Early View

Original article

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Running Title: Influenza and ARDS

Take home message: Influenza virus infection alone is associated with a better short-term prognosis than other causes of ARDS are.

ABSTRACT

Rationale

Influenza virus (IV)-related pathophysiology suggests that the prognosis of ARDS due to IV could be different from the prognosis of ARDS due to other causes. However, the impact of IV infection alone on the prognosis of ARDS patients compared to that of patients with other causes of ARDS has been poorly assessed.

Methods

We compared the 28-day survival from the diagnosis of ARDS with a $PaO_2/FiO_2 \leq 150$ mmHg between patients with and without IV infection alone. Data were collected prospectively and analyzed retrospectively. We first performed survival analysis on the whole population; second, patients with IV infection alone were compared with matched pairs using propensity score matching.

Main Results

The cohort admitted from October 2009 to March 2020 comprised 572 patients, including 73 patients (13%) with IV alone. On the first 3 days of mechanical ventilation, nonpulmonary Sequential Organ Failure Assessment (SOFA) scores were significantly lower in patients with IV infection than in the other patients. After the adjusted analysis, IV infection alone

remained independently associated with lower mortality at day 28 (hazard ratio: 0.51; 95% confidence interval: 0.26-0.99, p= 0.047). Mortality at day 28 was significantly lower in patients with IV infection alone than in other patients when propensity score matching was used (20% vs 38%, p= 0.02).

Conclusions

Our results suggest that patients with ARDS following IV infection alone have a significantly better prognosis at day 28 and less severe nonpulmonary organ dysfunction than do those with ARDS from causes other than IV infection alone.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by acute inflammatory lung injury associated with increased pulmonary vascular permeability, leading to the acute onset of bilateral alveolar infiltrates and hypoxemia [1]. ARDS is a heterogeneous syndrome with subphenotypes [2]. Despite lung-protective ventilation, specific therapies based on experimental studies have been unsuccessful to improve the outcome of ARDS, which continues to confer high mortality with estimates ranging from 26% to 58% [3–5]. Along these lines, although diffuse alveolar damage (DAD) has been considered as the usual histopathological hallmark of ARDS, more recent reports have revealed that the presence of DAD decreases significantly with the implementation of lung-protective ventilation, and several studies suggest that lung injury within the first week of ARDS is highly dependent on the ARDS etiology, which influences the prognosis of patients [1, 6]. For instance, autopsy of some patients with COVID-19-associated ARDS pneumonia found interstitial inflammatory infiltrates dominated by lymphocytes along with lung mechanical characteristics that led several authors to classify COVID-19-associated ARDS "nontypical" [7]. Influenza virus (IV) infection is a major and recurrent cause of ARDS that has been the focus of attention since the 2009 H1N1 pandemic of IV A (H1N1pdm2009) [8–10]. Particularities in histologic findings and in cytokine production in the lungs were described with IV-associated ARDS, suggesting that the mechanisms involved in lung injury could be specific; therefore, the prognosis of ARDS due to IV could be different from the prognosis of ARDS due to other causes [11–14]. Among important trials assessing treatments dedicated to ARDS, some were conducted before the 2009 H1N1 pandemic, and there is no systematic research of IV during epidemic periods of influenza [15–18]; some after 2009 and the exact proportion of patients with influenza was not always provided [19–21], or only patients with influenza were included [9, 22, 23]. Thus, the impact of IV infection alone on the prognosis of ARDS patients compared to that of

patients with other causes of ARDS remains unclear.

We wanted to focus on IV infection as cause of ARDS with the aim of evaluating the impact of influenza alone on the prognosis of ARDS patients. For that purpose, we assessed the short-term survival of patients admitted to our ICU over a 10-year period with ARDS due to IV infection alone or with ARDS due to other causes.

MATERIALS AND METHODS

Patients and setting

This study is a retrospective study performed on data collected prospectively in a mixed 21-bed ICU university. The database regarding ARDS patients admitted to our ICU was initiated in 2005 [15]. The study was approved by the hospital's ethics committee (N°16-117). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies (supplemental data). We included all patients aged older than 18 years who were admitted between October 1, 2009, and March 1, 2020, for ARDS (according to the American-European Consensus Conference criteria) with a PaO_2/FiO_2 ratio $\leq$ 150 mmHg [15, 19, 24] after at least 12 hours of lung-protective mechanical ventilation (MV) with an FiO_2 $\geq$50% and a positive end-expiratory pressure (PEEP) level $\geq$ 5 cmH$_2$O [25]. Of note, the study period was stopped before admission to the ICU of the first patients with SARS-CoV-2 infection in our ICU. Patients who received noninvasive ventilation only were excluded from the study. Since the 2009 H1N1 pandemic, systematic detection of IV in times of epidemics using real-time reverse transcriptase polymerase chain reaction (RT-PCR) from respiratory specimens collected at the time of admission to our ICU is routine practice in patients admitted with respiratory failure and/or fever. Up to January 2016, IV was detected using Argen (bioMérieux, Marcilly, France) according to the manufacturer's recommendations. Then, the Seegene Alplex Respiratory

panel (Eurobio, Les Ulis, France) became the routine method and was used in accordance with the manufacturer's protocol. All patients with influenza received double dose of oseltamivir treatment on the first day in the ICU for a maximum duration of ten days. All patients received selected digestive decontamination when mechanically ventilated [26].

Ventilatory settings

All patients were ventilated as follows: in assist-control mode, the initial tidal volume (Vt) was set at 6 ml per kilogram of predicted body weight (PBW), the PEEP level was selected from the PEEP-FiO_2 table proposed by the ARDS Network, 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 $\leq 10\ cmH_2O$ and $FiO_2 \leq 60\%$.

Prospective data collection

ARDS diagnosis and severity

When IV alone was isolated in respiratory samples obtained at ICU admission, ARDS was classified as IV ARDS alone. Etiological causes of non-IV ARDS alone were listed as IV associated with a copathogen, non-IV pneumonia, nonpulmonary sepsis, aspiration and miscellaneous [1, 19–21]. Trauma patients were admitted to another ICU in the hospital (surgical ICU). Based on the Berlin criteria [27], patients were retrospectively categorized according to whether they had severe ARDS ($PaO_2/FiO_2 \leq 100$ mmHg) or moderate ARDS ($PaO_2/FiO_2 > 100$ mmHg and ≤ 150 mmHg) on the first day of ARDS diagnosis. Consequently, patients were prospectively selected based on the 150 mmHg PaO2/FiO2 threshold used in 2005 and were classified retrospectively for severity based on the Berlin criteria.

Baseline characteristics of patients and causes of death

In addition to the diagnosis of IV infection, the following variables recorded upon ICU admission and during the ICU stay were included as control variables because they are potentially associated with ARDS and influenza prognosis [1, 4, 11, 28, 29]. Data collected for all patients were as follows: age, sex, the Simplified Acute Physiology Score (SAPS) II [30] (calculated within 24 hours after admission) and the daily Sequential Organ Failure Assessment (SOFA) score [31] (calculated on the first three days following ARDS diagnosis). Comorbidities included in the analysis were liver cirrhosis, obesity, diabetes mellitus, aplasia and/or recent chemotherapy for a solid tumor or hematologic disease, and previous coronary artery and/or valvular disease with treatment. Obesity was defined by a body mass index greater than or equal to 30 kilograms per square of the height in meters. The following causes of death were distinguished: primary infection-related organ failure, refractory hypoxemia, mesenteric ischemia, central nervous system disorder, end-of-life decision, and others [32].

Organ supports used in the ICU

Organ supports assessed for prognostic analysis were prone positioning, renal replacement therapy (RTT), vasopressors (dobutamine, epinephrine and norepinephrine at any dose), and extracorporeal membrane oxygenation (ECMO).

Respiratory parameters

The respiratory parameters recorded and included in the analysis were the lowest values of the PaO_2/FiO_2 ratio, the highest values of expiratory Vt and PEEP applied, the ventilator-measured end-inspiratory plateau pressure and the driving pressure (calculated as the ventilator-measured plateau pressure minus the applied PEEP).

Endpoints

The primary endpoint was to compare the 28-day survival from the diagnosis of ARDS between patients with and without IV infection alone. Secondary endpoints included a comparison of pulmonary and nonpulmonary organ dysfunction scores between IV-alone and non-IV-alone ARDS patients on the first three days of MV from the diagnosis of ARDS.

Statistical analysis

Data are expressed as percentages for categorical variables and as medians and interquartile ranges (IQRs, 25-75%) for continuous variables. The chi-square test was used to compare categorical variables, and the Mann-Whitney U test or Kruskal-Wallis test was used to compare continuous variables. Survival curves were constructed until day-28 from the diagnosis of ARDS by using the Kaplan-Meier method and compared by the log rank test. We first used a Cox proportional hazard model to determine whether infection with IV alone was independently associated with prognosis at day 28 in an unadjusted and adjusted analysis. For adjustments, variables were removed in a backward stepwise selection process based on a significance level with a P value of 0.10. Because patients were admitted over a ten-year period, during which the prognosis of ARDS may have changed, the year of admission was entered in the model as a continuous covariate. Furthermore, because of the collinearity between the SAPS II and SOFA scores, only the SAPS II was considered in the adjusted analysis. Then, we performed a propensity score (PS) matching (1/1 ratio) analysis in order to mitigate confounding bias. We used the E-value methodology to assess the robustness of the 28-day results to unmeasured confounding [33, 34]. The following variables were used in the calculation of the PS: age, year of admission to the ICU, comorbidities (i.e., diabetes mellitus, liver cirrhosis, valvular and/or coronary disease with treatment, COPD, obesity, aplasia and/or recent chemotherapy for a solid tumor or hematologic disease), ARDS severity according to

the Berlin criteria, and organ supports received in the ICU (i.e., prone positioning, ECMO, vasopressors and RRT). One patient with ARDS due to IV alone was matched with a patient with ARDS due to another cause with the closest absolute PS score, and the maximum distance allowed between two matched patients was set at 0.2 (i.e., caliper restriction). Tests were two-sided, and we considered p <0.05 as significant. Statistical analyses were performed using Statview 5.0 (SAS Institute Inc., Cary, NC, USA) and the Statistical Package for Social Sciences, version 20 (SPSS, IBM, Chicago, USA). The propensity score analysis was performed using R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) with the MatchIt package.

RESULTS

Patients

During the study period, 11,778 patients were admitted to our ICU, 6960 patients received MV, and 572 ARDS patients met the inclusion criteria. IV was isolated in 103 ARDS patients (18%). Among patients with IV infection, H1N1 A virus was involved in 48 patients (46%), H3N2 A virus in 45 patients (44%), and B virus in 10 patients (10%). At admission to the ICU, IV alone was isolated in 73 patients (13%) and was associated with another pathogen in 30 patients (5%) including *Streptococcus pneumoniae* (n=11), other group A streptococcus (n=1), *Staphylococcus aureus* (n=9), Gram-negative bacilli (n=4), and *Aspergillus fumigatus* (n=5). Etiologic causes in noninfluenza ARDS patients were as follows: noninfluenza pneumonia (n= 233) (40%), aspiration (n=89) (15%), nonpulmonary sepsis (n=81) (14%), and miscellaneous (n=67) (13%). The results for the comparisons of patient characteristics of those with IV alone and those with IV with other pathogens are shown in table 1. Although there was no difference for coexisting conditions, patients admitted to the ICU with IV alone differed significantly from the other patients in terms of

severity at the time of admission to the ICU and the need for organ supports during the ICU

stay (i.e., prone positioning, RTT) and for treatments (i.e., glucocorticoids and vasopressors).

Table 1: Baseline characteristics, interventions, and outcomes of patients with ARDS

	Whole population	Influenza virus alone		P Value
		Yes	No	
	n= 572	n= 73	n= 499	
Baseline characteristics				
SAPS II score, points median (IQR)	52 (38-67)	46 (35-61)	57 (40-69)	0.003
SOFA score, points median (IQR)	10 (8-13)	9 (7-11)	10 (8-14)	<0.0001
Age, years median (IQR)	58 (47-68)	59 (49-66)	58 (47-69)	0.51
Male gender, n (%)	364 (63)	48 (66)	316 (63)	0.66
Time of presentation to hospital to the ICU, days median (IQR)	2 (0-4)	2 (0-4)	2 (0-5)	0.74
Coexisting condition, n (%)				
Diabetes mellitus	66 (11)	8 (11)	58 (12)	0.86
Liver cirrhosis	63 (11)	9 (12)	54 (11)	0.70
Valvular and/or coronary disease with treatment	94 (17)	10 (14)	84 (17)	0.49
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	99 (17)	11 (15)	87 (17)	0.62
COPD	126 (22)	18 (25)	108 (22)	0.56
Obesity	147 (26)	19 (26)	128 (26)	0.94
Severe ARDS (PaO$_2$/FiO$_2 \leq$ 100 mmHg), n (%)	349 (61)	49 (67)	300 (60)	0.25
Interventions, n (%)				
Prone positioning	261 (44)	41 (56)	219 (44)	0.049
Neuromuscular blockers	568 (99)	73 (100)	495 (99)	0.98
Inhaled nitric oxyde	116 (20)	20 (27)	96 (19)	0.10
Extra corporeal membrane oxygenation	58 (10)	11 (15)	47 (9)	0.13
Glucocorticoids	336 (59)	29 (40)	307 (62)	0.004
Vasopressors	512 (89)	58 (79)	452 (91)	0.003

Renal-replacement therapy	217 (38)	18 (25)	199 (39)	0.01
Outcomes				
Ventilator associated pneumonia, n (%)	66 (11)	9 (12)	57 (11)	0.82
Mortality in the ICU, n (%)	230 (40)	21 (29)	209 (43)	0.03
Ventilator-free days at day-28, median (IQR)	2 (0-16)	5 (0-15)	0 (0-17)	0.14
Mortality at day 28, n (%)	197 (34)	15 (20)	182 (36)	0.007

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease.

Respiratory characteristics

During the first 3 days following the diagnosis of ARDS, the PaO_2/FiO_2 ratios and $PaCO_2$ values did not differ significantly between the two groups of patients. The applied PEEP levels were significantly higher in patients with IV infection alone, while the driving pressures did not differ significantly between the two groups of patients (supplemental online table 1a).

Organ dysfunction

During the first 3 days of MV following the diagnosis of ARDS, the nonpulmonary SOFA scores were significantly lower in patients with ARDS due to IV alone than in other ARDS patients, whereas the SOFA scores for pulmonary dysfunction did not differ significantly (Figure 1A). The cardiovascular, liver, renal, and neurological SOFA subscores on the first day of MV were significantly lower in patients with IV infection alone than in other patients (Figure 1B).

Prognostic analysis and propensity score matching

The overall mortality rate at day 28 for the study population was 34% (table 1). Mortality in the ICU and at day 28 and was significantly lower in patients with ARDS due to IV infection alone than in other patients (20% vs 36% and 29% vs 47% respectively, p= 0.02 after the two comparisons). Kaplan-Meier survival curves showed that survival differed significantly according to the etiology of ARDS, and patients with ARDS due to IV alone had highest survival rate (Figure 2, p< 0.0001 as determined by the log-rank test). The results of the nonadjusted analysis for mortality at day 28 performed on the whole population are listed in table 2.

Table 2. Unadjusted hazard ratios (HR) for 28-day mortality from the day of ARDS diagnosis

Variables	Unadjusted Hazard Ratio (95% CI)	*p* value
Influenza virus alone	0.52 (0.31-0.89)	0.02
Influenza virus and co-pathogen	0.76 (0.83-1.56)	0.46
Non-influenza virus pneumonia	1.10 (0.83-1.46)	0.49
Aspiration	0.64 (0.41-0.99)	0.048
Non-pulmonary sepsis	2.40 (1.73-3.32)	<0.001
Miscellaneous	0.86 (0.55-1.34)	0.51
Age (1-year increment)	1.023 (1.013-1.033)	<0.0001
Male gender	1.11 (0.83-1.60)	0.24
Time of presentation to hospital to the ICU (1-day increment)	1.24 (0.64-1.86)	0.59

Prognostic scores

SAPS II at admission (1-point increment)	1.031 (1.024-1.038)	<0.0001
SOFA score on day 1 of ARDS (1-point increment)	1.213 (1.171-1.256)	<0.0001
Coexisting condition		
Diabetes mellitus	1.10 (0.72-1.68)	0.67
Valvular and/or coronary disease with treatment	1.20 (0.84-1.72)	0.31
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	1.45 (1.06-2.01)	0.02
Cirrhosis	2.05 (1.42-2.95)	<0.0001
COPD	0.76 (0.53-1.07)	0.14
Obesity	1.05 (0.77-1.44)	0.75
Mechanical ventilation		
PaO_2/FiO_2 ratio* (1-mmHg increment)	0.990 (0.986-0.995)	<0.0001
Driving pressure* (1-point increment)	1.062 (1.035-1.089)	<0.0001
Organ support and treatments		
Treatment with vasopressors	2.88 (1.47-3.62)	0.02
Treatment with glucocorticoids	1.58 (1.14-2.06)	0.005
Renal replacement therapy	2.39 (1.84-3.18)	<0.001
Prone positioning	0.86 (0.64-1.13)	0.27
Extracorporeal membrane oxygenation	0.78 (0.45-1.29)	0.34

CI, Confident interval; SAPS, Simplified Acute Physiologic Score; MV, Mechanical Ventilation; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease.

* Worst data recorded between 12 and 24 hours of MV from the diagnosis of ARDS, after optimization of MV

After adjustments, IV infection alone remained independently associated with a better prognosis at day 28 (HR: 0.51; 95% CI: 0.26-0.99, p= 0.047). Extensive results are shown in supplemental online table 2A. Results were similar for 90-day mortality from the day of

ARDS diagnosis (see supplemental online table 2B). The E-value for the HR was 2.56 for the upper limit, and the CI was 1.09. The proportions for causes of death did not differ between IV alone and non-IV alone ARDS (p= 0.58) and were distributed as follows: primary infection-related multiple-organ failure (53% vs 50%), refractory hypoxemia (7% vs 16%), mesenteric ischemia (13% vs 5%), central nervous system disorder (7% vs 8%), end-of-life decision (0% vs 6%), and others (20% vs 14%).

The clinical characteristics of the 73 patients with ARDS due to a cause other than IV alone matched with patients with ARDS due to IV alone are shown in table 3. Patients with ARDS due to IV alone had a significantly lower 28-day mortality (Figure 3, p= 0.02 as determined by the log-rank test).

Table 3: Baseline characteristics, interventions, and outcomes of patients with ARDS after propensity score matching

	Influenza virus alone		P value
	Yes n= 73	No n= 73	
Cause of ARDS			
Influenza virus and copathogen	-	8 (11)	
Aspiration	-	14 (19)	
Non-influenza pulmonary infection	-	36 (49)	
Non-pulmonary sepsis	-	11 (15)	
Miscellaneous	-	4 (6)	
Baseline characteristics			
SAPS II score, points median (IQR)	47 (35-61)	45 (35-59)	0.87
SOFA score, points median (IQR)	9 (7-11)	10 (7-12)	0.18
Age, years median (IQR)	59 (48-65)	57 (48-68)	0.84
Male gender, n (%)	49 (67)	42 (58)	0.23
Coexisting condition, n (%)			
Diabetes mellitus	8 (11)	9 (12)	0.79
Liver cirrhosis	9 (12)	12 (16)	0.64
Valvular and/or coronary disease with treatment	10 (14)	11 (15)	0.81
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	11 (15)	11 (15)	0.99
COPD	18 (25)	12 (16)	0.69

Obesity	19 (26)	24 (33)	0.36
Severe ARDS (PaO$_2$/FiO$_2$ ≤ 100 mmHg), n (%)	50 (68)	46 (63)	0.49
Interventions, n (%)			
Prone positioning	41 (56)	39 (53)	0.99
Neuromuscular blockers	73 (100)	70 (100)	>0.99
Inhaled nitric oxyde	20 (27)	17 (23)	0.58
Extra corporeal membrane oxygenation	11 (15)	13 (18)	0.65
Glucocorticoids	30 (41)	28 (38)	0.73
Vasopressors	59 (81)	65 (90)	0.16
Renal-replacement therapy	19 (26)	18 (25)	0.85
Outcomes			
Ventilator associated pneumonia, n (%)	9 (12)	10 (14)	0.80
Mortality in the ICU, n (%)	21 (29)	32 (44)	0.06
Ventilator-free days at day-28, median (IQR)	6 (0-15)	0 (0-14)	0.13
Mortality at day-28, n (%)	15 (20)	28 (38)	0.02

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease.

Of note, mortality rates at day 28 did not differ significantly between patients with H1N1pdm2009 virus infection and those with H3N2 virus infection (15% vs 33%, p= 0.06).

DISCUSSION

We found in our study that in ARDS patients with a PaO$_2$/FiO$_2$ ratio ≤ 150 mmHg, a single IV infection remained independently associated with 28-day survival when compared with other causes of ARDS. Importantly, mortality at day 28 remained significantly lower when patients with IV infection alone were matched for both demographic and severity baseline characteristics with patients with non-IV infection alone. The lower mortality observed in patients with IV infection alone did not appear to be related to better lung function, as estimated by blood gas values and data recorded from ventilators, but rather to fewer nonpulmonary organ failures.

Several studies have found that the etiology of ARDS influences patient outcomes, since the causative agent induces specific lung injury that could be responsible for DAD, which is associated with the outcome of ARDS [1, 35]. Furthermore, comorbid conditions leading to ARDS, such as risk factors for aspiration pneumonia, impact patient outcomes heavily [1, 5, 6, 25, 28]. Causative agents trigger specific injuries to the lung through different mechanisms. For instance, direct caustic actions of a low pH on the airway epithelium during aspiration are followed by an acute neutrophilic inflammatory response that leads to the loss of pulmonary microvascular integrity and extravasation of fluid and protein into the airways and alveoli, which is different from lung injury in IV infection, which is characterized by the replication of IV in the respiratory epithelium followed by the loss of alveolar structure and lung inflammation. Pathological findings in IV-induced lung injury are different from the typical DAD found in ARDS patients and are associated with patient outcome; however, these injuries have been found in IV patients after a long duration of MV [11, 13, 14]. Although no clear data are available, the better outcome in IV-associated ARDS could be supported by its pathophysiological characteristics; it is known in severe respiratory viral infections that T-cells crucially contribute to virus clearance from infected lungs, to the resolution of lung inflammation and thus to a favorable outcome [36, 37]. An immune defect or a superinfection in IV-induced pneumonia is responsible for a longer duration of MV, which could induce lung injury and be responsible for a worse outcome. Steinberg et al. found that alveolar macrophages were increased in ARDS survivors than in nonsurvivors and reached the conclusions that sustained alveolar inflammation was associated with high mortality [38].

Although lung inflammation following IV infection can spread systematically and lead to multiorgan failure [11, 13, 14], our results for nonpulmonary SOFA subscores show that nonpulmonary organ dysfunction was more pronounced in non-IV alone ARDS patients than in patients with ARDS due to IV alone. It is generally admitted that sepsis-related ARDS is

associated with higher mortality than nonsepsis-related ARDS [1, 28]. We found differences in the outcomes not only between patients with extra pulmonary and pulmonary sepsis-related ARDS but also according to the pathogens involved.

Despite the clear specificity highlighted during the IV pandemic in 2009, the proportion of patients with IV infection alone is almost never specified in therapeutic trials conducted before 2009, such as trials assessing neuromuscular blockage [15], fluid management [18] or a protective ventilation strategy [39], or in trials conducted after 2009, such as those assessing prone positioning [20], conducting a large epidemiological survey on general practice [4] or assessing treatment with ECMO [20]. The recent pandemic of COVID-19 has highlighted the specificity of a causative agent responsible for ARDS, since despite ARDS criteria at admission, patients with SARS-CoV2-induced ARDS did not present strict ARDS parameters under mechanical ventilation [40]. We do believe that our results highlight the importance of classification in ARDS patients to achieve specific therapies, including ventilation protocols tailored according to patient subphenotype [2].

The main strength of the study is the large number of ARDS patients who all received lung-protective ventilation during the first days of MV since the diagnosis of ARDS. Our study has several limitations. The study was conducted at a single site; thus, the results may not be applicable to other hospitals. Because of the observational nature of the study and even though we compared matched patients using a PS, we cannot exclude uncontrolled confounders. Nevertheless, the result for the E-value suggests that an unmeasured or unknown confounder would have a substantially greater effect on 28-day mortality with a relative risk exceeding 2.56. In the present study, the unadjusted HRs for the 28-day mortality of cirrhosis and treatment with vasopressors were 2.05 and 2.88, respectively. Finally, we did not perform specific immune signature or biomarker analyses that may support our hypothesis, and we

acknowledge that such studies have to be performed before initiation of a therapeutic clinical trial based on specific ARDS causes.

CONCLUSION

IV was involved in one of ten patients with moderate to severe ARDS admitted to our ICU since the 2009 H1N1 pandemic. We found that IV infection alone was associated with a better short-term survival than other etiological causes of ARDS encountered in nontrauma patients. Extrapulmonary failure appeared less severe in patients with IV infection alone than in the other patients, explaining in part the better short-term prognosis in these patients.

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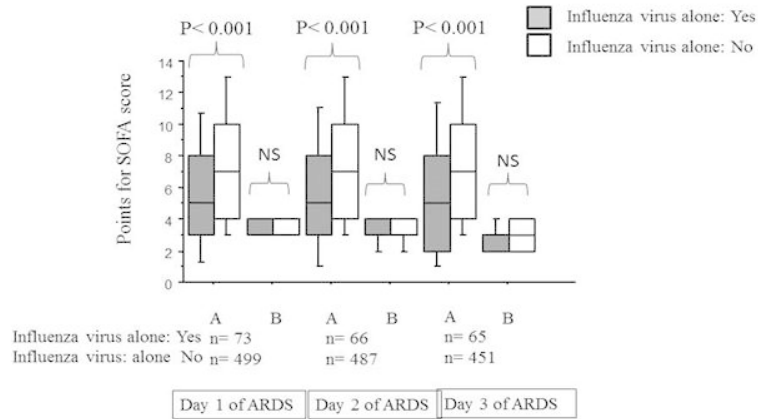
Figure 1A

A: SOFA score for the extra-pulmonary organ dysfunctions
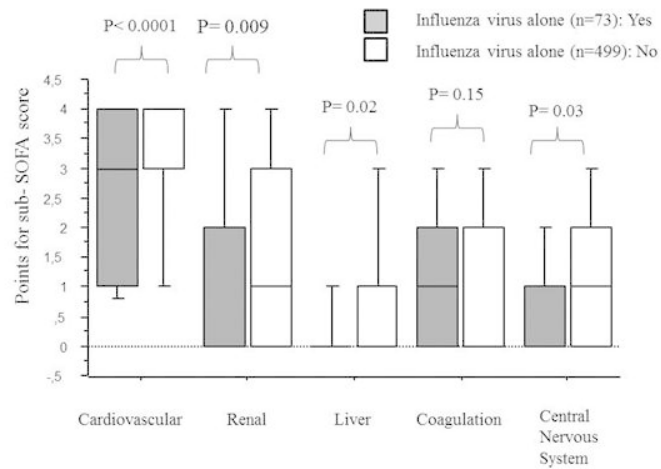B: SOFA score for the pulmonary organ dysfunction

Figure 1B

Figure 1A and 1B: SOFA scores distinguished between pulmonary and nonpulmonary organ dysfunction on the first 3 days of mechanical ventilation (MV) (Figure 1A), and SOFA subscores on the first day of MV (Figure 1B) were compared between patients with and without influenza alone.
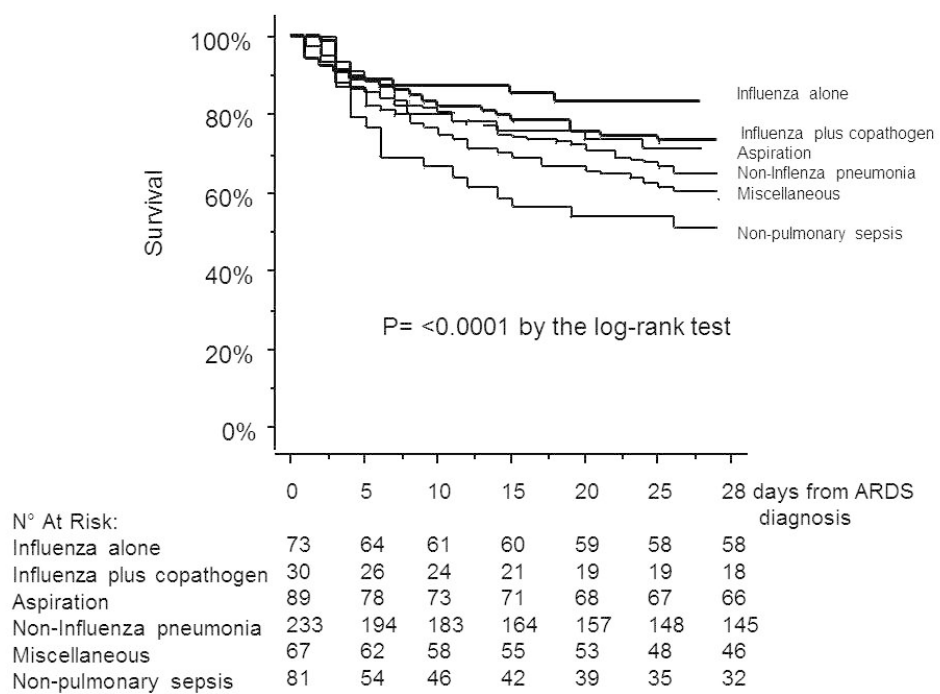
Figure 2: Cumulative 28-day mortality from admission to the ICU in the whole population.
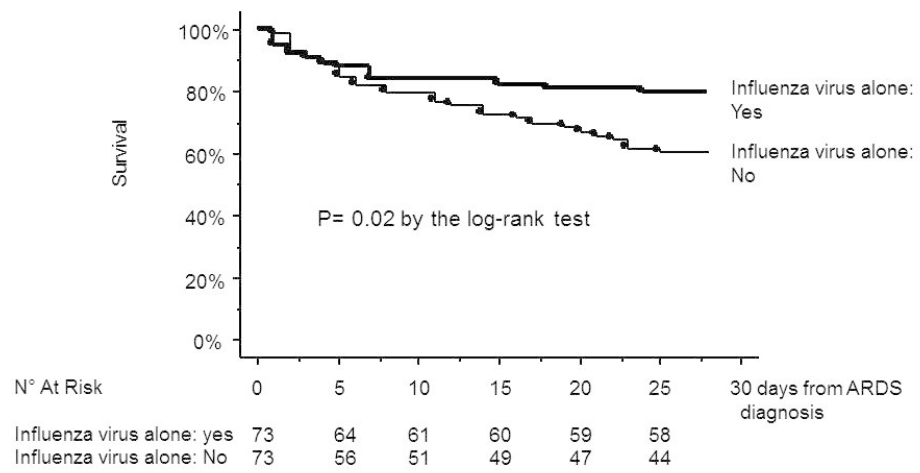
Figure 3: Cumulative 28-day mortality from admission to the ICU in the matched population.

Supplemental table 1a: Ventilator settings, respiratory system mechanics, and results of arterial blood gas measurements recorded on the first three days of mechanical ventilation from the diagnosis of ARDS*

Day from ARDS diagnosis	Day 1		Day 2		Day 3	
	Influenza virus alone		Influenza virus alone		Influenza virus alone	
	Yes	No	Yes	No	Yes	No
(number of patients)	(73)	(499)	(66)	(487)	(65)	(451)
PEEP, cmH_2O, median (IQR)	12 (9-14)	10 (8-12)††	12 (10-14)	10 (8-13)††	12 (10-14)	9 (8-12)††
Driving pressure, cmH_2O median (IQR)	14 (12-16)	15 (12-18)	13 (10-16)	14 (11-17)	13 (10-15)	14 (11-18)
PaO_2/FiO_2, mmHg, median (IQR)	83 (63-115)	90 (68-120)	121 (91-157)	120 (86-160)	137 (102-207)	143 (100-201)
$PaCO_2$, median (IQR)	55 (46-64)	54 (46-65)	50 (45-57)	49 (42-58)	48 (41-53)	46 (40-53)
Arterial PH, median (IQR)	7.27 (7.17-7.35)	7.25 (7.14-7.34)	7.31 (7.22-7.36)	7.28 (7.19-7.37)	7.34 (7.26-7.40)	7.33 (7.24-7.41)

* Using the worst recorded blood gas values and highest values for levels of PEEP, expiratory tidal volume (Vt), plateau pressure and calculated driving pressure.

† Yes vs No, p< 0.05; †† Yes vs No, p< 0.01

Definition of abbreviation: Vt, tidal volume; PBW, predicted body weight, IQR; interquartile ranges; FiO_2, fraction of inspired oxygen; PaCO2 partial pressure of arterial carbon dioxide; PaO2 partial pressure of arterial oxygen, PEEP positive end-expiratory pressure.

Supplemental online table 2A. Adjusted hazard ratios (HR) for 28-day mortality from the day of ARDS diagnosis

Variables [a]	Adjusted Hazard Ratio (95% CI)	p value
Influenza virus alone	0.51 (0.26-0.99)	0.047
Aspiration	0.75 (0.46-1.23)	0.25
Non-pulmonary sepsis	1.60 (1.09-2.43)	0.02
Age (1-year increment)	1.020 (1.009-1.032)	0.0006
SAPS II at admission (1-point increment)	1.020 (1.012-1.028)	<0.0001
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	1.39 (0.95-2.05)	0.09
Cirrhosis	2.89 (1.88-4.31)	<0.0001
PaO_2/FiO_2 ratio* (1- mmHg increment)	0.994 (0.989-.0.999)	0.02
Driving pressure* (1-point increment)	1.045 (1.035-1.102)	<0.0001
Treatment with vasopressors	1.06 (0.53-2.15)	0.86
Treatment with glucocorticoids	1.67 (120-2.33)	0.72
Renal replacement therapy	2.39 (1.84-3.18)	<0.001

CI, Confident interval; SAPS, Simplified Acute Physiologic Score; MV, Mechanical Ventilation; SOFA, Sequential Organ Failure Assessment

* Worst data recorded between 12 and 24 hours of MV from the diagnosis of ARDS, after optimization of MV

Supplemental table 2B. Unadjusted and adjusted hazard ratios for 90-day mortality from the day of ARDS diagnosis

Variables	Unadjusted Hazard Ratio (95% CI)	p Value	Adjusted Hazard Ratio (95% CI)	p Value
Influenza virus alone	0.59 (0.38-0.92)	0.02	0.59 (0.35-0.99)	0.048
Influenza virus and co-pathogen	0.79 (0.43-1.56)	0.79		
Non-influenza virus pneumonia	1.17 (0.91-1.51)	0.22		
Aspiration	0.63 (0.43-0.93)	0.02		
Non-pulmonary sepsis	1.93 (1.41-2.64)	<0.01	1.42 (0.98-2.07)	0.06
Miscellaneous	0.98 (0.67-1.44)	0.94		
Age (1-year increment	1.024 (1.015-1.032)	<0.0001	1.018 (1.008-1.029)	0.005
Male gender	1.14 (0.88-1.48)	0.32		
SAPS II at admission (1-point increment)	1.029 (1.022-1.035)	<0.0001	1.017 (1.010-1.024)	<0.0001
Diabetes mellitus	1.13 (0.74-1.78)	0.98		
Valvular and/or coronary disease with treatment	1.20 (0.84-1.72)	0.10		
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	1.95 (1.47-2.58)	<0.01	1.89 (1.36-2.61)	0.001

Cirrhosis	1.79 (1.23-2.53)	<0.0001	2.96 (1.99-4.41)	<0.0001
COPD	0.68 (0.49-1.13)	0.24		
Obesity	1.07 (0.81-1.43)	0.61		
PaO$_2$/FiO$_2$ ratio* (1-mmHg increment)	0.992 (0.988-0.996)	<0.0001	0.996 (0.991-1.000)	0.05
Driving pressure* (1-point increment)	1.057 (1.028-1.078)	<0.0001	1.070 (1.045-1.095)	<0.001
Treatment with vasopressors	3.03 (1.65-5.54)	0.003		
Treatment with glucocorticoids	1.68 (1.28-2.20)	0.002		
Renal replacement therapy	2.08 (1.62-2.67)	<0.0001	1.43 (1.07-1.92)	0.02
Prone positioning	1.02 (0.79-1.32)	0.85		
Extracorporeal membrane oxygenation	1.03 (0.69-1.54)	0.87		

CI, Confident interval; SAPS, Simplified Acute Physiologic Score; MV, Mechanical Ventilation; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease.

* Worst data recorded between 12 and 24 hours of MV from the diagnosis of ARDS, after optimization of MV