

Impact of sustained arterial CO₂ retention in patients with moderate or severe acute respiratory distress syndrome

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Supplementary Appendix

	Item No	Recommendation
Title and abstract	1	<p>Indicate the study's design with a commonly used term in the title or the abstract</p> <p>Cohort study</p> <hr/> <p>Provide in the abstract an informative and balanced summary of what was done and what was found: Done</p>
Introduction		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p>Lung protective ventilation (PV) is the cornerstone of management of ARDS Lung protective ventilation may lead to important CO₂ retention There is uncertainty regarding the beneficial or harmful effect of hypercapnia. Impact of CO₂ retention on the outcome of ARDS patients has been assessed only in three previous cohorts of patients not managed uniformly for mechanical ventilation.</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p>To determine whether severe hypercapnia (PaCO₂ ≥ 50 mmHg) is associated with ICU mortality in patients receiving invasive ventilation with tidal volume set to 6 mL.kg⁻¹ predictive body weight as required in LPV. We suspected that severe hypercapnia could be associated with worst outcome in these patients..</p>
Methods		
Study design	4	<p>Present key elements of study design early in the paper</p> <p>Retrospective analysis of data collected prospectively with no missing data. Assessment for ICU survival on the whole population and after matching process</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p> <p>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</p>
Participants	6	<p>Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p style="padding-left: 40px;">Patients with ARDS and PaO₂/FiO₂ ratio ≤ 150 mmHg (n= 930) Data base started in 2006 Short-term follow-up (ICU discharge)</p> <hr/> <p>(b) For matched studies, give matching criteria and number of exposed and unexposed</p> <p>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, PaO₂/FiO₂ ratio on Day 1, respiratory system compliance on Day 1, driving pressure on Day 1, and ventilatory ratio on Day 1</p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</p> <p>Outcomes and predictors were described and defined; potential confounders</p>

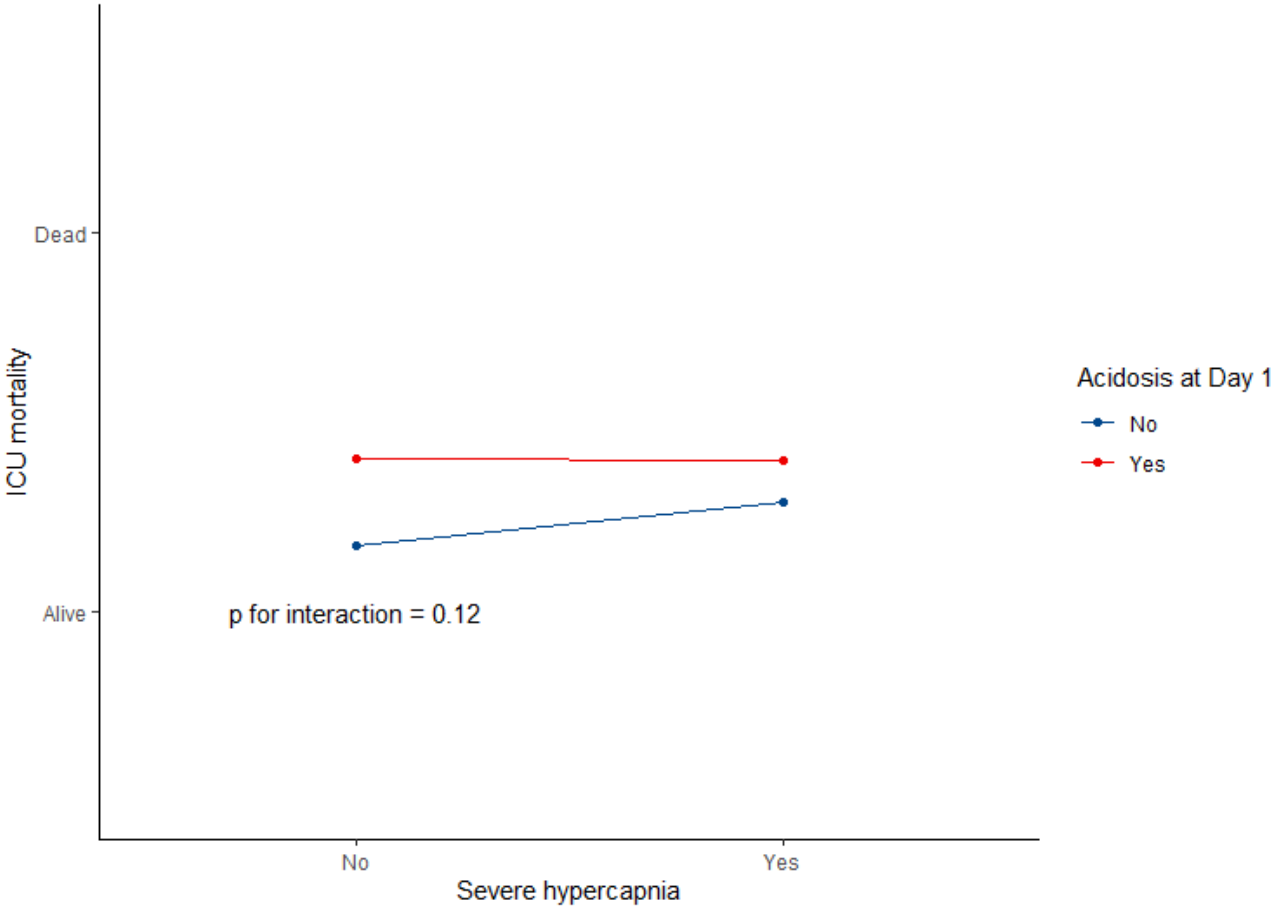
		discussed.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Source of data: data base of our ICU Statistical tests used for comparisons were 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
Results		
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
Discussion		
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
Other information		
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.

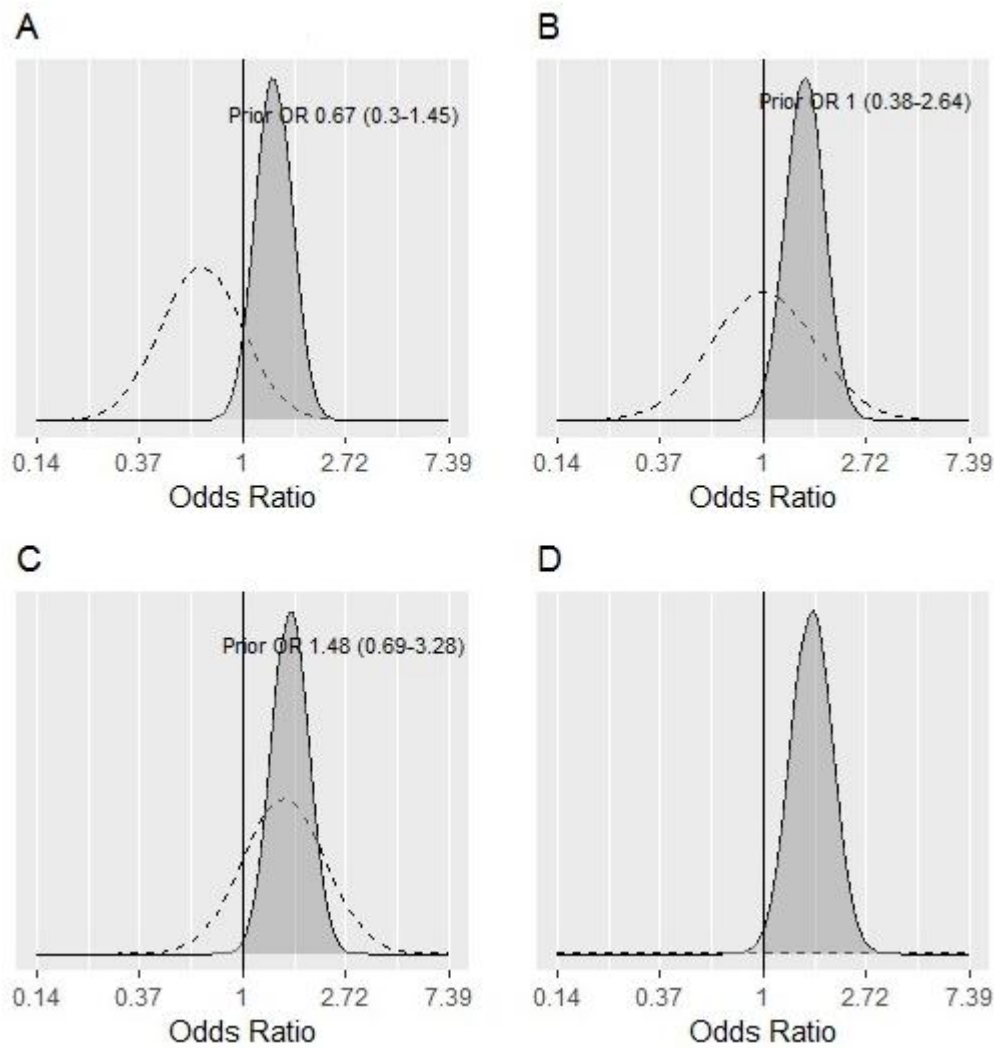
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, 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>.

Supplementary Figure 1



Supplementary Figure 1: Interaction plot between severe hypercapnia and acidosis at day 1 defined by a pH < 7.35 according to ICU mortality.

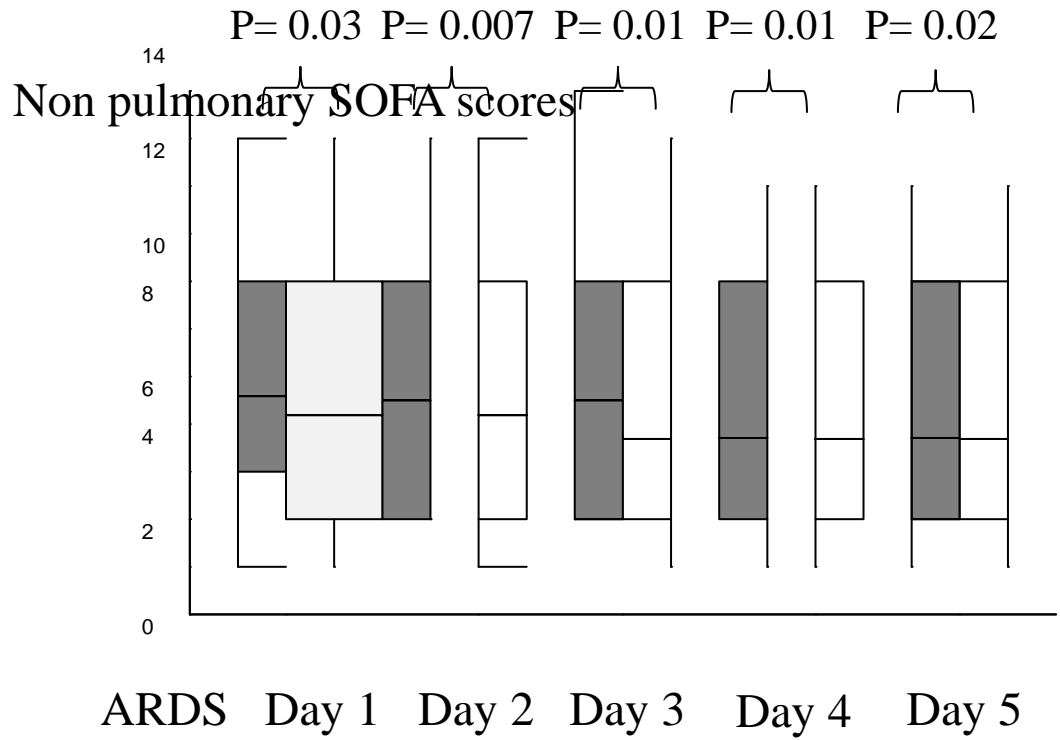
Supplementary figure 2



Supplementary Figure 2: Graphical representation of reference priors (dashed lines) and data-derived priors (thick 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.

Supplementary Figure 3

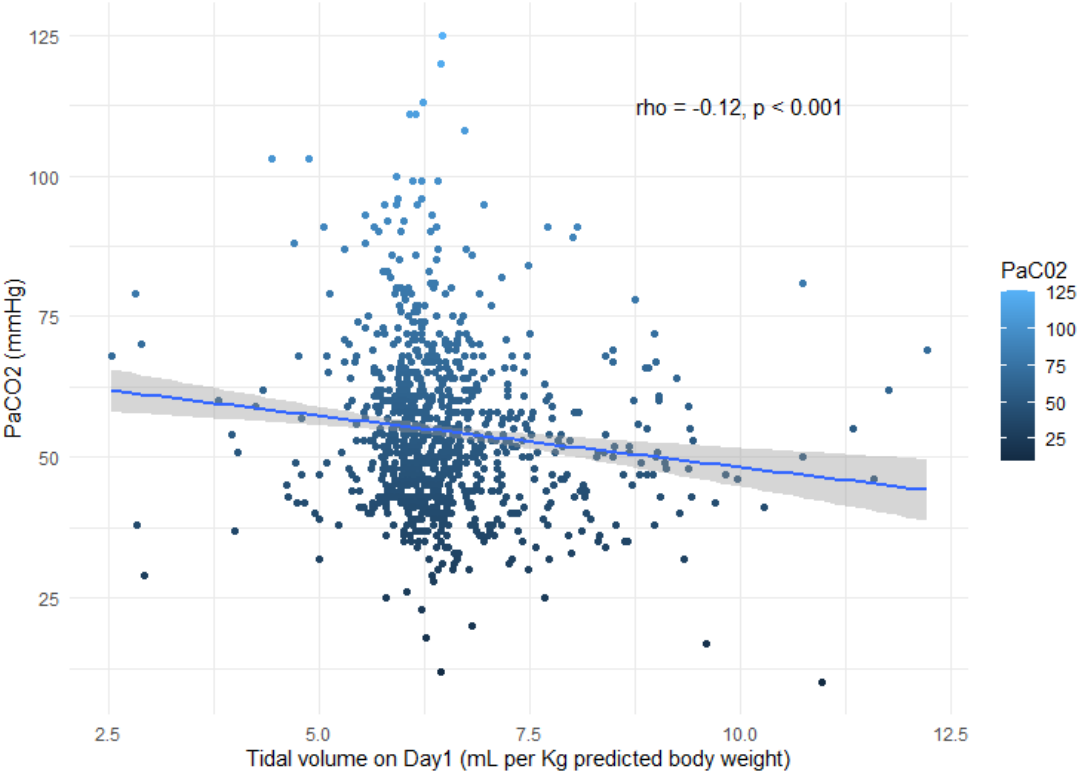
- Severe sustained hypercapnia on the day of assessment: Yes
- Severe sustained hypercapnia on the day of assessment: No

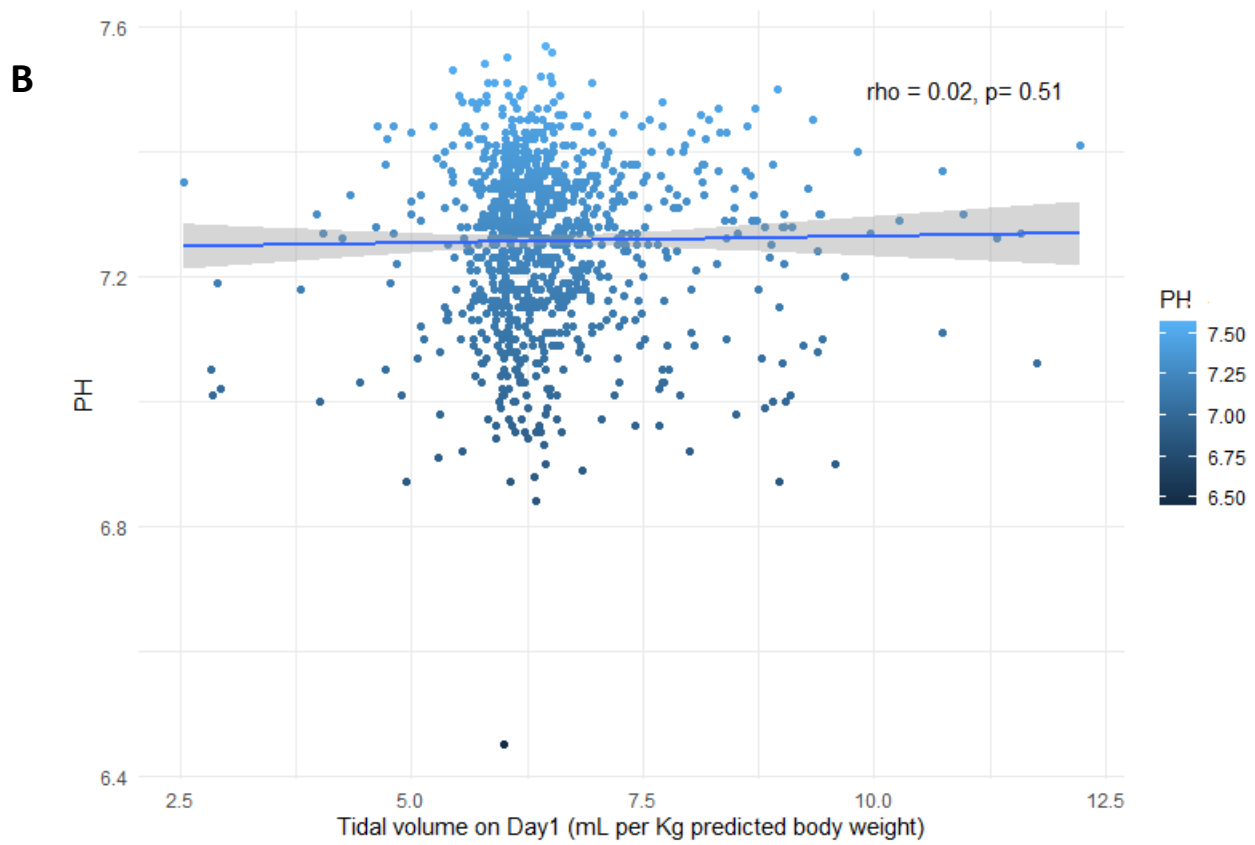


Supplementary Figure 3: Non-pulmonary SOFA scores compared between patients with and without sustained severe hypercapnia ($\text{PaCO}_2 \geq 50$ mmHg)

Supplementary Figure 4

A





Supplemental Figure 4: Respective correlations between PaCO₂ and Tidal volume at day 1 (A), and between PH and tidal volume at day 1 (B).

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	
Baseline characteristics			
SAPS II score, points mean (SD)	62 ± 21	46 ± 18	<0.001
SOFA score, points median (IQR)	12 (9-15)	8 (6-11)	<0.001
Age, years mean (SD)	61 ± 14	56 ± 15	<0.001
Male gender, n (%)	219 (68)	382 (63)	0.14
Base excess, mEq/L median (IQR)	-4.35 (-9.64--0.72)	-1.21(-5.21-1.80)	<0.001
BMI, kg/m ² median (IQR)	26 (23-31)	27 (23-32)	0.37
Coexisting condition, n (%)			
Diabetes mellitus	41 (13)	85 (14)	0.58
Liver cirrhosis	50 (15)	30 (5)	<0.001
Valvular and/or coronary disease with treatment	75 (23)	104 (17)	0.020
Aplasia and/or recent chemotherapy for solid tumor or haematologic disease	77 (24)	64 (11)	<0.001
COPD	60 (19)	140 (22)	0.11
Obesity	107 (33)	215 (35)	0.48
Ventilatory management on the first day of ARDS			
PaCO ₂ , 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)	<0.001
PaO ₂ /FiO ₂ , mmHg median (IQR)	86 (63-109)	94 (74-121)	<0.001
PEEP, cmH ₂ O median (IQR)	10 (8-13)	10 (8-12)	0.027
Plateau pressure, cmH ₂ O median (IQR)	27 (22-29)	25 (22-28)	<0.001
Driving pressure, cmH ₂ O median (IQR)	15 (13-19)	14 (11-17)	<0.001
RSC, ml/cmH ₂ 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)	<0.001
Reason for ARDS			
Pneumonia	177 (55)	423 (70)	<0.001
Aspiration	37 (11)	82 (14)	0.37
Non-pulmonary sepsis	39 (12)	27 (5)	<0.001
Miscellaneous	70 (22)	75 (12)	< 0.001
Interventions, n (%)			
Prone positioning	135 (42)	296 (49)	0.038
Extra corporeal membrane oxygenation	37 (11)	40 (7)	0.01
Inhaled nitric oxide	102 (32)	64 (11)	<0.001
Glucocorticoids	234 (72)	387 (64)	0.007
Vasopressors	305 (94)	503 (83)	<0.001
Renal-replacement therapy	163 (50)	127 (21)	<0.001

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)	Breathing frequency (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)

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 ₂ 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 ₂ 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 ₂ 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]	31.65 [25.06, 39.68]	31.08 [24.75, 39.10]	32.18 [25.73, 40.45]	32.92 [25.83, 42.00]
PaO ₂ /FiO ₂ (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.

