ARDS, both being more frequently used in patients with COVID-19 (**Table 1**, Population after matching). 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) (**Supplemental Figure 1**). 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 cause of death differed significantly between COVID-19 and Influenza patients (p= 0.04) when assessed on the whole population and were distributed as follows: primary infection-related multiple-organ failure (23% vs 57%), refractory hypoxemia (50% vs 17%), mesenteric ischemia (10% vs 7%), central nervous system disorder (7% vs 10%), end-of-life decision (7% vs 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 MV. 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.

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 surrogates markers of increased dead space such as VR and V_{Ecorr} were higher the first four days of ARDS in influenza patients than in COVID-19 patients. Although authors suggested that a high dead space fraction, related to the conjunction of alveolar edema 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, VR, 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 with oxygenation indices, pulmonary dead-space fraction is a more sensitive marker of changes in pulmonary function in response to 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 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] was higher in ARDS patients with infection due to influenza. However, DP that is a surrogate for cyclic lung train during MV and predicts lung injury did not differ between influenza and COVID-19 patients and we did not find that Crs

values were different between the two groups. Crs is related to the volume of aerated available for tidal ventilation during viral pneumonia (17,18). Taken together, our results for DP and Crs do not suggest that the proportion of lung available for ventilation differ significantly between influenza and COVID-19 patients with moderate to severe ARDS. Overall, overlap across COVID-19 and influenza patients noted after exploratory analysis do not allow to physician to distinguish and consequently manage differently these two groups of patients at initiation of MV.

In accordance with previous studies [6, 7, 33], patients with COVID-19 were more often obese, hypertensive, whereas patients with influenza were more often immunocompromised. Noteworthy, 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 previously reported by Tang Xiao 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 hospitalized 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 treatment used between influenza and COVID-19 patients with 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 minimize 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 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 the first four days of ARDS. In contrast, DP 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 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.

Legend for Figure 1

Ratio of partial pressure of arterial oxygen (PaO_2) over fraction of inspired oxygen (FiO_2) (A), PaCO2 (B), ventilatory ratio (C) and (D) corrected minute ventilation in matched patients with COVID-19 and influenza from day 1 to day 5 of moderate to severe acute respiratory distress syndrome. Boxplots display medians, 10th, 25th, 75th, and 90th percentiles. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$, ns: non-significant.

Legend for Figure 2

Principal correspondence analysis (PCA) of COVID-19 and influenza ARDS with PaO_2/FiO_2 ratio ≤ 150 mmHg. Two dimensions (Dim1 and Dim2) are represented on the x and y axis. Ventilatory variables entered into the analysis correspond to the ones listed in Table 2.

Table 1: Characteristics of COVID-19 ARDS and Influenza 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
Baseline characteristics						
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 gender	163 (66.8)	65 (61.3)	0.39	43 (62.3)	42 (60.9)	1
Aged-adjusted Charlson comorbidity Index	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
Symptoms, days[a]	7 (5-10)	6 (4-9)	0.006	7.0 (4.0-10.0)	5.0 (3.0-9.0)	0.11
Treatment with HFNO 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
Lymphocytes count, Giga/l	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 coinfection	13 (5.3)	27 (25.4)	<0.001	7 (10.1)	13 (18.8)	0.15
Coexisting condition						
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
Valvular and/or coronary 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	27 (11.1)	18 (17.0)	0.02	9 (13)	12 (17.4)	0.64

tumor or hematological disease						
COPD	39 (16.0)	26 (24.5)	0.082	10 (14.5)	18 (26.1)	0.14
Severe ARDS (PaO_2/FiO_2<100 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
Interventions						
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
Outcomes						
Ventilator-free day 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. Definition of abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; AKI, Acute kidney injury; ARDS, Acute Respiratory Distress Syndrome; ECMO, Extracorporeal Membrane oxygenation; HFOT, high flow oxygen therapy; SAPS, simplified acute physiology score; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease.

[a] Duration of symptoms suggestive of infection due to influenza virus or Sars-CoV-2

Table 2: Ventilatory parameters at day 1 of 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
PaO_2/FiO_2, mmHg	97 (79-129.2)	83 (62.2-114)	0.001	97 (78-127)	86 (65-114)	0.09
$PaCO_2$, mmHg	47.5 (42-55)	55 (46-64.8)	<0.001	47 (42-58)	55 (46-62)	0.014
Tidal volume, $ml.kg^{-1}$ 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, $cycles.min^{-1}$	26 (24-28)	28 (25-30)	0.02	27 (25-30)	28 (24-30)	0.87
PEEP set, cmH_2O	12 (10-12)	12 (10-14)	0.19	12 (10-12)	12 (9-14)	0.65
Plateau pressure, cmH_2O	24.5 (22-27)	26.5 (24.0-29)	<0.001	25 (23-28)	26 (24-28)	0.55
Respiratory system compliance, mL/cmH_2O	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_2O	13 (11-16.0)	14 (12.0-16.7)	0.01	15 (11-16)	14 (12-16)	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/mn	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 [(4 x Driving Pressure) + respiratory rate]	80 (70-89)	84 (75-94)	0.004	85 (70-93.02)	84 (75-94)	0.67

Data are presented as median (interquartile range). Definition of abbreviations: PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PBW, predicted body weight; V_{Ecorr}, corrected minute ventilation.

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

	Population before matching (n= 340)			**Population after matching (n= 138)**		
	COVID-19 or Influenza ARDS			COVID-19 or Influenza ARDS		
Model term (repeated values from day 1 to day 5 of ARDS)	Estimate	95% CI[a]	*p*-value	Estimate	95% CI[a]	*p*-value
PaO_2/FiO_2, mmHg	-36.17	-26.64- -17.11	<0.0001	-31.49	-44.97- -18.00	<0.0001
$PaCO_2$, mmHg	5.14	3.56-6.76	<0.0001	6.96	4.22-9.69	<0.0001
Tidal volume, ml kg^{-1} PBW	0.02	-0.13-0.19	0.72	0.03	-0.12-0.18	0.71
Respiratory rate, cycles min^{-1}	0.78	0.13-1.42	0.02	0.23	-0.81-1.29	0.65
PEEP set, cmH_2O	-0.14	-0.64-0.35	0.56	-0.22	-1.07-0.62	0.62
Plateau pressure, $comH_2O$	0.94	0.20-1.68	0.01	0.94	0.20-1.68	0.10
Respiratory system compliance, cmH_2O, mL/cmH_2O	-0.92	-3.08-1.24	0.40	-2.01	-5.42-1.38	0.25
Driving pressure, cmH_2O	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/mn	1.88	1.17-2.58	<0.0001	1.68	0.54-2.83	0.004
Index [(4 x Driving Pressure) + respiratory rate]	4.05	1.04-7.06	0.008	5.29	0.10-10.48	0.06

[a] Coefficient estimates from a linear mixed effects model on the repeated values. A random intercept was modelled per patient.

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Authors have no conflict of interest to disclose.

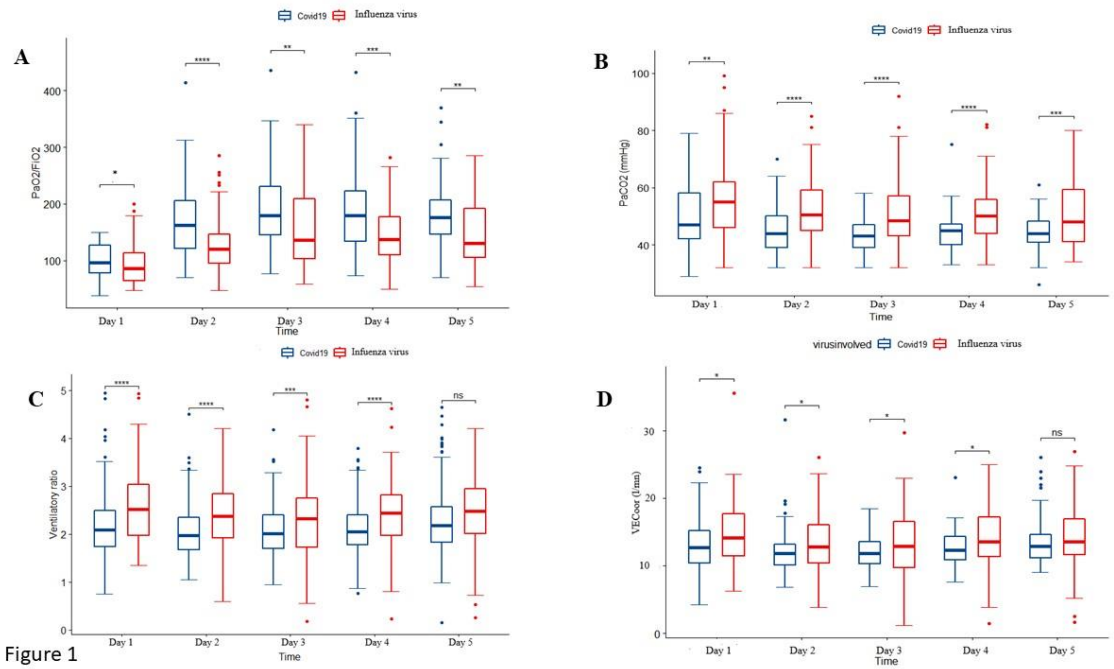
A
Covid19
Influenza virus
PaO2/FiO2
Day 1
Day 2
Day 3
Day 4
Day 5
Time
B
PaCO2 (mmHg)
C
Ventilatory ratio
D
virusinvolved
VECorr (l/mn)
ns

Figure 1

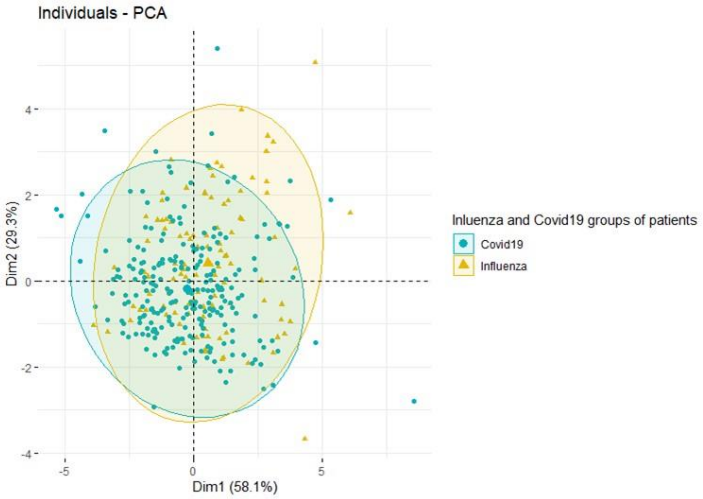
Individuals - PCA
Dim2 (29.3%)
Dim1 (58.1%)
4
2
0
-2
-4
-5
0
5
Inluenza and Covid19 groups of patients
Covid19
Influenza

Figure 2

Influenza and COVID-19 associated moderate to severe-ARDS

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Supplemental data

Supplemental figure: Sepsis Organ Failure Assessment (SOFA) scores from day 1 to day 5 of moderate to severe acute respiratory distress syndrome