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► **To cite this version:**

Adel Maamar, Flora Delamaire, Florian Reizine, Mathieu Lesouhaitier, Benoit Painvin, et al.. Impact of Arterial CO(2) Retention in Patients With Moderate or Severe ARDS. *Respiratory Care*, 2023, 68 (5), pp.582-591. 10.4187/respcare.10507 . hal-04061274

**HAL Id: hal-04061274**

**<https://hal.science/hal-04061274>**

Submitted on 12 Jul 2023

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## **Impact of arterial CO<sub>2</sub> retention in patients with moderate or severe acute respiratory distress syndrome**

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### **Conflict of interest:**

Participating hospital obtained local ethic committee, and a waiver or informed consent was granted in all cases. The investigators declare that they have no conflicts of interest related to this manuscript, and have full control of all of the primary data. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Financial support:** None.

**Author Contributions:** All authors contributed to the study conception and design as well as to the acquisition, analysis, or interpretation of data. AG and AM conducted the statistical analysis. AM, FD, FR, AG and JMT drafted the manuscript, and all authors critically revised the manuscript and approved the final version.

**Abstract**

**Background:** Lung protective ventilation (LPV, reduced tidal volume and limited plateau pressure) may lead to carbon dioxide (CO<sub>2</sub>) retention. Data about the impact of hypercapnia in patients with acute respiratory distress syndrome (ARDS) are scarce and conflicting.

**Methods:** We performed a noninterventional cohort study with patients admitted from 2006 to 2021 with ARDS and a PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq$  150 mmHg. We examined the association between severe hypercapnia (PaCO<sub>2</sub>  $\geq$  50 mmHg) on the first five days after the diagnosis of ARDS and death in the intensive care unit (ICU) for 930 patients. All patients received LPV.

**Results:** Severe hypercapnia was noted in 552 patients (59%) on the first day of ARDS (Day 1), and 323 (34.7%) died in the ICU. Severe hypercapnia on Day 1 was associated with mortality in the unadjusted (odds ratio (OR) 1.54, 95% confidence interval (CI) 1.16-1.63, p= 0.003) and adjusted (OR 1.47, 95% CI 1.08-2.43, p= 0.04) models. In the Bayesian analysis, the posterior probability that severe hypercapnia was associated with ICU death was above 90% in four different priors, including a septic prior for this association. Sustained severe hypercapnia on Day 5, defined as severe hypercapnia present from Day 1 to Day 5 was noted, in 93 patients (12%). After propensity-score matching, severe hypercapnia on Day 5 remained associated with ICU mortality (OR = 1.73, 95% CI 1.02-2.97, p= 0.047).

**Conclusions:** Our results suggest that severe hypercapnia is associated with mortality in ARDS patients who receive LPV. Our results deserve further evaluation of the strategies and treatments aiming to control CO<sub>2</sub> retention.

**Key words:** hypercapnia, ARDS, cohort study, mortality.

## Introduction

Lung protective ventilation (LPV) is the cornerstone of management of acute respiratory distress syndrome (ARDS) <sup>1</sup> aiming for limited plateau pressures less than or equal to 28-30 cmH<sub>2</sub>O and a reduced tidal volume (Vt) of 6 mL.kg<sup>-1</sup> predicted body weight (PBW). LPV may lead to carbon dioxide (CO<sub>2</sub>) retention in some patients <sup>2</sup>. Unlike the deleterious effects of excessive tidal volume in ARDS patients, the effects of hypercapnia were not clearly established, allowing the emergence of permissive hypercapnia with LPV <sup>2,3</sup>. Therefore, hypercapnia should be considered as the witness of the mechanical ventilation settings, not a therapeutic goal to achieve. Several years ago, it has been hypothesized that inducing hypercapnia could have been beneficial in patients with acute respiratory failure by attenuating lung inflammation and injury <sup>4</sup>. However, hypercapnia has been associated with impaired alveolar epithelial function, induced immunosuppression, pulmonary hypertension and diaphragmatic dysfunction <sup>5-10</sup>. Along these lines, devices allowing extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) to facilitate ultraprotective ventilation have been recently developed <sup>11-13</sup>. The impact of CO<sub>2</sub> retention on the outcomes of ARDS patients has been mostly assessed in secondary analyses of multicentre studies with conflicting results <sup>14 15 16</sup>. Unfortunately, in these studies, patients were not managed uniformly for mechanical ventilation (MV) since patients received either MV with Vt set to 8 mL.kg<sup>-1</sup> or more, or noninvasive ventilation. Recently, the results of a systematic review and meta-analysis <sup>17</sup> suggested that, in patients managed similarly for MV, the development of hypercapnia was associated with worst prognosis compared to non hypercapnic patients. As a consequence, it has been suggested that pH should also be considered, since pH shift could lead to important organ dysfunction <sup>18</sup>. Herein, we assessed the impact of hypercapnia and acidosis on the outcome of ARDS patients managed with LPV. Furthermore, since prone positioning <sup>19</sup> and neuromuscular blockades <sup>20</sup> have been proven to be effective in patients with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio below 150 mmHg, the threshold of 150 mmHg

$\text{PaO}_2/\text{FiO}_2$  is important to assess therapeutic approaches in ARDS patients <sup>21</sup> and has been selected to conduct our study.

## Methods

### Patients

Data were recorded prospectively in ARDS patients older than 18 years who were admitted to the ICU from January 2006 to June 2021, with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 150$  mmHg after at least 12 hours of lung-protective MV. All the patients had bilateral infiltrates on chest radiography, no criteria for heart failure according to catheterism and/or echocardiographic results, acute disease, and results of blood gas values obtained while ventilated with positive end expiratory pressure (PEEP)  $\geq 5$  cm H<sub>2</sub>O. Thus, patients were prospectively selected based on the 150 mmHg  $\text{PaO}_2/\text{FiO}_2$  threshold used since 2006 and were classified retrospectively for severity based on the Berlin criteria defined in 2012 <sup>22</sup>. The study was approved by the hospital's ethics committee (Number 21.105), and we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies. Informed consent was not required in compliance with French legislation on observational studies of anonymized data. At least one blood gas value was available for each day of assessment for all patients. The patients were mechanically ventilated in assist-control mode with the initial  $V_t$  set at 6 mL.kg<sup>-1</sup> PBW. The PEEP level was selected from the PEEP- $\text{FiO}_2$  table proposed by the ARDS network <sup>23</sup>, and the end-inspiratory plateau pressure was measured at least every 2 hours to be kept  $< 28\text{-}30$  cmH<sub>2</sub>O, as long as the  $\text{PaO}_2/\text{FiO}_2$  ratio remained below 200 mmHg. In addition, the respiratory rate was set to maintain the arterial pH between 7.20 and 7.45. Patients with a pH  $< 7.20$  and a  $\text{PaCO}_2 > 60$  mmHg and/or a plateau pressure  $> 32$  cmH<sub>2</sub>O were managed according to the ACURASYS protocol <sup>20</sup>, including an increase in the respiratory rate up to 35 breaths/minute and a decrease in tidal volume in steps of 1 mL.kg<sup>-1</sup> g

up to 4 mL.kg<sup>-1</sup>. Buffering of the acidosis induced by hypercapnia was not a practice, and ECCO2R was not available during the study period. ARDS due to pulmonary infection (i.e., bacterial and/or viral and/or fungal pneumonia) was distinguished from ARDS due to other causes (i.e., aspiration, non-pulmonary infection, and miscellaneous causes). There were no trauma patients.

We collected the following baseline characteristics: the Simplified Acute Physiology Score (SAPS) II<sup>24</sup> (calculated within 24 hours after admission) and the daily Sequential Organ Failure Assessment (SOFA) score<sup>25</sup> (calculated for the first 5 days after ARDS diagnosis); comorbidities including liver cirrhosis, obesity, diabetes mellitus, aplasia and/or recent chemotherapy for a solid tumour or haematologic disease; previous coronary artery and/or valvular disease with treatment; and organ support used in the ICU. The highest PaCO<sub>2</sub> and lowest pH values within the first 5 days of MV were recorded. The additional respiratory parameters recorded and included in the analysis were the lowest values of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, the highest values of expiratory V<sub>t</sub>, PEEP applied and ventilator-measured end-inspiratory plateau pressure.

## Definitions

From Day 1 to Day 5, we calculated the driving pressure, respiratory compliance, and ventilatory ratio. The driving pressure was defined as the plateau airway pressure minus the PEEP. Respiratory system compliance (RSC, ml/cmH<sub>2</sub>O) was defined as the V<sub>t</sub> divided by the difference between the plateau pressure and PEEP. The ventilatory ratio (VR) [minute ventilation (mL/mn) x PaCO<sub>2</sub> (mmHg)]/(PBW x 100 x 37.5)] was calculated because it is a simple index that correlates well with the dead space fraction in ARDS patients<sup>26</sup>. The base excess was calculated on Day 1 using the Siggard-Anderson equation<sup>27</sup> (Base excess = 0.02786 x PaCO<sub>2</sub> x 10<sup>(pH-6.1)</sup> + 13.77 x pH - 124.58). To compare our results with those of previous

studies, the patients were assessed for mortality in the ICU and were dichotomized according to whether their PaCO<sub>2</sub> was less than 35 mmHg (hypocapnia)<sup>7,14,16</sup> or greater than or equal to 50 mmHg (severe hypercapnia)<sup>15</sup>. Sustained severe hypercapnia was defined as a PaCO<sub>2</sub> ≥ 50 mmHg for 5 consecutive days (from Day 1 to Day 5).

### Statistical analysis

Data are expressed as counts and percentages for categorical variables. Continuous variables were initially assessed for normality and are presented as the means and standard deviations (SDs) and as medians and interquartile ranges (IQRs, 25-75%) when not normally distributed. The chi-square test was used to compare categorical variables, and the Mann–Whitney U test was used to compare continuous variables.

We first analysed data recorded on Day 1 of admission for ARDS. In the first step, we performed a frequentist analysis to assess whether severe hypercapnia was independently associated with ICU mortality. Thus, we performed a multivariable logistic regression model by entering ICU mortality with the following a priori defined variables: age, sex, SAPS II score, SOFA at day 1, pH at day1, respiratory rate (RR), BMI, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, respiratory system compliance (RSC), driving pressure (DP), and ventilatory ratio. These variables were chosen based on the results of previous studies<sup>15,16</sup>. To make the comparisons of the results easier, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, RSC, DP, and ventilator ratio were calculated using values recorded on Day 1. Because patients were admitted over a 15-year period, the year of admission was entered in the model as a continuous variable. For adjustments, variables were removed in a backwards stepwise selection process based on a significance level with a P value of 0.10. We tested for an interaction between acidosis (pH < 7.35) and severe hypercapnia. COPD, pneumonia, and a plateau pressure above 28 cmH<sub>2</sub>O on Day 1 were also entered in the multivariable logistic regression. COPD was forced in the model because patients may have been previously exposed



to prolonged periods of hypercapnia. Pneumonia was forced in the model because the effect of hypercapnia on pulmonary infection remains a matter of debate<sup>5,9</sup>. A plateau pressure greater than 28 cmH<sub>2</sub>O, rather than 30 cmH<sub>2</sub>O, was also forced in the model to assess the possible association of increased CO<sub>2</sub> retention with a decreased plateau pressure. The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Correlations between variables were assessed using spearman test.

In addition, we used a Bayesian logistic regression model to estimate the posterior probability for severe hypercapnia on Day 1 of admission for ARDS to be associated with ICU mortality. The results were expressed using ORs and 95% credible intervals (CrIs). We first created four priors: a prior in which severe hypercapnia was associated with the highest risk of mortality (OR of 1.48, slightly lower than the one calculated in the frequentist analysis (95% CrI, 0.68-3.26; mean log (OR) of 0.4 and SD of 0.4), a neutral prior (OR of 1 (95% CrI, 0.37-2.75; mean log (OR) of 0 and SD of 0.5)), a null prior, and a prior in which severe hypercapnia was associated with the lowest risk of mortality (OR of 0.67 (95% CrI, 0.31-1.45; mean log (OR) of -0.4 and SD of 0.4)).

In the second step, a propensity score (PS) near neighbour with 0.25 caliper matching (2/1 ratio) method was applied to assess whether sustained hypercapnia was associated with prognosis. For this, patients were assessed on Day 5 after the diagnosis of ARDS. For calculation of the propensity score, we used the same variables as those entered in the multivariable logistic regression model (i.e., age, sex, SAPS II score, respiratory rate on Day 1, PaO<sub>2</sub>/FiO<sub>2</sub> ratio on Day 1, respiratory system compliance on Day 1, driving pressure on Day 1, and ventilatory ratio on Day 1). Tests were two-sided, and we considered a  $p < 0.05$  to be significant. Statistical analyses were performed using R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

## Study population

Overall, 930 consecutive patients with ARDS and a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 150$  mmHg admitted from January 2006 to June 2021 who received LPV were included in the analysis (see Additional file 1 for Study flow chart). Among them, 323 patients (34.7%) died in the ICU. Of note, rates of mortality in the ICU varied from one year to another all along the study period but no significant trend was observed (see **Additional file 1, Table 1**). All patients received neuromuscular blocking agents planned for at least the first 48 hours of invasive MV<sup>20</sup>. On Day 1, the plateau pressure was less than or equal to 28 cmH<sub>2</sub>O in 710 (76%) patients. The baseline characteristics of the patients were distinguished based on whether severe hypercapnia was noted on Day 1 are shown in **Table 1**. Hypercapnia was more frequent in patients with a plateau pressure lower than 28 cmH<sub>2</sub>O (**Figure 1A**). Hypocapnia was noted in 34 patients (4%), and severe hypercapnia was noted in 552 patients (59%).

## Severe hypercapnia on Day 1 and ICU mortality

The results for comparisons between patients who died in the ICU and those who survived are shown in **Additional file 1, Table 2**.  $\text{PaCO}_2$  values recorded on the first day of ARDS were significantly higher in patients who died in the ICU than in patients who survived their ICU stay. Locally estimated scatterplot smoothing (LOESS) analysis of the relationship between mortality and the highest  $\text{PaCO}_2$  on Day 1 showed an increase in mortality with increasing  $\text{PaCO}_2$  (**Figure 1B**). In the unadjusted (OR 1.54, 95% CI 1.16-1.63,  $p=0.003$ ) and adjusted analyses (OR 1.47, 95% CI 1.08-2.43,  $p=0.04$ ), severe hypercapnia was associated with ICU mortality, while no statistically significant interaction was found between severe hypercapnia and acidosis defined by a  $\text{pH} < 7.35$  ( $P$  for interaction = 0.12). The variance inflation factor between severe hypercapnia and the ventilator ratio calculated on Day 1 was 1.41. The results for the Bayesian analysis are shown in **Table 2**. The posterior probability of an OR greater than

1 was above 90% for all priors. The four prior and posterior distributions are shown in **Additional file, Figure 2**.

#### Severe sustained hypercapnia and ICU mortality

The proportions of patients with sustained severe hypercapnia decreased progressively from Day 1 to Day 5 but remained present on Day 5 in 12% of our patients. ICU mortality was significantly higher when patients with sustained severe hypercapnia were compared with those without sustained hypercapnia on Day 2 (39% vs. 29%, respectively), Day 3 (42% vs. 27%), Day 4 (46% vs. 24%), and Day 5 (42% vs. 24%); mortality rates increased with time in patients with sustained hypercapnia (Cochrane Armitage test for trend,  $p < 0.01$ ) (**Figure 2**). After propensity-score matching, patients with severe hypercapnia on Day 5 had a higher risk of death in the ICU than matched patients without hypercapnia on Day 5 (OR = 1.73, 95% CI 1.02-2.97,  $p < 0.05$ ) (**Table 3**). Of note, non-pulmonary SOFA scores were significantly higher in patients with sustained hypercapnia (see **Additional file, Figure 3**).

#### Ventilatory management of the patients

PaCO<sub>2</sub> was correlated with V<sub>t</sub> according to PDW but not PH (Supplemental figure 4A and 4B). In addition, there was no significant change in V<sub>t</sub>/PBW, RR, and PP noted on day 1 of ARDS during the study period (Supplemental Table 3). Extensive results for ventilator variables recorded from Day 1 to Day 5 for the ARDS patients are shown in **Additional file, Table 3**. After comparisons between patients with and without severe hypercapnia, V<sub>t</sub>/PBW did not differ significantly between the groups. Plateau pressures were higher in patients with sustained severe hypercapnia than in patients without sustained severe hypercapnia.

#### Discussion

In our study, we found that severe hypercapnia during the first 24 hours of ICU stay was independently associated with mortality in the ICU in ARDS patients with P/F  $\leq$  150 mmHg who

received LPV. The results of the propensity score analysis performed for sustained severe hypercapnia on Day 5 reinforced the observation that a significant retention of CO<sub>2</sub> still present after a few days of MV was associated with the worst outcomes in the ICU. In addition, sustained severe hypercapnia was associated with increased non-pulmonary SOFA scores. Since all patients included in our study were ventilated as recommended (a tidal volume of 6 mL.kg<sup>-1</sup> PBW and plateau pressure less than or equal to 28 cmH<sub>2</sub>O), we believe that sustained hypercapnia could be considered an independent risk factor for mortality.

In a large database of ARDS and non-ARDS mechanically ventilated patients for acute respiratory failure from 2000 to 2013, Tiruvoipati et al.<sup>28</sup> found that hypercapnic acidosis and compensated hypercapnia during the first 24 hours of ICU admission were associated with increased hospital mortality. However, the study population included an unknown proportion of ARDS patients since the most common reasons for MV were post cardiac surgery, cardiac arrest, or cardiogenic shock. To the best of our knowledge, only three clinical studies<sup>14-16</sup> have focused on the relationship between CO<sub>2</sub> retention and prognosis in ARDS patients, which reported conflicting results. The ARMA trial<sup>14</sup> compared 12 to 6 mL.kg<sup>-1</sup> PBW of Vt and reported that 1) hypercapnic acidosis had no effect on mortality in patients who received 6 mL.kg<sup>-1</sup> PBW of Vt and that 2) hypercapnic acidosis was associated with reduced 28-day mortality in the group that received 12 mL.kg<sup>-1</sup> PBW of Vt. The authors suggested that hypercapnic acidosis had no harmful effect and could protect against ventilator-induced lung injury. In an ancillary study performed from LUNG SAFE population<sup>29</sup>, Madotto F et al.<sup>16</sup> reported an association between ICU mortality and hypocapnia within the first two days of MV. Significant differences in the ventilator management strategies could be responsible for these discrepant results. For instance, in the LUNG SAFE study, patients with a PaO<sub>2</sub>/FiO<sub>2</sub> > 150 mmHg were included and could be under non-invasive ventilation or ventilated with 8 mL.kg<sup>-1</sup> or more of tidal volume. Furthermore, less than one-third of the included patients had their

plateau pressure recorded; 21.7% of the patients received neuromuscular blockades and less than 10% were in prone positioning. Finally, our findings are in accordance with those previously published by Nin N et al. <sup>15</sup>, who assessed the impact of hypercapnia on the first 48 hours of MV only while in more than 10% of the patients  $V_t$  was greater than 8 ml/kg.

In a recent meta-analysis, Gendreau et al found also that hypercapnia was associated with mortality in ARDS patients receiving identical ventilation strategies <sup>17</sup>. However, because of the observational and retrospective nature of the study, we cannot determine causal relationship between severe hypercapnia and ICU mortality. Nevertheless, the question is raised to determine whether severe hypercapnia is a causal agent for mortality or only a marker of ARDS severity. Ventilatory ratio, a surrogate of dead space which is a prognostic factor in ARDS was significantly higher in patients with severe hypercapnia. This result suggests that hypercapnia was only a marker of severity. Nevertheless, severe hypercapnia on day 1 of ARDS remained associated with mortality after adjustment on ventilator ration and was also associated on day 5 after that patients were matched on variables including ventilator ratio. Consequently, harmful effects of hypercapnia cannot be excluded. The use of different animal models has led to the publication of contradictory results on the effects of hypercapnia <sup>2,5,6,9,30,31-34</sup>. The main reported short-term harmful effect of hypercapnia was alveolar epithelial cell dysfunction through inhibition of the NF- $\kappa$ B pathway <sup>35</sup>. This impaired cell function leads to decreased alveolar fluid reabsorption and tissue repair <sup>36,37</sup>. As reported in a randomized animal study, prolonged hypercapnic acidosis was associated with more structural damage and lower static compliance than normocapnia and worsened bacterial infection-induced lung injury <sup>38</sup>.

Interestingly, it has been suggested that acidosis may have more deleterious effects than hypercapnia, leading authors to suggest to conduce LPV with pH for target in patients with respiratory acidosis <sup>18</sup>. However unlike PaCO<sub>2</sub>, pH was not correlated with  $V_t$  in our patients.

We believe that our findings have clinical implications. In accordance with the results previously reported by Nin et al.<sup>15</sup>, PaCO<sub>2</sub> values above 50 mmHg should alert physicians. Therefore, strategies to control CO<sub>2</sub> retention, based on ventilator management or the extracorporeal elimination of carbon dioxide may have a positive impact on outcomes. However, it remains to be demonstrated that the sustained normalization of PaCO<sub>2</sub> may improve the prognosis of patients with ARDS<sup>39</sup>.

### **Strengths and limitations**

We report a large population of patients with moderate to severe ARD manage homogeneously for mechanical MV. Employing frequentist analysis and Bayesian analysis, we found that severe hypercapnia was associated with ICU mortality. In addition, patients were assessed for hypercapnia on the first five days MV, longer than most previous studies. Because of its observational nature, our study has a number of limitations. First, only associations, and not causal inference, can be drawn from the findings. The study period is long and an historical bias cannot be excluded, especially because of changes in the management of MV. However, year of admission was taken into account in analyses and we did not observe changes in Vt during the study period. Secondly, the study was conducted in a single centre; thus, the results may not be applicable to other hospitals. Despite adjustments for variables that are potentially associated with prognosis and CO<sub>2</sub> retention, we cannot exclude the possibility that unmeasured confounders could have influenced the relationship between severe hypercapnia and ICU mortality. Ventilator parameters were documented several times daily but not the results of arterial blood gases; consequently, we were unable to determine if severe hypercapnia was seen throughout the day of sampling or only during a short period of the day. The highest, but not the lowest, PaCO<sub>2</sub> values were recorded; consequently, the impact of hypocapnia was probably underestimated.

### **Conclusions**

Our results suggest that severe hypercapnia in moderate to severe ARDS patients receiving LPV is associated with ICU mortality and that mortality increases with the duration of severe hypercapnia. Our results deserve further evaluation of the strategies and treatments aiming to control CO<sub>2</sub> retention.

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## Figure legends

### Figure 1

Density probability function of PaCO<sub>2</sub> stratified by plateau pressure (A) and PaCO<sub>2</sub> LOESS curves of the relationship between ICU mortality and PaCO<sub>2</sub> on Day 1 of ARDS (B)

### Figure 2

Patients compared for ICU mortality rates based on whether sustained severe hypercapnia was noted on each of the first five days after ARDS diagnosis

**Quick Look***Current knowledge:*

Recent evidence suggests that hypercapnia could have harmful clinical effects in patients with ARDS. The impact of hypercapnia on the outcomes of ARDS patients has been mostly assessed in studies including patients not managed uniformly for mechanical ventilation.

*What This Paper Contributes To Our Knowledge:* In ARDS patients who all received lung protective ventilation, PaCO<sub>2</sub> equal or higher than 50 mmHg on the first day of ARDS is associated with mortality in the Intensive care Unit.

Table 1: Baseline characteristics of patients, reason for ARDS, and interventions

	PaCO <sub>2</sub> ≥ 50 mmHg Day 1		P value
	Yes n= 552	No n= 378	
<b>Baseline characteristics</b>			
SAPS II score, points median (IQR)	48 (36-65)	46 (34-63)	0.36
SOFA score, points median (IQR)	9 (7-12)	8 (6-12)	0.01
Age, years mean (SD)	58 (15)	57 (15)	0.25
Male gender, n (%)	349 (63)	252 (67)	0.31
Base excess, mEq/L median (IQR)	-1.70 (-6.39-2.06)	-2.26 (-7.16-0.88)	0.01
BMI, kg/m <sup>2</sup> median (IQR)	27 (23-32)	27 (23-31)	0.20
<b>Coexisting condition, n (%)</b>			
Diabetes mellitus	79 (14)	47 (12)	0.47
Liver cirrhosis	44 (8)	36 (9)	0.48
Valvular and/or coronary disease with treatment	73 (19)	106 (19)	0.99
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	95 (17)	46 (12)	0.04
COPD	129 (23)	71 (19)	0.11
Obesity	200 (36)	122 (32)	0.24
<b>Ventilatory management</b>			
pH, median (IQR)	7.22 (7.13-7.30)	7.34 (7.27-7.40)	<0.0001
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg median (IQR)	88 (66-115)	97 (75-121)	0.008
PEEP, cmH <sub>2</sub> O median (IQR)	10 (8-12)	10 (8-12)	0.34
Plateau pressure, cmH <sub>2</sub> O median (IQR)	26 (22-29)	25 (21-28)	<0.001
Driving pressure, cmH <sub>2</sub> O median (IQR)	15 (12-18)	14 (11-17)	<0.001
RSC, ml/cmH <sub>2</sub> O median (IQR)	27.5 (21.7-35.0)	30.8 (24.3-39.3)	<0.001
Ventilatory ratio, median (IQR)	2.8 (2.4-3.4)	1.8 (1.6-2.2)	<0.0001
<b>Reason for ARDS</b>			
Pneumonia	347 (63)	253 (67)	0.23
Aspiration	72 (13)	47 (12)	0.86
Non-pulmonary sepsis	38 (7)	28 (7)	0.86
Miscellaneous	95 (17)	50 (13)	0.12
<b>Interventions, n (%)</b>			
Prone positioning	261 (47)	170 (45)	0.53
Extra corporeal membrane oxygenation	48 (9)	29 (8)	0.66
Inhaled nitric oxide	119 (22)	47 (12)	<0.001
Glucocorticoids	356 (64)	265 (70)	0.09
Vasopressors	493 (89)	315 (83)	0.008
Renal-replacement therapy	181 (33)	109 (29)	0.22

<b>Death in the ICU, n (%)</b>	213 (38)	110 (29)	0.004
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Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; RSC, respiratory system compliance; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease.

Table 2: Odds ratio, 95% Credible Interval, and probability that severe hypercapnia is greater than specified thresholds

Death in the ICU		
Prior	OR (95% Credible Interval)	Probability OR > 1
Optimistic prior: (Severe hypercapnia is associated with mortality)	1.56 (1.10-2.20)	98%
Neutral prior	1.49 (1.03-2.18)	98%
Null prior	1.59 (1.07-2.37)	98%
Sceptic prior: (Severe hypercapnia is not associated with mortality)	1.33 (1.05-1.89)	96%

Abbreviations: OR, odds ratio.

Table 3: Comparison of patients according to severe hypercapnia on day 5 after matching\*

	Sustained PaCO <sub>2</sub> ≥ 50 mmHg at Day 5		P value
	Yes n= 93	No n= 186	
<b>Baseline characteristics</b>			
SAPS II score, points median (IQR)	42 (34-56)	41 (32-57)	0.57
SOFA score, points median (IQR)	8 (6-12)	8 (6-11)	0.93
Age, years mean (SD)	60 (14)	59 (15)	0.84
Male gender, n (%)	65 (68)	117 (66)	0.50
Base excess, mEq/L median (IQR)	-1.70 (-6.39-2.06)	-2.26 (-7.16-0.88)	0.01
<b>Coexisting condition, n (%)</b>			
Diabetes mellitus	8 (8)	23 (12)	0.41
Liver cirrhosis	5 (5)	11 (6)	0.48
Valvular and/or coronary disease with treatment	17 (18)	44 (24)	0.32
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	15 (16)	37 (20)	0.47
COPD	32 (33)	41 (22)	0.06
Obesity	30 (31)	69 (37)	0.40
<b>Ventilatory management</b>			
pH, median (IQR)	7.34 (7.32-7.35)	7.35 (7.35-7.36)	0.15
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg median (IQR)	92 (72-117)	96 (69-130)	0.60
PEEP, cmH <sub>2</sub> O median (IQR)	10 (7-12)	10 (9-12)	0.07
Plateau pressure, cmH <sub>2</sub> O median (IQR)	28 (23-30)	28 (25-29)	0.28
Driving pressure, cmH <sub>2</sub> O median (IQR)	15 (12-18)	14 (11-17)	0.88
RSC, ml/cmH <sub>2</sub> O median (IQR)	25.4 (18.7-32.1)	24.5 (20.2-30.0)	0.65
Ventilatory ratio, median (IQR)	3.0 (2.4-3.7)	2.9 (2.3-3.5)	0.48
<b>Reason for ARDS</b>			
Pneumonia	71 (74)	124 (67)	0.26
Aspiration	6 (6)	21 (11)	0.25
Non-pulmonary sepsis	4 (4)	9 (5)	0.99
Miscellaneous	15 (16)	32 (17)	0.89
<b>Interventions, n (%)</b>			
Prone positioning	50 (52)	95 (51)	0.97
Extra corporeal membrane oxygenation	10 (10)	17 (9)	0.89
Inhaled nitric oxide	26 (27)	27 (14)	0.02
Glucocorticoids	80 (83)	166 (89)	0.23
Vasopressors	80 (83)	166 (89)	0.22
Renal-replacement therapy	55 (57)	130 (70)	0.13
<b>Death in the ICU, n (%)</b>	<b>38 (43)</b>	<b>56 (30)</b>	<b>0.048</b>

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; RSC, respiratory system compliance; SAPS, simplified acute physiology score; SD, standard

deviation; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease.

\*variables used for propensity score matching: age, sex, SAPS II score, and respiratory rate, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, respiratory system compliance, driving pressure, and ventilator ratio recorded or calculated at day 1 of ARDS.



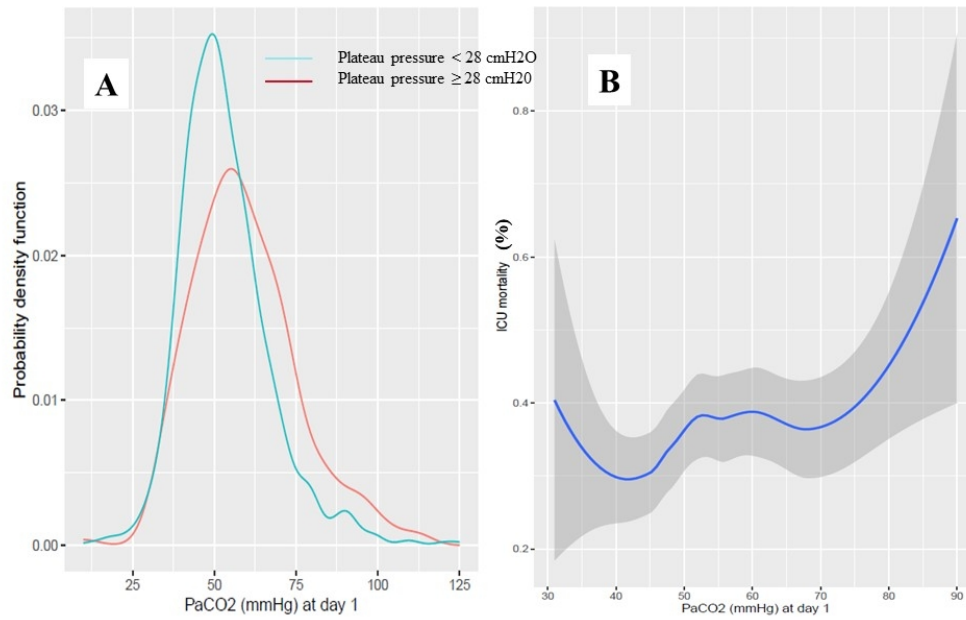


Figure 1:

Density probability function of PaCO<sub>2</sub> stratified by plateau pressure (A) and PaCO<sub>2</sub> LOESS curves of the relationship between ICU mortality and PaCO<sub>2</sub> on Day 1 of ARDS (B)

254x190mm (96 x 96 DPI)

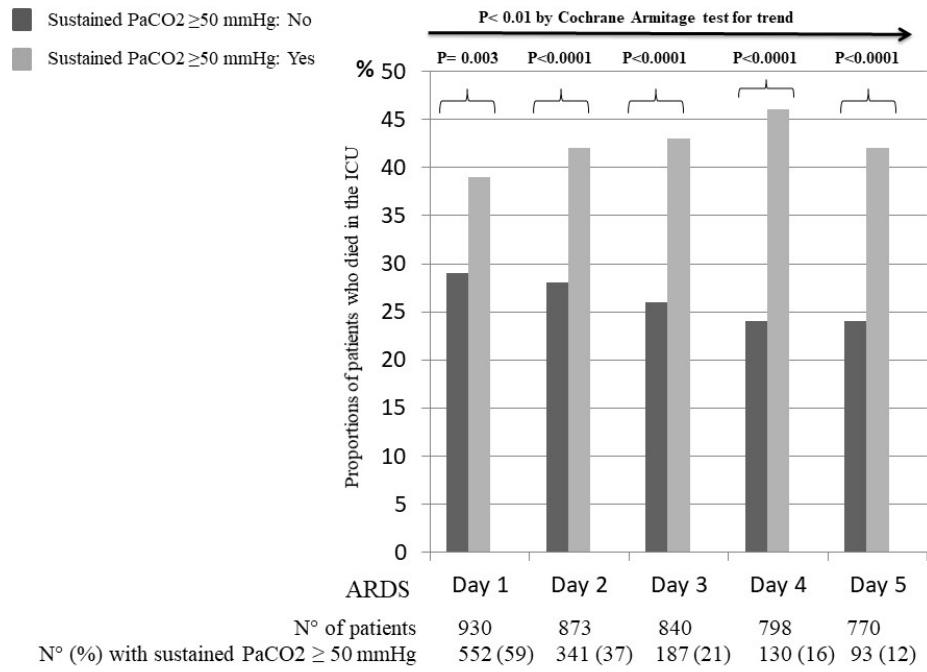


Figure 2

Patients compared for ICU mortality rates based on whether sustained severe hypercapnia was noted on each of the first five days after ARDS diagnosis

254x190mm (96 x 96 DPI)

## **Impact of sustained arterial CO<sub>2</sub> retention in patients with moderate or severe acute respiratory distress syndrome**

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## **Supplemental Appendix**

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

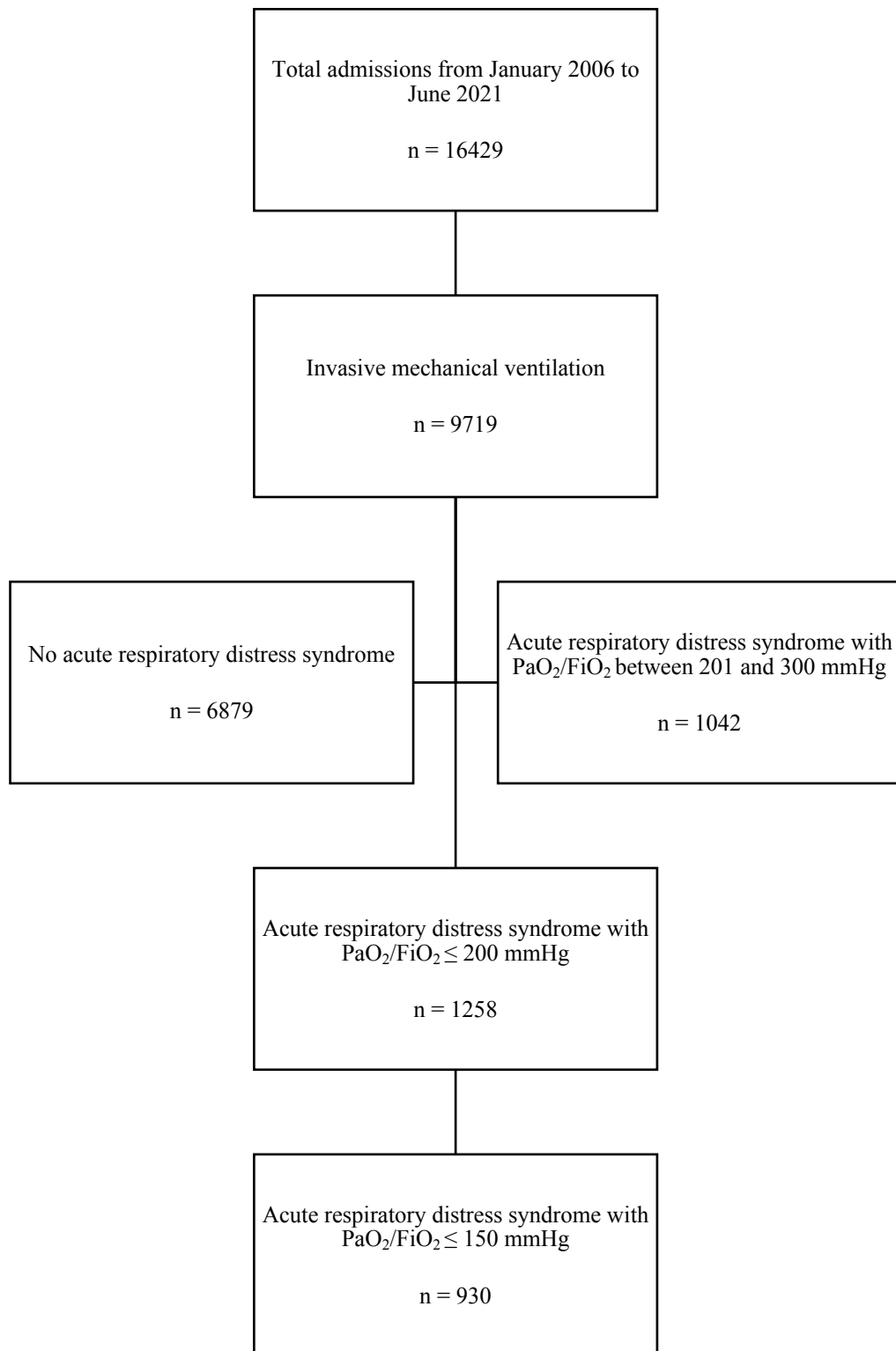
	Item No	Recommendation
<b>Title and abstract</b>	1	Indicate the study's design with a commonly used term in the title or the abstract Cohort study Provide in the abstract an informative and balanced summary of what was done and what was found: Done
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Lung protective ventilation (PV) is the cornerstone of management of ARDS Lung protective ventilation may lead to important CO <sub>2</sub> retention There is uncertainty regarding the beneficial or harmful effect of hypercapnia. Impact of CO <sub>2</sub> retention on the outcome of ARDS patients has been assessed only in three previous cohorts of patients not managed uniformly for mechanical ventilation.
Objectives	3	State specific objectives, including any prespecified hypotheses To determine whether severe hypercapnia (PaCO <sub>2</sub> ≥ 50 mmHg) is associated with ICU mortality in patients receiving invasive ventilation with tidal volume set to 6 mL.kg <sup>-1</sup> predictive body weight as required in LPV. We suspected that severe hypercapnia could be associated with worst outcome in these patients..
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper Retrospective analysis of data collected prospectively with no missing data. Assessment for ICU survival on the whole population and after matching process
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Setting: a mixed 21-bed ICU in a university hospital Study period: from January 2006 to June 2021 Follow-up period: from diagnosis of ARDS until ICU discharge
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Patients with ARDS and PaO <sub>2</sub> /FiO <sub>2</sub> ratio ≤ 150 mmHg (n= 930) Data base started in 2006 Short-term follow-up (ICU discharge)  (b) For matched studies, give matching criteria and number of exposed and unexposed Patients assessed on Day 5 of ARDS. The following variables were used for calculation of the propensity score: age, sex, SAPS II score, respiratory rate on Day 1, PaO <sub>2</sub> /FiO <sub>2</sub> ratio on Day 1, respiratory system compliance on Day 1, driving pressure on Day 1, and ventilatory ratio on Day 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Outcomes and predictors were described and defined; potential confounders discussed.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Source of data: data base of our ICU Statistical tests used for comparisons were described in the statistical section
Bias	9	Describe any efforts to address potential sources of bias Frequentist analysis including non-adjusted and adjusted analysis. In addition a Bayesian analysis was performed.
Study size	10	Explain how the study size was arrived at No sample-size calculation. The high number of patients limited the risk to perform an underpowered study.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Comparisons between proportions of patients. Patients alive at Day 5 of ARDS were included in a matched study with the aim to assess the impact of sustained severe hypercapnia.
Statistical methods	12	Describe all statistical methods, including those used to control for confounding First step: unadjusted and adjusted analysis was performed to determine the impact of severe hypercapnia noted on Day 1 of ARDS. In addition a Bayesian analysis was performed with four different priors, including a septic prior for this association. Second step, matched analysis to assess the impact of sustained hypercapnia on Day 5. <i>(b)</i> Describe any methods used to examine subgroups and interactions Interaction between acidosis and hypercapnia was assessed. <i>(c)</i> Explain how missing data were addressed No missing data If applicable, explain how loss to follow-up was addressed No patients loss to follow-up for the day of end-point <i>(e)</i> Describe any sensitivity analyses
<b>Results</b>		
Participants	13*	<i>(a)</i> Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed: Done <i>(b)</i> Give reasons for non-participation at each stage: NA <i>(c)</i> Consider use of a flow diagram: Done
Descriptive data	14*	<i>(a)</i> Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders: Done <i>(b)</i> Indicate number of participants with missing data for each variable of interest: NA <i>(c)</i> Summarise follow-up time (eg, average and total amount): ICU length of stay
Outcome data	15*	Report numbers of outcome events or summary measures over time: Done in

figure 2		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included: Done (including pneumonia and COPD forced in models) (b) Report category boundaries when continuous variables were categorized: Done (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives: Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias: Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence: Done
Generalisability	21	Discuss the generalisability (external validity) of the study results Done
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based None

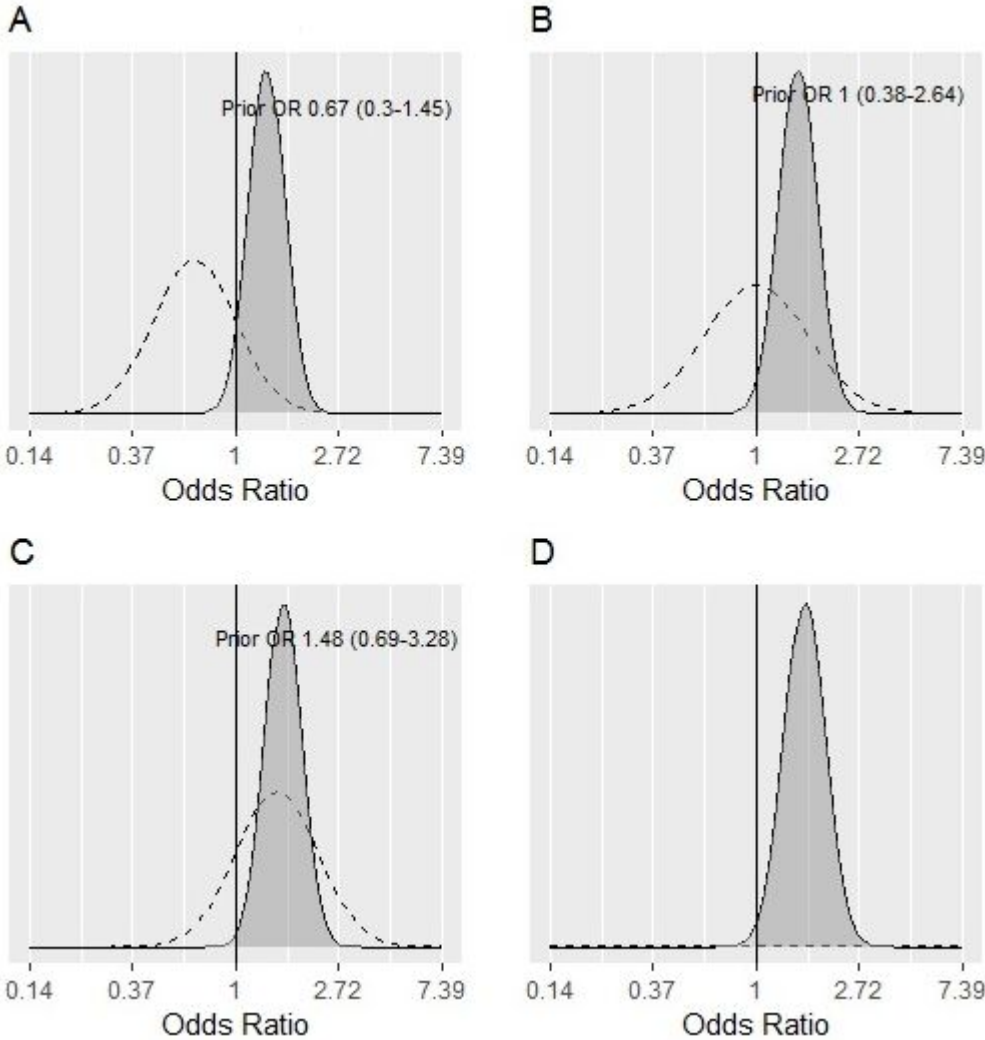
\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

**Supplemental Figure 1**

Supplemental Figure 1: diagram flowchart of patients.

Supplemental figure 2

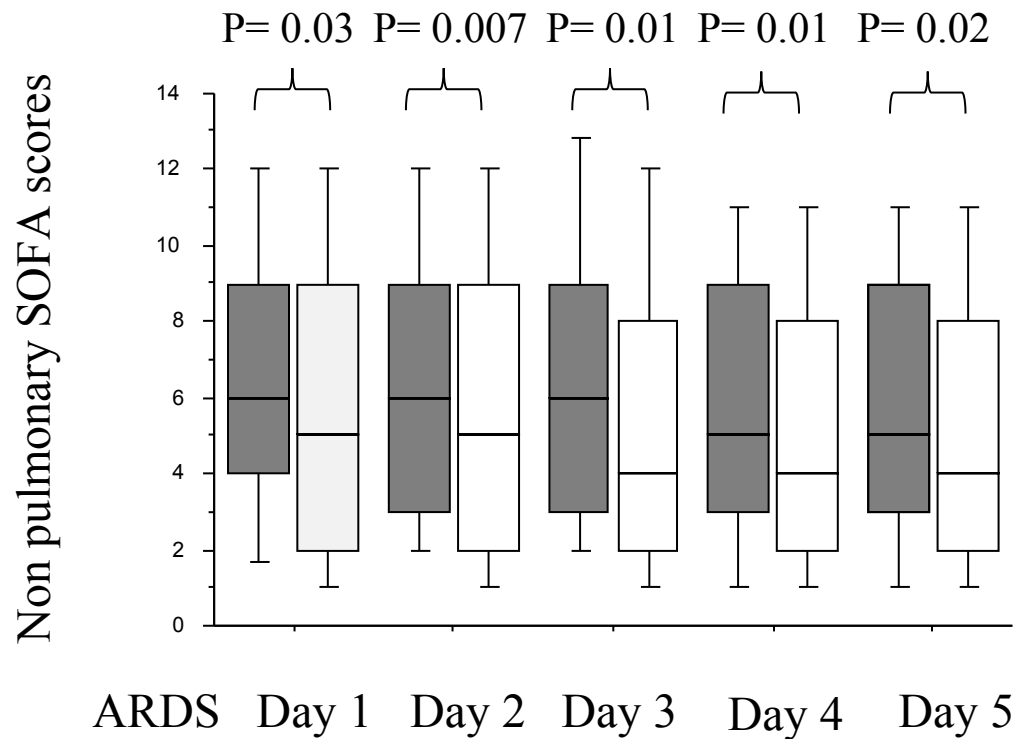


Supplemental Figure 2: Graphical representation of reference priors (dashed lines) and data-derived priors (thicked lines). Each prior distribution represents a belief about the probability that severe hypercapnia is associated with death in the ICU. A: “sceptic” prior (severe hypercapnia is not associated with ICU mortality); B, neutral prior; C, “optimistic” prior (hypercapnia is associated with mortality in the ICU); D, null prior in which all effects size were equally plausible.



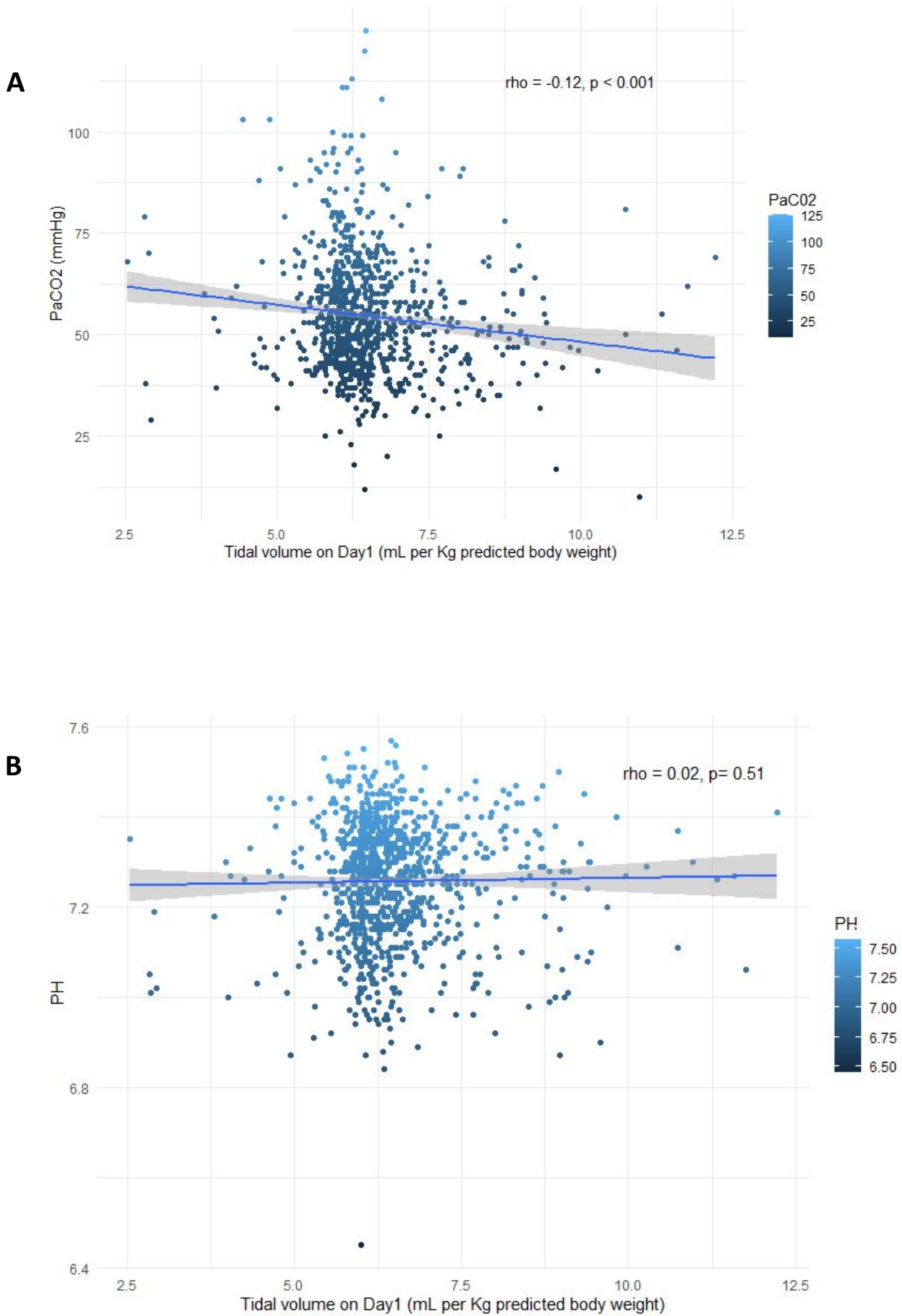
**Supplemental figure 3**

- Severe sustained hypercapnia on the day of assessment: Yes
- Severe sustained hypercapnia on the day of assessment: No



Supplemental Figure 3: Non-pulmonary SOFA scores compared between patients with and without sustained severe hypercapnia ( $\text{PaCO}_2 \geq 50$  mmHg)

## Supplemental figure 4



Supplemental Figure 4 : Respective correlations between PaCO<sub>2</sub> and Tidal volume at day 1 (A), and between PH and tidal volume at day 1 (B)

**Supplemental table 1**

Supplemental Table 1: Baseline characteristics of patients, reason for ARDS, and interventions compared for death in the ICU

	Death in the ICU		P value
	Yes n= 323	No n= 607	
<b>Baseline characteristics</b>			
SAPS II score, points mean (SD)	62 ± 21	46 ± 18	<0.0001
SOFA score, points median (IQR)	12 (9-15)	8 (6-11)	<0.0001
Age, years mean (SD)	61 ± 14	56 ± 15	<0.0001
Male gender, n (%)	219 (68)	382 (63)	0.14
Base excess, mEq/L median (IQR)	-4.35 (-9.64-.072)	-1.21(-5.21-1.80)	<0.0001
BMI, kg/m <sup>2</sup> median (IQR)	26 (23-31)	27 (23-32)	0.37
<b>Coexisting condition, n (%)</b>			
Diabetes mellitus	41 (13)	85 (14)	0.58
Liver cirrhosis	50 (15)	30 (5)	<0.0001
Valvular and/or coronary disease with treatment	75 (23)	104 (17)	0.02
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	77 (24)	64 (11)	<0.0001
COPD	60 (19)	140 (22)	0.11
Obesity	107 (33)	215 (35)	0.48
<b>Ventilatory management on the first day of ARDS</b>			
PaCO <sub>2</sub> , mmHg median (IQR)	54 (47-64)	51 (44-61)	0.002
pH, median (IQR)	7.22 (7.13-7.30)	7.34 (7.27-7.40)	<0.0001
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg median (IQR)	86 (63-109)	94 (74-121)	<0.0001
PEEP, cmH <sub>2</sub> O median (IQR)	10 (8-13)	10 (8-12)	0.03
Plateau pressure, cmH <sub>2</sub> O median (IQR)	27 (22-29)	25 (22-28)	<0.0001
Driving pressure, cmH <sub>2</sub> O median (IQR)	15 (13-19)	14 (11-17)	<0.0001
RSC, ml/cmH <sub>2</sub> O median (IQR)	27 (21-35)	29 (24-38)	0.002
Ventilatory ratio, median (IQR)	2.55 (2.02-3.18)	2.29 (1.82-2.91)	<0.0001
<b>Reason for ARDS</b>			
Pneumonia	177 (55)	423 (70)	<0.0001
Aspiration	37 (11)	82 (14)	0.37
Non-pulmonary sepsis	39 (12)	27 (5)	<0.0001
Miscellaneous	70 (22)	75 (12)	0.0003
<b>Interventions, n (%)</b>			
Prone positioning	135 (42)	296 (49)	0.04
Extra corporeal membrane oxygenation	37 (11)	40 (7)	0.01
Inhaled nitric oxide	102 (32)	64 (11)	<0.0001
Glucocorticoids	234 (72)	387 (64)	0.007

Vasopressors	305 (94)	503 (83)	<0.0001
Renal-replacement therapy	163 (50)	127 (21)	<0.0001

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; IQR, interquartile range; RSC, respiratory system compliance; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease.

### Supplemental table 2:

Expiratory tidal volume (Vte) according to predicted body weight (PBW), respiratory rate, and plateau pressure recorded on day 1 of ARDS each year of the study period. Data are presented as medians and interquartile ranges (IQR).

Year of study	Mortality rate in the ICU (%)	Vte/PBW (ml/kg)	Respiratory rate (breaths/minute)	Plateau pressure (cmH2O)
2006	38	6.63 (6.16-7.73)	24 (21-26)	28 (22-30)
2007	30	6.44 (6.00-7.43)	24 (21-26)	26 (21-30)
2008	47	6.29 (6.00-6.84)	25 (22-27)	24 (20-29)
2009	38	6.38 (6.05-6.68)	28 (24-30)	25 (22-29)
2010	42	6.60 (6.04-7.73)	28 (24-32)	27 (20-29)
2011	42	6.56 (6.12-7.40)	28 (25-31)	26 (23-27)
2012	46	6.43 (6.06-7.42)	27 (24-30)	25 (22-30)
2013	37	6.19 (5.85-6.73)	28 (24-30)	26 (22-29)
2014	45	6.44 (6.16-6.83)	28 (25-30)	27 (24-29)
2015	35	6.13 (5.91-6.53)	26 (25-30)	25 (21-28)
2016	30	6.31 (5.82-6.70)	28 (25-30)	23 (23-28)
2017	33	6.41 (5.97-6.63)	28 (24-30)	25 (20-28)
2018	43	6.18 (5.97-6.63)	28 (24-30)	25 (22-27)
2019	45	6.22 (5.92-6.51)	29 (25-30)	27 (24-30)
2020	29	6.20 (5.99-6.59)	28 (25-30)	25 (21-28)

2021	28	6.22 (5.98-6.44)	26 (24-26)	24 (22-27)
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### Supplemental Table 3

Supplemental Table 3: Ventilatory variables compared each day from day 1 to day 5 of ARDS whether patients presented or not the day of assessment severe sustained hypercapnia

	ARDS Day 1	ARDS Day 2	ARDS Day 3	ARDS Day 4	ARDS Day 5
Plateau Pressure (cmH <sub>2</sub> O)					
Sustained severe hypercapnia : yes	26.00 [22.00, 29.00]	26.00 [22.00, 28.00]	26.00 [23.00, 29.00]	26.00 [23.50, 29.00]	26.50 [24.00, 30.00]
Sustained severe hypercapnia : no	25.00 [21.00, 28.00]	24.00 [21.00, 27.00]	24.00 [21.00, 26.00]	23.00 [20.00, 26.00]	23.00 [20.00, 26.00]
Vte/PBW (ml/kg)					
Sustained severe hypercapnia : yes	6.25 [6.00, 6.71] NS	6.21 [5.88, 6.61]	6.28 [5.92, 6.72] NS	6.34 [5.89, 6.88]	6.34 [5.84, 6.90]
Sustained severe hypercapnia : no	6.30 [6.01, 6.84]	6.26 [6.00, 6.76]	6.29 [5.97, 6.68]	6.42 [6.06, 7.01]	6.57 [6.12, 7.46]
Driving pressure (cmH <sub>2</sub> O)					
Sustained severe hypercapnia : yes	15.00 [12.00, 18.00]	14.00 [11.00, 18.00]	14.00 [11.00, 18.25]	15.00 [12.00, 19.00]	16.00 [12.00, 19.25]
Sustained severe hypercapnia : no	14.00 [11.00, 17.00]	13.00 [10.00, 16.00]	13.00 [11.00, 16.00]	13.00 [10.00, 16.00]	13.00 [10.00, 16.00]
Ventilatory ratio					
Sustained severe hypercapnia : yes	2.84 [2.37, 3.38]	2.72 [2.40, 3.19]	2.76 [2.47, 3.17]	2.82 [2.48, 3.24]	2.91 [2.49, 3.42]
Sustained severe hypercapnia : no	1.85 [1.59, 2.16]	1.87 [1.58, 2.21]	1.91 [1.58, 2.24]	1.98 [1.65, 2.34]	2.05 [1.68, 2.40]
Respiratory system compliance (ml/cmH <sub>2</sub> O)					
Sustained severe hypercapnia : yes	27.47 [21.76, 35.00]	28.39 [21.42, 37.09]	28.29 [21.23, 37.22]	27.56 [20.44, 33.81]	26.77 [19.62, 33.77]
Sustained severe hypercapnia : no	30.85 [24.36, 39.35]	1.87 [1.58, 2.21]	31.08 [24.75, 39.10]	32.18 [25.73, 40.45]	32.92 [25.83, 42.00]
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)					
Sustained severe hypercapnia : yes	88.00 [65.75, 115.00]	111.00 [83.00, 147.00]	128.00 [92.75, 165.25]	133.00 [101.00, 173.00]	124.00 [90.75, 162.00]
Sustained severe hypercapnia : no	97.00 [75.00, 121.00]	142.00 [103.00, 193.50]	164.00 [118.00, 222.00]	179.00 [134.50, 232.00]	183.00 [138.00, 228.00]

All comparisons differed significantly ( $p < 0.05$ ) between patients with or without severe hypercapnia defined by  $\text{PaCO}_2 \geq 50$  mmHg, except for Vte/PBW at day 1 of ARDS.

Abbreviations: ARDS, acute respiratory distress syndrome; Vte, expiratory tidal volume; PBW, predicted body weight.