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Patterns and impact of arterial CO_2 management in patients with Acute Respiratory Distress Syndrome: Insights from the LUNG SAFE study

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Abbreviation List: AHRF: Acute Hypoxemic Respiratory failure; ARDS: Acute Respiratory Distress Syndrome; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive Care Units; NMBA: neuromuscular blocking agent; PP: prone positioning; PF ratio: PaO_2/FiO_2; PEEP: Positive End Expiratory Pressure; SIRS: systemic inflammatory response syndrome.

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Abstract

Background: Considerable variability exists regarding CO_2 management in early ARDS, with the impact of arterial CO_2 tension on management and outcomes poorly understood.

Research Question: To determine the prevalence and impact of hypo- and hypercapnia on the management and outcomes of patients with early ARDS enrolled in the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study, an international multicenter observational study.

***Study Design and Methods*:** Our primary objective was to examine the prevalence of Day 1 and sustained (day 1 and 2) of hypocapnia ($PaCO_2$ < 35mmHg), normocapnia ($PaCO_2$ 35-45mmHg) and hypercapnia ($PaCO_2$ > 45mmHg) in patients with ARDS. Secondary objectives included elucidating the effect of CO_2 tension on ventilatory management, and examining the relationship with ARDS outcome

Results: Of 2,813 patients analyzed, 551 (19.6%, 95%CI: 18.1-21.1) were hypocapnic, 1,018 (36.2%, 95%CI: 34.4-38.0) were normocapnic, while 1,214 (43.2%, 95%CI: 41.3-45.0) were hypercapnic, on day 1. Sustained hypocapnia was seen in 252 (9.3%, 95%CI: 8.2-10.4), sustained normocapnia in 544 (19.3%, 95%CI: 17.9-20.8) and sustained hypercapnia in 654 (24.1%, 95%CI: 22.5-25.7) patients. Hypocapnia was more frequent and severe in patients receiving non-invasive ventilation but was also observed in patients on controlled mechanical ventilation. Sustained hypocapnia was more frequent in middle income countries, while sustained hypercapnia was more frequent in Europe. ARDS severity profile was highest in sustained hypercapnia, and these patients received more protective ventilation. There was no independent association between arterial CO_2 and outcome. In propensity matched analyses, hospital mortality was 36% in both sustained normocapnic and hypercapnic patients (P=1.0). ICU mortality was higher in patients with mild to moderate ARDS receiving sustained hypocapnia (38.1%) compared to normocapnia (27.1%).

Interpretation: There was no evidence for benefit or harm with hypercapnia. Of concern, ICU mortality was higher with sustained hypocapnia in mild-moderate ARDS.

(**Word count 299**)

Introduction

The potential for high lung stretch to directly injure the lungs – termed ventilation induced lung injury (VILI) – is now well recognized [1,2]. Protective ventilatory strategies that reduce lung stretch improve survival in patients with acute respiratory distress syndrome (ARDS) [2,3]. In patients with ARDS, a key 'enabler' of lung protective ventilation has been the reduction of tidal and minute ventilation, which can lead to a 'permissive' hypercapnia [4,5]. However, concerns with respect to potential deleterious effects of hypercapnia. Preclinical studies show hypercapnia can exert both beneficial and harmful [6-10] effects. Hypocapnia is also seen in patients with ARDS, and has the potential to exert deleterious effects [7,11,12]; indeed it is one of the criteria for the systemic inflammatory response syndrome (SIRS) [13]. Hypocapnia may also indicate an unnecessarily high alveolar ventilation which may increase VILI.

There are no definitive guidelines on how to manage $PaCO_2$ in patients with ARDS. We wished to examine how $PaCO_2$ was managed in patients with ARDS enrolled in the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) study. Our primary objective was to examine the prevalence of hypocapnia ($PaCO_2$ < 35mmHg), normocapnia ($PaCO_2$ 35-45mmHg) and hypercapnia ($PaCO_2$ > 45mmHg), on days 1 and 2 of ARDS. Secondary objectives included characterizing the illness severity and ventilatory management of patients with sustained hypo, normo- and hypercapnia, and examining the impact of $PaCO_2$ on days 1 and 2 with subsequent outcomes in patients with ARDS. Our overarching hypotheses were that altered arterial CO_2 tensions were prevalent in ARDS, and that these alterations in CO_2 tension exerted effects on patient outcomes, in the LUNG SAFE patient cohort.

Methods

Study Design, Patients, and Data Collection

The detailed methods and protocol for data collection have published elsewhere [14]. LUNG SAFE was an international (49 countries), multicenter (459 ICUs in 435 hospitals), prospective cohort study, with a 4-week enrollment window in the winter season in both hemispheres [14]. National and site coordinators (***Appendix 1***) obtained ethics committee approval, and either patient consent or ethics committee waiver of consent as appropriate. Additional methodological details are available in the Online Supplemental.

Patients admitted to a study ICU that underwent invasive or non-invasive ventilation were enrolled in LUNG SAFE. Exclusion criteria were: (1) age<16 years; and (2) inability to obtain informed consent (where required). Following enrolment, patients were evaluated daily for acute hypoxemic respiratory failure (AHRF), and if this condition was present, patients were classified as having ARDS based on whether or not they fulfilled all of the Berlin criteria [14].

Given the study focus on early $PaCO_2$ management in patients with ARDS, we restricted the study population to patients that fulfilled ARDS criteria within 48 hours of onset of AHRF. All data were recorded for each patient at the same time each day, normally as close as possible to 10 AM. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis.

Data Definitions and Statistical analyses

For the purposes of this analysis the following definitions were applied on day 1 of ARDS: hypocapnia ($PaCO_2$ < 35mmHg), normocapnia ($PaCO_2$ 35-45mmHg) and hypercapnia ($PaCO_2$ > 45mmHg). Patients were considered to have sustained hypo, normo- and hypercapnia if their $PaCO_2$ remained in the same category on day 2 as it was on day 1 following ARDS onset. Because base excess was not collected in LUNG SAFE, we estimated this parameter applying Henderson-Hasselbalch equation, based on pH and $PaCO_2$ measures [15]. Progression of ARDS severity was defined at the second day of ARDS and classified as: resolved (no fulfillment of Berlin ARDS criteria), improvement (improvement of ARDS class severity from day 1 to day 2), stable (no change in ARDS class severity), worsened (worsening of ARDS class severity from day 1 to day 2). For certain analyses, we dichotomized patients based on a PaO_2/FiO_2 (PF ratio) of 150 mmHg, and termed these groups mild-moderate ARDS and moderates-severe ARDS respectively. Other data definitions are in the online supplement and/or have been previously reported [14,16,17].

Categorical data are reported as counts and percentages, while continuous data are reported as mean and standard deviation or median and interquartile range, according to the symmetry of data distribution. To assess differences among three groups (sustained hypo, normo- and hypercapnia) we performed chi-squared test (or Fisher exact test) for discrete variables, analysis of variance (ANOVA) (or Kruskal-Wallis test) for continuous variables. Bonferroni correction was applied to determine significance in the setting of multiple comparisons. Chi-square test (or Fisher exact test), Student's T-test (or Wilcoxon Mann Whitney test) were used to assess differences between groups in discrete and continuous distributions of parameters, respectively. The same approach was used to assess differences among groups in a subset of patients with control mechanical ventilation during the first day of ARDS.

Locally estimated scatterplot smoothing (LOESS) method was used to inspect the relationship between hospital mortality and $PaCO_2$, minute ventilation and acid-base parameters (base excess, pH) measured on day 1 of ARDS in patients with sustained hypo-, normo- or hypercapnia. We applied generalized linear mixed models (logistic-link function and binomial distribution) with random intercept for taking into account the correlation among patients within the same ICU of enrolment, in order to assess relationship between hospital and ICU mortality and factors associated with CO_2 management, considering all possible confounders (demographic characteristics, illness severity and ventilator setting measured at the first day of ARDS, resolution of ARDS). Results were reported as odds ratio (OR) with 95% confidence interval (CI). The independent predictors were identified through a stepwise regression approach. This approach combines forward and backward selection methods in an iterative procedure (with a significance level of 0.05 both for entry and retention) to select predictors in the final multivariable model.

Propensity score matching method was applied to evaluate the possible impact of sustained normocapnia versus sustained hypercapnia on main outcomes (mortality, ventilation free days and duration of mechanical ventilation (MV)) in patients with ARDS. The matching algorithm used was the greedy method, and patients were matched (1:1 match without replacement), using a caliper of 0.2 standard deviation of the logit of the propensity score and the similarity of the matched groups was assessed by the standardized differences of each independent variable used in the propensity score estimation. A standardized difference of less 0.10 was considered as indicator of negligible imbalance between groups. Statistical significance of the difference in the ventilation free days and in the duration of MV was evaluated with Wilcoxon signed-rank test, while for difference in proportions of deaths we applied McNemar's test. Survival probability in these matched groups was

estimated using the Kaplan-Meier approach and assuming that patients discharged alive from hospital before 90 days were alive on day 90. Statistical difference between survival curves was assessed through Klein and Moeschberger test. The same approach was also apply to evaluate the possible impact of sustained normocapnia versus sustained hypocapnia on main outcomes.

All p-values were two-sided, with p-values <0.05 considered as statistically significant. Statistical analyses were performed with R, version 3.5.2. (R Project for Statistical Computing, http://www.R-project.org) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Of the 3,022 (10.4%) patients that fulfilled ARDS criteria in the LUNG SAFE cohort, the 2,813 patients that developed ARDS in the first 48 hours were managed with either invasive (n=2,377) or non-invasive (n=436) mechanical ventilation [***Figure e1***] constituted the study population.

Prevalence of hypo and hypercapnia

On day 1 of ARDS, 551 (19.6%, 95%CI: 18.1-21.1) patients were hypocapnic, 1,018 (36.2%, 95%CI: 34.4-38.0) were normocapnic, and 1,214 (43.2%, 95%CI: 41.3-45.0) were hypercapnic [***Figure e1***]. The $PaCO_2$ varied with ARDS severity; hypercapnia was more frequent in patients with moderate-severe ARDS (PF ratio<150 mmHg), and by type of ventilation, with hypocapnia more frequent in non-invasively ventilated patients [***Figure 1***, ***Supplemental Table e1***]. More severe hypercapnia ($PaCO_2$ ≥60 mmHg) was less common, occurring in 14.3% (95%CI: 13.0-15.6) of patients, of whom (146/402) 36.3% (95%CI: 31.6-41.0) had severe ARDS. Median $PaCO_2$ on day 1 was 43 mmHg (IQR: 36.0-51.9). By day 2, the frequency of normocapnia had increased while the frequency of hypo-, and hypercapnia (particularly severe hypo- and hypercapnia) had decreased.

Sustained hypo-, normo- and hypercapnia

Prevalence: Sustained hypocapnia was seen in 252 (9.3%, 95%CI: 8.2-10.4), sustained normocapnia in 544 (20.0%, 95%CI: 18.5-21.5) and sustained hypercapnia in 654 (24.1%, 95%CI: 22.5-25.7) patients [***Supplemental Figure e1***]. Patients with sustained hypercapnia had a higher prevalence of COPD, a lower frequency of immune incompetence, liver failure, and more pneumonia and less trauma as ARDS risk factors [***Table 1***]. Sustained hypocapnia

was more frequent in middle income countries, while sustained hypercapnia was more frequent in European countries. A sub-analysis, confined to patients in which mechanical ventilation was controlled demonstrated that hypocapnia was present in 12.7% (95%CI: 10.4-15.0) of patients under controlled ventilation [***Supplemental Table e2***].

Illness Severity: ARDS severity profile was highest in patients with sustained hypercapnia, with lower PF ratio and lung compliance compared to patients with sustained normocapnia or hypocapnia [***Table 2***]. In contrast, non-pulmonary SOFA scores were significantly higher in patients with sustained hypocapnia. PF ratio improved by day 2 in patients with sustained hypo-, normo- and hypercapnia, although PF ratio remained significantly lower in patients with sustained hypercapnia [***Supplemental Table e3***]. In patients with PF ratio < 150 mmHg, peak and plateau pressures were significantly higher in patients with sustained hypercapnia [***Figure 2 A-C***].

Ventilatory Management: The proportion of patients undergoing controlled mechanical ventilation was significantly lower in patients with sustained hypocapnia [***Table 2***]. Day 1 tidal volumes were significantly lower in sustained hypercapnia, while respiratory rates and minute volumes were significantly higher in sustained hypocapnia patients [***Table 2; Figure 2 D-F***]. PEEP levels were higher, while the proportion receiving protective mechanical ventilation was higher, in patients with sustained hypercapnia on both day 1 and 2 of ARDS [***Table 2 and e3***]. The use of neuromuscular blockade, of prone positioning, and of any adjunct were all highest in patients with sustained hypercapnia [***Table 2***].

Outcomes: There were no differences between the groups in regard to the evolution of ARDS from day 1 to day 2 [***Table 3***]. There were no between group differences in the length of ICU or hospital stay, in ICU or hospital mortality or in the limitation of life sustaining measures in the ICU [***Table 3***].

LOESS analyses of the relationship between unadjusted mortality risk and day 1 $PaCO_2$ showed increased mortality risk with more severe degrees of hypocapnia [***Figure 3A***]. There was an increase in mortality risk with increasing base deficit [***Figure 3B***], with decreasing pH [***Figure 3C***], and with increasing minute ventilation [***Figure 3D***].

Multivariable analyses of the factors associated with hospital mortality in these patients identified age, pH, respiratory rate, immunocompromised status, lack of adjunct use, and non pulmonary SOFA score, mechanical ventilation, PEEP and total respiratory rate as independently associated with outcome. The same predictors were found for ICU mortality, with the addition of PF ratio (<150 mmHg; ≥150 mmHg). $PaCO_2$, both as a continuous variable and dichotomized by category (sustained hypo-, normo- or hypercapnia) was not associated with ICU or hospital mortality in these analyses, either in the whole population or when dichotomized by PF ratio of 150 [***Table 4, Supplemental Table e4***].

In a propensity matched analysis, there were no differences between the sustained normocapnia and hypercapnia groups in regard to the duration of invasive mechanical ventilation, the length of ICU or hospital stay, ICU (32 vs 32%, respectively) or hospital mortality (36 vs 36%, respectively) or in the limitation of life sustaining measures in the ICU [***Table 5 and Supplemental Table e5***]. A Kaplan-Meier analysis of hospital survival showed no significant between group differences [***Figure 4A***].

In a propensity matched analysis, there were no overall differences between the sustained normocapnia and hypocapnia groups in regard to the duration of invasive mechanical ventilation, the length of ICU or hospital stay, ICU (33 vs 39%, respectively) or hospital mortality (39 vs 44%, respectively) or in the limitation of life sustaining measures in the ICU [***Table 6 and Supplemental Table e6***]. Of concern, ICU mortality was significantly higher in patients with mild to moderate ARDS receiving sustained hypocapnia (38%) versus sustained

normocapnia (27%) [***Table 6***]. In a subsequent multi-variate analysis restricted to patients with sustained normocapnia and sustained hypocapnia and with PF ratio ≥150 mmHg, lower PCO_2 was associated with increased ICU and hospital mortality [***Table e7***]. A Kaplan-Meier analysis of hospital survival showed no significant between group differences [***Figure 4B***].

DISCUSSION

Both hypo- and hypercapnia were prevalent on days 1 and 2 of ARDS, with sustained hypo- and hypercapnia present in a significant minority of patients. Patients with sustained hypercapnia had more severe ARDS than patients with sustained normocapnia or hypocapnia. Of concern, patients with ARDS managed with hypocapnia and normocapnia received less protective mechanical ventilation, with higher tidal and minute volumes and higher respiratory rates the 'cost' of maintaining normocapnia/hypocapnia in these patients. We did not find any evidence in our patient cohort for a direct effect – beneficial or harmful - of hypercapnia. In contrast, we did find evidence for potential harm with hypocapnia in patients with mild to moderate ARDS receiving sustained hypocapnia.

Protective ventilation using lower tidal volumes reduces mortality in ARDS patients [2,3]. In the absence of clinical trials examining the effects of hypercapnia independent of changes in ventilatory strategy, the potential for hypercapnia to impact on outcome – either for benefit or harm – remains a source of controversy. There is substantial data from preclinical models demonstrating potentially beneficial effects including suppressive effects of hypercapnia on the pro-inflammatory response to injury [11,13,18-26], potent anti-oxidant effects [27], and also potentially harmful effects including reduced wound healing [10], reduced neutrophil and macrophage phagocytosis and reduced bacterial killing [9].

In the clinical context, a secondary analysis of the ARMA trial [2] found an association between the presence and severity of hypercapnic acidosis on day 1 and lower mortality in patient that received traditional – but not protective – tidal volume ventilation [28]. In

contrast, Nin et al found that a $PaCO_2$ of over 50mmHg in patients with moderate-severe ARDS during the first 48 hours was associated with a higher ICU mortality in a secondary analysis of three non-interventional cohort studies, and suggested that this 'severe' hypercapnia could no longer be considered 'safe' [29]. A number of small clinical studies of 'induced' or 'permitted' hypercapnia in other settings, such as patients undergoing pancreaticoduodenal surgery [30], or pulmonary lobectomy [31] suggest that hypercapnia is well tolerated, and may have some beneficial effects.

In the LUNG SAFE cohort, while milder degrees of hypercapnia were prevalent in early ARDS, and the proportion of patients with permissive hypercapnia increased with greater ARDS severity, median arterial CO_2 tension remained in the normal range at all 3 levels of ARDS severity. We specifically wished to examine patients with sustained conditions in order to determine any potential impact on management and/or outcome. Patients with sustained hypercapnia had more severe ARDS, with worse oxygenation and higher airway pressures. Pulmonary causes of ARDS, particularly pneumonia, were highest in this group. The ventilatory management of patients with sustained hypercapnia did differ from the other groups, with more patients receiving controlled ventilation, muscle paralysis and protective lung ventilation strategies that resulted in lower tidal and minute ventilation. Despite these patients having more severe ARDS, crude mortality rates were comparable to that seen in the sustained normocapnia and hypocapnia groups.

These data suggest that many physicians are reluctant to allow hypercapnia to facilitate lower tidal volumes in patients with ARDS. Indeed, ongoing concerns regarding hypercapnia may constitute a barrier to the institution of protective lung ventilation strategies by

clinicians. The 'cost' of this is illustrated by the fact that patients managed with normocapnia received less protective lung ventilation.

The potential for hypocapnia to exert deleterious effects in the critically ill is long recognized [13,25], with potentially harmful effects in ARDS first suggested in 1971 [32]. Hypocapnia *per se* may directly injure the lung *via* several mechanisms, including increased lung permeability and edema [12], decreased compliance [33] potentially mediated via surfactant inhibition [34], and potentiation of acute inflammation [11,35,36]. In experimental models, many of these adverse effects can be ameliorated by normalizing alveolar CO_2 [12,34,35,37]. Hypocapnia can attenuate hypoxic pulmonary vasoconstriction thereby increasing intrapulmonary shunt [38]. The potential for hypocapnia to worsen brain injury [7,39] and other acute systemic organ injury [25] is also increasingly recognized. Hypocapnia may also be associated with higher mortality in patients with ARDS because high tidal volume ventilation (usually used to achieve hypocapnia) directly causes lung injury.

In the LUNG SAFE cohort, we found that hypocapnia was prevalent, with approximately 1 in 5 patients being hypocapnic on day 1 of ARDS and 1 in 10 having sustained hypocapnia. These patients had less severe ARDS, with better oxygenation and lower peak and plateau pressures. In contrast, non-pulmonary SOFA scores were significantly higher in patients with sustained hypocapnia, while pneumonia was less common, suggesting a different pattern of ARDS, with perhaps greater systemic involvement.

Of concern, fewer patients with sustained hypocapnia received protective ventilation, and these patients received higher tidal and minute volumes and higher respiratory rates, which constitutes the 'ventilatory cost' of hypocapnia. The rationale for these patients receiving hypocapnia was not clear, with pH being highest in this group, suggesting compensation for

metabolic acidosis was not a factor. Hypocapnia was more prevalent and more severe in patients receiving non-invasive ventilation, and in patients from middle income countries, both factors that have been associated with higher mortality risk in the LUNG SAFE cohort [16,40]. While respiratory drive may have played a role in driving hypocapnia in some of these patients, 12.7% of patients under controlled ventilation had sustained hypocapnia suggesting that their clinicians may have been providing unnecessarily high stress and strain to the lungs of these patients. This potentially could have led to the increased mortality in hypocapnic patients.

We conducted a number of different analyses to examine the potential for a role for CO2 tension on patient outcome from ARDS, including LOESS modelling, multivariate analyses and propensity matched analyses. The findings across these analyses regarding hypercapnia were quite consistent, in that no link between elevated CO2 tension and outcome was found. Our findings of a lack of a direct effect of hypercapnia on outcomes in this cohort should provide some reassurance regarding the safety of hypercapnia in patients with ARDS.

In contrast, we did find evidence for potential harm with hypocapnia in patients with mild to moderate ARDS receiving sustained hypocapnia compared to normocapnia. ICU mortality was significantly higher in patients with a PF ratio ≥ 150 mmHg at day 1 of ARDS in patients with sustained hypocapnia. A multivariate analysis restricted to patients with sustained normocapnia and sustained hypocapnia and with PF ≥150 mmHg, found that lower PCO_2 was associated with increased ICU and hospital mortality. This supports the findings in the propensity matched analysis, suggesting this finding is robust. The higher frequency of mild-moderate ARDS in hypocapnic patients may explain why this effect was not detected in patients with PF < 150 mmHg. Hypocapnia was more frequent in patients receiving non-

invasive ventilation, which has been associated with worse outcomes in the LUNG SAFE cohort [16], suggesting the need for caution regarding hypocapnia in patients with ARDS.

This study has several limitations. While we instituted a robust data quality control program in which all centers were requested to verify data that appeared inconsistent or erroneous, we did not have access to the source data for the patients in the enrolling ICUs, and it is possible that not all patients with ARDS in participating centers were enrolled. We cannot make causal inferences for any associations seen, given the observational nature of our study. Our dataset comprises daily arterial blood gas and FiO_2 data, taken at a standardized time each morning. It is possible that these data do not properly reflect the spectrum of FiO_2 use and PaO_2 data over the course of that day. It is possible that clinicians could have reduced FiO_2 on the basis of the arterial blood gas analyses, thereby reducing exposure time. Given this, in these analyses, we focused on patients that were hypo-, normo- and hypercapnic on both days 1 and 2 of ARDS. Lastly, our assumption that inpatients at day 90 survived to hospital discharge is a further limitation.

In conclusion, both hypo- and hypercapnia were prevalent in early ARDS in the LUNG SAFE cohort. Patients with ARDS receiving sustained hypercapnia had more severe ARDS and received more protective mechanical ventilation, while hypocapnia was more frequent and severe in patients receiving non-invasive ventilation. There was no evidence for benefit or harm with hypercapnia in our cohort. In contrast, ICU mortality was higher in patients with mild to moderate ARDS receiving sustained hypocapnia, suggesting the need for caution regarding ARDS patients with sustained hypocapnia.

FIGURE LEGENDS

Figure 1. Density probability functions of $PaCO_2$ in study population (n=2,813) stratified by PF ratio and by mechanical ventilation, at day 1 (Panel A, C) and at day 2 (Panel B, D) of ARDS.

Figure 2. Relationship between ARDS severity and ventilator variables at day 1 of ARDS in patients with sustained hypocapnia, sustained normocapnia and sustained hypercapnia. **Panel A.** Boxplot of peak inspiratory pressure. **Panel B.** Boxplot of plateau pressure. **Panel C.** Boxplot of driving pressure. **Panel D.** Boxplot of tidal volume. **Panel E.** Boxplot of total respiratory rate. **Panel F.** Boxplot of minute ventilation.

Notes:

[1]p< 0.05 sustained hypocapnia versus sustained normocapnia (Bonferroni's correction)

[2]p< 0.05 sustained hypocapnia versus sustained hypercapnia (Bonferroni's correction)

[3]p< 0.05 sustained normocapnia versus sustained hypercapnia (Bonferroni's correction)

Figure 3. LOESS curves of the relationship between hospital mortality and $PaCO_2$ and acid-base parameters in patients with sustained hypocapnia, sustained normocapnia and sustained hypercapnia, stratified by ARDS severity.

Panel A. relationship between hospital mortality and PaCO2 at day 1 of ARDS. **Panel B.** relationship between hospital mortality and base excess at day 1 of ARDS. **Panel C.** relationship between hospital mortality and pH at day 1 of ARDS. **Panel D.** relationship between hospital mortality and minute ventilation at day 1 of ARDS.

Figure 4. Propensity matched analyses of mortality rates.

Panel A. Survival probability during hospital stay in matched sample (n=550) between sustained normocapnia and sustained hypercapnia.

Panel B. Survival probability during hospital stay in matched sample (n=374) between sustained normocapnia and sustained hypocapnia.

Notes

1. Kaplan Meier's approach assumed as censored those patients discharged alive before day 90.
2. The number of patients at risk reported at the bottom of the figure is referred to as the end of the corresponding day.

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Table 5. Management factors and main outcomes in matched sample with sustained normocapnia and sustained hypercapnia.

Parameter	Sustained normocapnia	Sustained hypercapnia	p-value
N	275	275	-
Tidal volume (ml/kg IBW), mean ± SD	7.68 ± 1.88	7.39 ± 2.02	0.0297
Plateau pressure (cmH_2O), mean ± SD	23.01 ± 6.11	24.55 ± 6.46	0.9429
Driving pressure (cmH_2O), mean ± SD	14.70 ± 5.31	15.51 ± 6.15	0.6787
PEEP (cmH_2O), mean ± SD	8.18 ± 2.89	8.71 ± 3.35	0.0460
Minute ventilation (l/min), mean ± SD	9.71 ± 3.11	9.31 ± 3.38	0.1011
PIP (cmH_2O), mean ± SD	27.40 ± 9.56	27.12 ± 8.56	0.9113
Total respiratory rate (breaths/min), mean ± SD	20.84 ± 6.27	20.52 ± 6.34	0.5182
Base excess (mEq/l), mean ± SD	-3.55 ± 5.07	3.72 ± 6.59	<.0001
FiO_2, median [IQR]	0.60 [0.45-0.80]	0.60 [0.40-0.80]	0.3913
P_aO_2 / FiO_2 < 150 mmHg, n (%)	133 (48.36)	124 (45.09)	0.4437
Outcomes			
Duration of invasive mechanical ventilation (days), median [IQR]			
All patients	8.0 [4.0-17.0]	10.0 [5.0-20.0]	0.4364
Survivors at ICU discharge	8.0 [4.0-15.0]	9.0 [4.0-19.0]	0.7836
Length of stay in ICU (days), median [IQR]			
All patients	11.0 [6.0-21.0]	12.0 [7.0-24.0]	0.2516
Survivors at ICU discharge	11.0 [7.0-21.0]	12.0 [7.0-25.0]	0.9710
Length of stay in hospital (days), median [IQR]			
All patients	18.0 [10.0-35.0]	20.0 [11.0-39.0]	0.6996
Survivors at hospital discharge	27.0 [15.0-43.0]	25.0 [14.0-45.0]	0.7376
ICU mortality, n (%)			
All patients	87 (31.64)	88 (32.00)	1.0000
P_aO_2/FiO_2 < 150 mmHg at day 1	51 (38.35)	45 (36.29)	0.5235
Hospital mortality*, n (%)			
All patients	98 (35.64)	99 (36.13)	1.0000
P_aO_2/FiO_2 < 150 mmHg at day 1	54 (40.60)	48 (38.71)	0.5572
Limitation of life sustained measures in ICU, n (%)	60 (21.82)	68 (24.73)	0.4705

Abbreviation: FiO_2: fraction of inspired oxygen; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; P_aO_2: partial pressure arterial oxygen; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure;
** For 1 patient with sustained hypercapnia, vital status was missing.*

Note 1: sustained normocapnia was defined as 35 ≤ P_aCO_2 < 45 mmHg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as P_aCO_2 ≥ 45 mmHg during the first 48 hours from ARDS onset.

Note 2: statistical tests accounted for the matched nature of the sample (paired t-test or Wilcoxon signed rank test for continuous variables, McNemar's test for dichotomous variables).

Table 6. Management factors and main outcomes in matched sample with sustained normocapnia and sustained hypocapnia.

Parameter	Sustained normocapnia	Sustained hypocapnia	p-value
N	187	187	-
Tidal volume (ml/kg IBW), mean ± SD	7.69 ± 1.93	8.11 ± 2.15	0.0511
Plateau pressure (cmH_2O), mean ± SD	22.38 ± 5.33	21.23 ± 5.19	0.8746
Driving pressure (cmH_2O), mean ± SD	14.55 ± 4.50	13.63 ± 4.10	0.7822
PEEP (cmH_2O), mean ± SD	7.57 ± 2.55	7.61 ± 2.65	0.9153
Minute ventilation (l/min), mean ± SD	9.72 ± 3.50	11.05 ± 3.93	0.0009
PIP (cmH_2O), mean ± SD	24.31 ± 10.06	24.44 ± 8.57	0.9003
Total respiratory rate (breaths/min), mean ± SD	20.49 ± 6.41	22.85 ± 6.21	0.0002
Base excess (mEq/l), mean ± SD	-1.22 ± 4.60	-6.05 ± 5.18	<.0001
FiO_2, median [IQR]	0.50 [0.40-0.80]	0.50 [0.40-0.70]	0.4830
P_aO_2 / FiO_2 < 150 mmHg, n (%)	69 (36.90)	72 (38.50)	0.8358
Outcomes			
Duration of invasive mechanical ventilation (days), median [IQR]			
All patients	8.00 [4.00-16.00]	10.00 [6.00-18.00]	0.1248
Survivors at ICU discharge	7.00 [4.00-16.00]	10.00 [5.00-18.00]	0.4289
Length of stay in ICU (days), median [IQR]			
All patients	10.00 [6.00-18.00]	12.00 [7.00-21.00]	0.4339
Survivors at ICU discharge	10.00 [6.00-18.00]	13.00 [7.00-22.00]	0.5953
Length of stay in hospital (days), median [IQR]			
All patients	19.00 [10.00-34.00]	19.00 [10.00-34.00]	0.9749
Survivors at hospital discharge	26.00 [16.00-43.00]	27.00 [15.50-39.50]	0.7547
ICU mortality, n (%)			
All patients	61 (32.62)	72 (38.50)	0.2780
P_aO_2/FiO_2 < 150 mmHg at day 1	29 (42.03)	28 (38.89)	0.7744
P_aO_2/FiO_2 ≥ 150 mmHg at day 1	32 (27.12)	44 (38.26)	0.0410
Hospital mortality*, n (%)			
All patients	72 (38.50)	81 (44.26)	0.2660
P_aO_2/FiO_2 < 150 mmHg at day 1	30 (43.48)	33 (46.48)	0.5488
P_aO_2/FiO_2 ≥ 150 mmHg at day 1	42 (35.59)	48 (42.86)	0.1102
Limitation of life sustained measures in ICU, n (%)	51 (27.27)	50 (26.74)	1.0000

Abbreviation: FiO_2: fraction of inspired oxygen; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; P_aO_2: partial pressure arterial oxygen; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure;

** For 1 patient with sustained hypercapnia, vital status was missing.*

Note 1: sustained normocapnia was defined as 35 ≤ P_aCO_2 < 45 mmHg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as P_aCO_2 ≥ 45 mmHg during the first 48 hours from ARDS onset.

Note 2: statistical tests accounted for the matched nature of the sample (paired t-test or Wilcoxon signed rank test for continuous variables, McNemar's test for dichotomous variables).

Table 1. Main characteristics of study population stratified by condition (sustained hypocapnia, sustained normocapnia and sustained hypercapnia).

Parameter	Sustained hypocapnia	Sustained normocapnia	Sustained hypercapnia	p-value
Patients, n (%)				
All	252 (17.38)	544 (37.52)	654 (45.10)	-
Enrolled in European high income countries	96 (11.85)	302 (37.28)	412 (50.86)	-
Enrolled in non-European high income countries	64 (17.68)^	150 (41.44)	148 (40.88)^	-
Enrolled in middle income countries	92 (33.09)^#	92 (33.09)	94 (33.81)^	-
Comparison among Areas, p-value	<.0001	0.0948	<.0001	
Age (years), mean ± SD	62.36 ± 16.38	60.55 ± 16.67	61.61 ± 16.30	0.3724
Males, n (%)	151 (59.92)	340 (62.50)	422 (64.53)	0.4199
BMI (kg/m^2), median [IQR]	24.84 [22.15-28.58]	25.81 [22.68-30.42]	26.93 [22.86-31.49]*†	<.0001
Clinical recognition of ARDS, n (%)				
At baseline	88 (34.92)	160 (29.41)	208 (31.80)	0.2873
During ICU stay	155 (61.51)	322 (59.19)	402 (61.47)	0.6889
ARDS less than 24 hours	51 (20.24)	114 (20.96)	98 (14.98)†	0.0180
Chronic disease§, n (%)				
COPD	21 (8.33)	80 (14.71)*	260 (39.76)*†	<.0001
Diabetes mellitus	50 (19.84)	116 (21.32)	151 (23.09)	0.5297
Immune-incompetence (all-types)	72 (28.57)	113 (20.77)*	111 (16.97)*	0.0005
Chronic cardiac failure	17 (6.75)	48 (8.82)	80 (12.23)*	0.0244
Chronic renal failure	30 (11.90)	54 (9.93)	63 (9.63)	0.5847
Chronic liver failure	17 (6.75)	24 (4.41)	12 (1.83)*†	0.0010
Risk factors for ARDS, n (%)				
None	14 (5.56)	46 (8.46)	64 (9.79)	0.1241
Only non-pulmonary	46 (18.25)	133 (24.45)	80 (12.23)†	<.0001
Only pulmonary	157 (62.30)	289 (53.13)*	424 (64.83)†	0.0001
Both	35 (13.89)	76 (13.97)	86 (13.15)	0.9075
Risk factors for ARDS§, n (%)				
Pneumonia	162 (64.29)	282 (51.84)*	447 (68.35)†	<.0001
Extra-pulmonary sepsis	47 (18.65)	94 (17.28)	92 (14.07)	0.1511
Aspiration of gastric contents	36 (14.29)	78 (14.34)	73 (11.16)	0.2028
Pancreatitis	11 (4.37)	10 (1.84)	8 (1.22)*	0.0097
Pulmonary vasculitis	2 (0.79)	4 (0.74)	4 (0.61)	0.9186
Trauma	7 (2.78)	44 (8.09)*	11 (1.68)†	<.0001
Inhalation	6 (2.38)	10 (1.84)	14 (2.14)	0.8691
Pulmonary contusion	6 (2.38)	30 (5.51)	17 (2.60)†	0.0137
Burn	0 (0.00)	1 (0.18)	2 (0.31)	1.0000
Non cardiogenic shock	15 (5.95)	35 (6.43)	38 (5.81)	0.9004
Drowning	0 (0.00)	0 (0.00)	1 (0.15)	1.0000
Drug overdose	5 (1.98)	9 (1.65)	12 (1.83)	0.9427
Blood transfusion	6 (2.38)	30 (5.51)	19 (2.91)†	0.0272
Other risk factors	5 (1.98)	18 (3.31)	11 (1.68)	0.1648
ICU characteristics				
Academic hospital, n (%)	181 (76.37)	412 (77.74)	467 (73.43)	0.2222
% of ICU on hospital beds, median [IQR]	2.47 [1.54-4.00]	2.61 [1.54-4.17]	2.60 [1.58-4.33]	0.6942
Beds per physician, median [IQR]	4.50 [3.00-9.40]	4.50 [2.67-9.00]	4.50 [2.67-9.00]	0.4817
Beds per nurse, median [IQR]	1.50 [0.94-2.00]	1.50 [1.00-2.00]	1.33 [1.00-2.00]	0.3995

Abbreviations: ARDS: acute respiratory distress syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; SD: standard deviation.
** p-value < 0.05, comparison with "Sustained hypocapnia" (Bonferroni correction).*
† p-value < 0.05, comparison with "Sustained normocapnia" (Bonferroni correction).
^ p-value < 0.05, comparison with "European high income countries" (Bonferroni correction).
 # p-value < 0.05, comparison with "non-European high income countries" (Bonferroni correction).
§ Sum of percentages is greater than 100%, because patient could have more than one chronic disease/risk factor.
Note 1: sustained hypocapnia was defined as P_aCO_2 < 35 mmHg during the first 48 hours from ARDS onset; sustained normocapnia was defined as 35 ≤ P_aCO_2 < 45 mmHg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as P_aCO_2 ≥ 45 mmHg during the first 48 hours from ARDS onset.
Note 2: For categorical data, statistical difference among groups was tested with Chi-Square or Fisher exact test, according to number of expected cases. For continuous data, statistical difference among groups was tested with ANOVA or Kruskal-Wallis test based on Normal data distribution.

Table 2. Illness severity (on day 1 of ARDS) and ventilatory management in patients with sustained hypocapnia, sustained normocapnia and sustained hypercapnia

Parameter	Sustained Hypocapnia (n=252)	Sustained Normocapnia (n=544)	Sustained Hypercapnia (n=654)	p-value
Illness Severity				
Gas exchange				
P_aO_2/FiO_2 (mmHg), mean ± SD	172.05 ± 64.51	177.29 ± 66.17	151.08 ± 63.97*†	<.0001
P_aO_2/FiO_2 < 150 mmHg, n (%)	103 (40.87)	218 (40.07)	347 (53.06)*†	<.0001
P_aO_2/FiO_2 < 100 mmHg, n (%)	39 (15.48)	82 (15.07)	171 (26.15)*†	<.0001
SpO_2 (%), median [IQR]	96.0 [94.0-98.0]	96.0 [94.0-99.0]	96.0 [93.0-98.0]*†	<.0001
P_aCO_2 (mmHg), mean ± SD	29.54 ± 3.62	39.56 ± 2.65	60.72 ± 15.33	N/A
pH, mean ± SD	7.40 ± 0.10	7.37 ± 0.09*	7.29 ± 0.12*†	<.0001
SOFA scores, mean ± SD				
SOFA score	9.45 ± 3.74	8.47 ± 3.74*	8.86 ± 3.88	0.0217
Adjusted SOFA score	9.46 ± 4.02	8.76 ± 3.88	9.02 ± 4.04	0.0511
Non-pulmonary SOFA score	6.62 ± 3.62	5.76 ± 3.71*	5.81 ± 3.74*	0.0242
Adjusted non-pulmonary SOFA score	6.49 ± 4.06	5.79 ± 3.88*	5.74 ± 3.96*	0.0192
Component – Respiration	2.79 ± 0.69	2.76 ± 0.70	3.04 ± 0.71*†	<.0001
Component – Coagulation	1.26 ± 1.41	0.92 ± 1.23*	0.90 ± 1.34*	0.0002
Component – Liver	0.79 ± 1.12	0.57 ± 0.97	0.41 ± 0.84*†	<.0001
Component – Cardiovascular	1.77 ± 1.72	1.82 ± 1.74	1.90 ± 1.76	0.4396
Component – Central nervous system	1.81 ± 1.67	1.68 ± 1.60	1.73 ± 1.72	0.7327
Component – Renal	0.82 ± 1.12	0.71 ± 1.11	0.73 ± 1.08	0.2912
Ventilatory Management				
Invasive mechanical ventilation, n (%)	190 (75.40)	474 (87.13)*	538 (82.26)	0.0002
Controlled ventilation, n (%)	102 (41.98)	308 (57.46)*	391 (61.29)*	<.0001
FiO_2, median [IQR]	0.50 [0.40-0.70]	0.50 [0.40-0.75]	0.60 [0.45-0.90]*†	<.0001
Set respiratory rate (breaths/min), mean ± SD	17.51 ± 6.06	17.77 ± 6.22	18.22 ± 6.76	0.3805
Total respiratory rate (breaths/min), mean ± SD	23.59 ± 6.34	20.83 ± 6.59*	21.29 ± 6.81*	<.0001
Tidal volume (ml/kg IBW), mean ± SD	8.04 ± 2.11	7.80 ± 1.89	7.37 ± 1.98*†	<.0001
High tidal volume (>8 ml/kg IBW), n (%)	102 (45.74)	186 (37.96)	176 (29.83)*†	<.0001
Dynamic compliance (ml/cmH_2O), mean ± SD	44.90 ± 54.98	39.47 ± 41.48	29.92 ± 21.03*†	<.0001
PEEP (cmH_2O), mean ± SD	7.54 ± 2.60	7.89 ± 2.84	8.70 ± 3.41*†	<.0001
PIP (cmH_2O), mean ± SD	23.31 ± 8.98	24.77 ± 9.11	27.51 ± 8.64*†	<.0001
Plateau pressure measured, n (%)	65 (25.79)	155 (28.49)	152 (23.24)	0.1167
Plateau pressure (cmH_2O), mean ± SD	21.29 ± 5.19	22.21 ± 5.92	25.07 ± 6.41*†	<.0001
Driving pressure (cmH_2O), mean ± SD	13.77 ± 4.19	13.88 ± 5.13	15.64 ± 6.30†	0.0234
Minute ventilation (l/min), mean ± SD	11.19 ± 4.01	9.74 ± 3.19*	9.46 ± 3.61*	<.0001
Standardized minute ventilation (l/min), median [IQR]	7.78 [6.16-9.74]	9.23 [7.53-11.21]*	13.10 [10.08-16.87]*†	<.0001
Use of adjunctive measures day1-day2, n (%)				
Non-invasive ventilation	64 (25.40)	80 (14.71)*	125 (19.11)	0.0013
Neuromuscular blockade	12 (4.76)	59 (10.85)*	149 (22.78)*†	<.0001
Recruitment maneuvers	30 (11.90)	76 (13.97)	118 (18.04)*	0.0350
Prone position	3 (1.19)	13 (2.39)	49 (7.49)*†	<.0001
ECMO	5 (1.98)	8 (1.47)	18 (2.75)	0.3063
Inhaled vasodilators	13 (5.16)	21 (3.86)	41 (6.27)	0.1726
HFOV	4 (1.59)	3 (0.55)	1 (0.15)*	0.0376

None of the above	144 (57.14)	336 (61.76)	297 (45.41)*†	<.0001

Abbreviations: ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; HFOV: high frequency oscillatory ventilation; IBW: ideal body weight; IQR: interquartile range [first and third quartile]; P_aCO_2: partial pressure arterial carbon dioxide; P_aO_2: partial pressure arterial oxygen; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure SD: standard deviation; SOFA: sequential organ failure assessment.

** p-value < 0.05, comparison with "Sustained hypocapnia" (Bonferroni correction).*

† p-value < 0.05, comparison with "Sustained normocapnia" (Bonferroni correction).

Note 1: sustained hypocapnia was defined as P_aCO_2 < 35 mmHg during the first 48 hours from ARDS onset; sustained normocapnia was defined as 35 ≤ P_aCO_2 < 45 mmHg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as P_aCO_2 ≥ 45 mmHg during the first 48 hours from ARDS onset.

Note 2: For categorical data, statistical difference among groups was tested with Chi-Square or Fisher exact test, according to number of expected cases. For continuous data, statistical difference among groups was tested with ANOVA or Kruskal-Wallis test based on Normal data distribution.

Table 3. Outcomes of patients with sustained hypocapnia, sustained normocapnia and sustained hypercapnia.

Parameter	Sustained Hypocapnia (n=252)	Sustained Normocapnia (n=544)	Sustained Hypercapnia (n=654)	p-value
Progression of ARDS (from day 1 to day 2)°				
Resolved ARDS	68 (27.31)	141 (26.16)	127 (19.48)*†	0.0067
Improvement ARDS severity	54 (21.69)	100 (18.55)	144 (22.09)	0.2975
No change ARDS severity	91 (36.55)	244 (45.27)	312 (47.85)*	0.0093
Worsened ARDS severity	36 (14.46)	54 (10.02)	69 (10.58)	0.1594
Duration of invasive mechanical ventilation (days), median [IQR]				
All patients	10.0 [6.0-18.0]	8.0 [4.0-15.0]*	9.0 [5.0-16.0]	0.0236
Survivors at ICU discharge	9.0 [5.0-18.0]	7.0 [4.0-14.0]	10.0 [5.0-16.0]†	0.0213
Length of stay in ICU (days), median [IQR]				
All patients	11.5 [7.0-20.0]	10.0 [6.0-19.0]	11.0 [6.0-20.0]	0.3576
Survivors at ICU discharge	11.5 [7.0-20.0]	10.0 [6.0-19.0]	11.0 [7.0-21.0]	0.3600
Length of stay in hospital (days), median [IQR]				
All patients	18.0 [10.0-34.0]	18.0 [10.0-33.5]	17.00 [9.0-31.0]	0.4023
Survivors at hospital discharge	26.0 [14.0-38.0]	23.0 [14.0-40.0]	22.0 [13.0-40.0]	0.7819
ICU mortality, n (%)				
All patients	94 (37.30)	160 (29.41)	220 (33.64)	0.0686
P_aO_2/FiO_2 < 150 mmHg at day 1 (n=668)	41 (39.81)	78 (35.78)	128 (36.89)	0.7831
P_aO_2/FiO_2 ≥ 150 mmHg at day 1 (n=782)	53 (35.57)	82 (25.15)	92 (29.97)	0.0607
Hospital mortality, n (%)				
All patients	106 (42.74)	187 (34.38)	245 (37.52)	0.0764
P_aO_2/FiO_2 < 150 mmHg at day 1 (n=668)	47 (46.08)	83 (38.07)	137 (39.48)	0.3780
P_aO_2/FiO_2 ≥ 150 mmHg at day 1 (n=782)	59 (40.41)	104 (31.90)	108 (35.29)	0.1956
Limitation of life sustained measures in ICU, n (%)	72 (28.57)	135 (24.82)	160 (24.46)	0.4200
By 48 hours from ARDS onset	13 (5.16)	22 (4.04)	28 (4.28)	0.7686

Abbreviations: ARDS: acute respiratory distress syndrome; FiO_2: fraction of inspired oxygen; ICU: intensive care unit; IQR: interquartile range [first and third quartile]; P_aO_2: partial pressure arterial oxygen.

** p-value < 0.05, comparison with "Sustained hypocapnia" (Bonferroni correction).*

† p-value < 0.05, comparison with "Sustained normocapnia" (Bonferroni correction).

° Progression of ARDS was not available for 10 patients (0.69%).

Note 1: sustained hypocapnia was defined as P_aCO_2 < 35 mmHg during the first 48 hours from ARDS onset; sustained normocapnia was defined as 35 ≤ P_aCO_2 < 45 mmHg during the first 48 hours from ARDS onset; sustained hypercapnia was defined as P_aCO_2 ≥ 45 mmHg during the first 48 hours from ARDS onset.

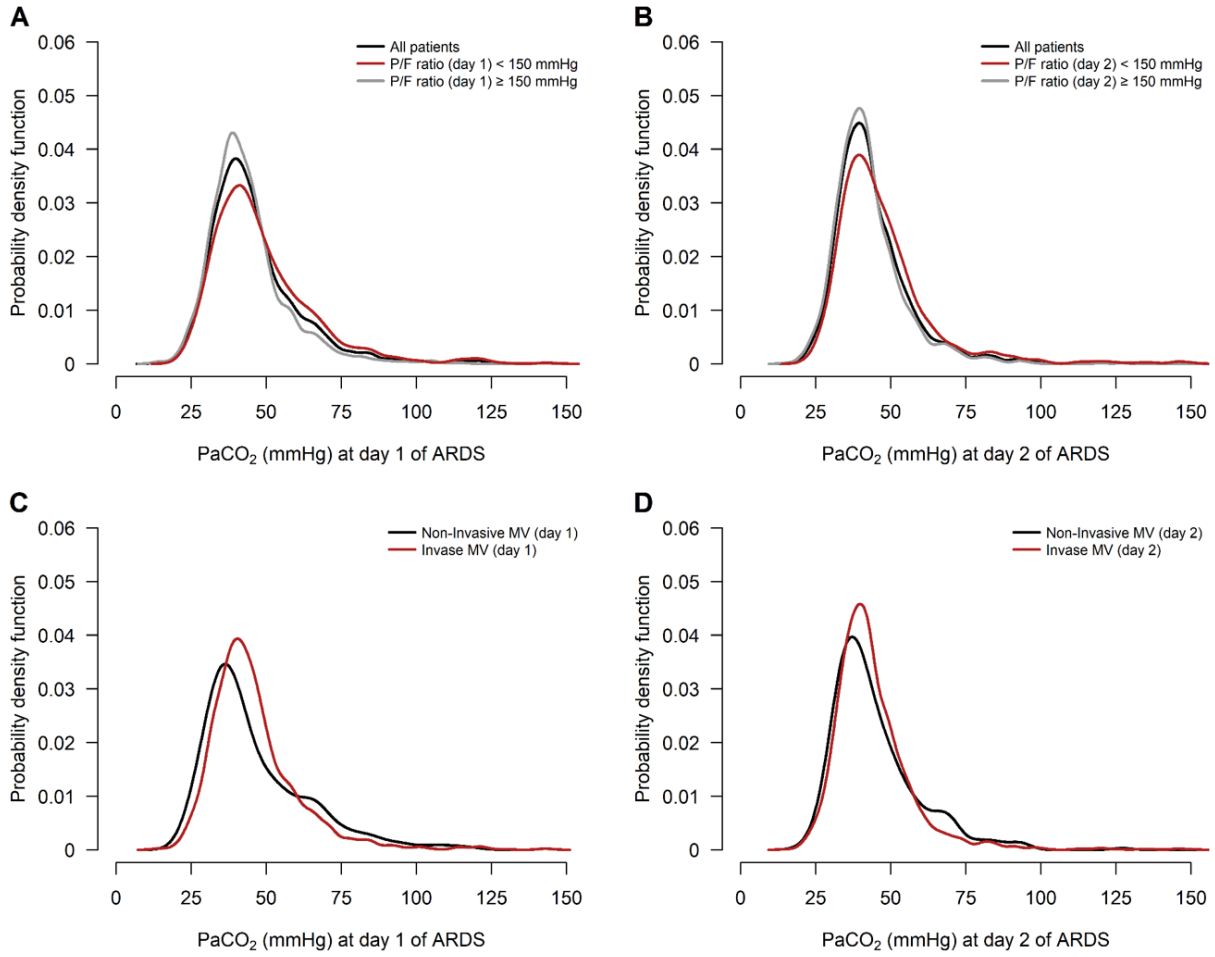
Note 2: For categorical data, statistical difference among groups was tested with Chi-Square. For continuous data, statistical difference among groups was tested with Kruskal-Wallis test.

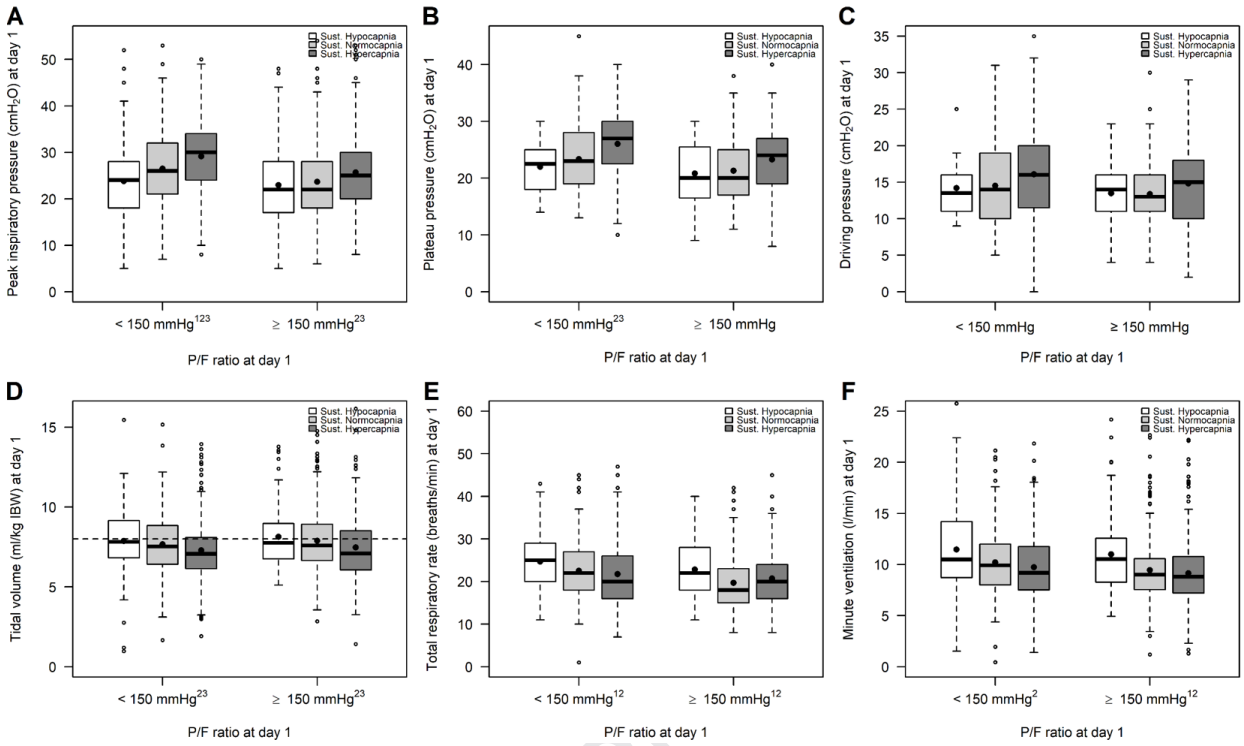
Table 4. Factors at day 1 of ARDS associated with hospital and ICU mortality (90 days) in patients with sustained hypocapnia, sustained normocapnia and sustained hypercapnia (n=1,450). Effects estimates evaluated by mixed-effects logistic regression model.

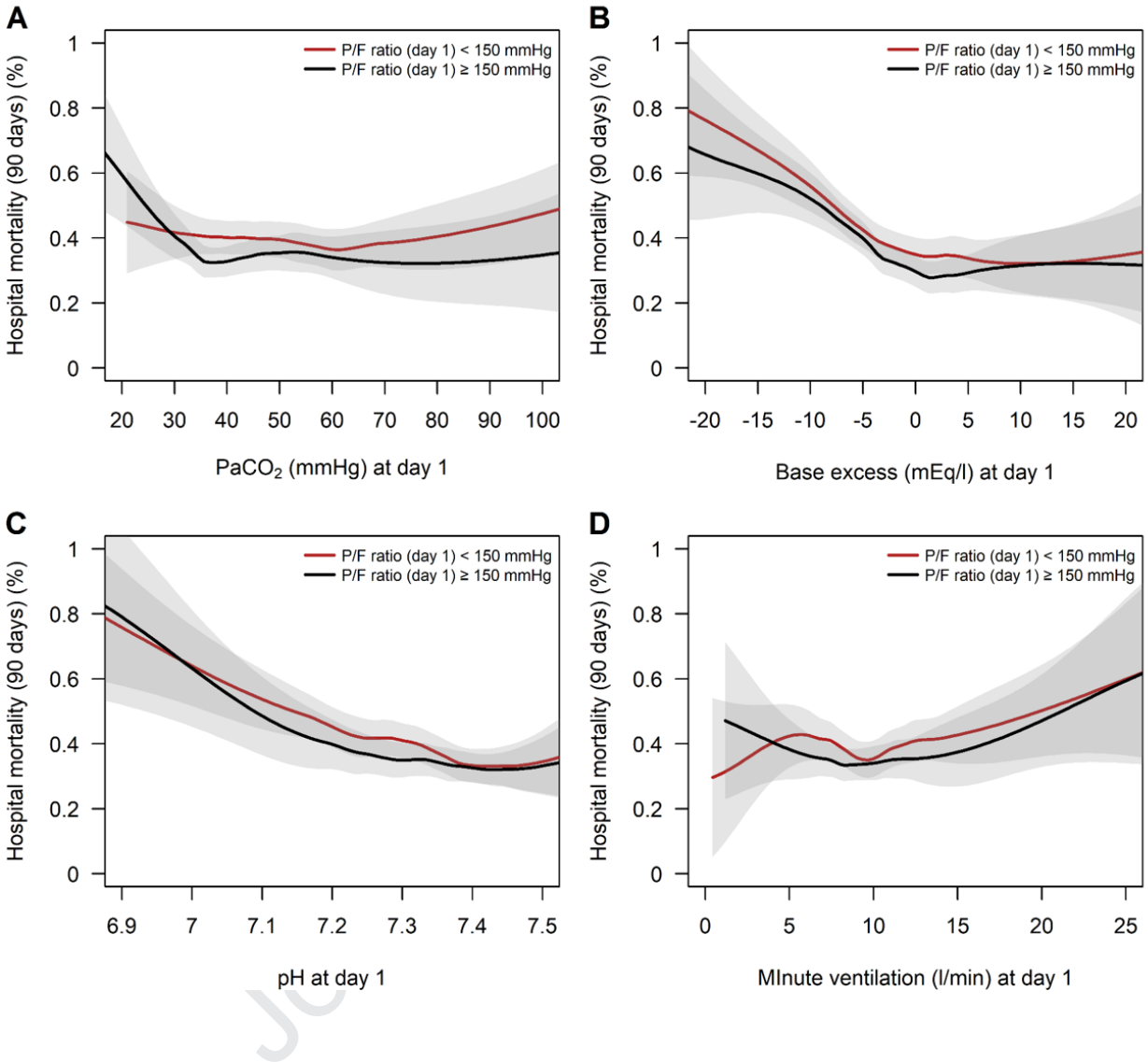
Parameters	Odds ratio (95% CI)	p-value
Outcome: hospital mortality – Model on 93.4% of study population (1,355 patients)		
Age (years)	1.028 (1.019 ; 1.035)	<.0001
BMI (kg/m^2)	0.980 (0.963 ; 0.997)	0.0211
Immune-incompetence (ref. No)	2.627 (1.938 ; 3.561)	<.0001
Chronic liver failure (ref. No)	3.815 (1.886 ; 7.717)	0.0002
ARDS risk factors (ref. None)	1.652 (1.020 ; 2.677)	0.0413
pH (0.01 unit)	0.976 (0.965 ; 0.987)	<.0001
Adjusted non-pulmonary SOFA score	1.085 (1.047 ; 1.124)	<.0001
Total respiratory rate (breaths/min)	1.043 (1.023 ; 1.063)	<.0001
PEEP (cmH_2O)	0.948 (0.908 ; 0.990)	0.0179
Adjunctive measures* during day 1 or day 2 (ref. No)	1.432 (1.079 ; 1.900)	0.0128
Invasive mechanical ventilation (ref. No)	1.504 (1.033 ; 2.192)	0.0333
Outcome: ICU mortality – Model on 93.8% of study population (1,360 patients)		
Age (years)	1.022 (1.013 ; 1.031)	<.0001
BMI (kg/m^2)	0.981 (0.963 ; 0.999)	0.0367
Immune-incompetence (ref. No)	2.229 (1.633 ; 3.043)	<.0001
Chronic liver failure (ref. No)	3.558 (1.768 ; 7.160)	0.0004
pH (0.01 unit)	0.976 (0.964 ; 0.987)	<.0001
Adjusted non-pulmonary SOFA score	1.088 (1.048 ; 1.129)	<.0001
Total respiratory rate (breaths/min)	1.043 (1.022 ; 1.065)	<.0001
PEEP (cmH_2O)	0.946 (0.903 ; 0.991)	0.0191
Adjunctive measures* during day 1 or day 2 (ref. No)	1.585 (1.176 ; 2.137)	0.0025
Non-invasive mechanical ventilation (ref. No)	0.634 (0.428 ; 0.940)	0.0233
PaO_2 / FiO_2 ≥ 150 mmhg (ref. < 150 mmHg)	0.755 (0.575 ; 0.991)	0.0432

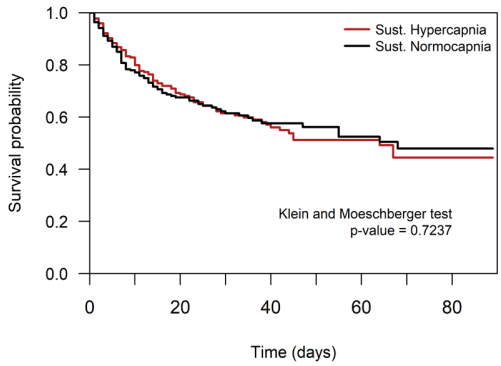
Abbreviations: BMI: body mass index; CI: confidence interval; ICU: intensive care unit; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; SOFA: sequential organ failure assessment.

** We considered as adjunctive measures performed during day 1 and/or day 2, the following procedures or treatment: neuromuscular blockade, recruitment maneuvers, prone position, extracorporeal membrane oxygenation (ECMO), inhaled vasodilators, high frequency oscillatory ventilation (HFOV).*

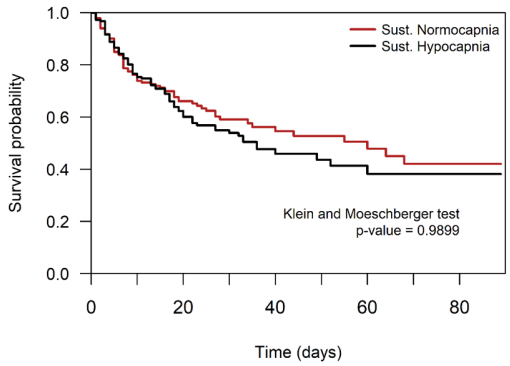

A
All patients
P/F ratio (day 1) < 150 mmHg
P/F ratio (day 1) ≥ 150 mmHg
Probability density function
0.06
0.05
0.04
0.03
0.02
0.01
0
0
25
50
75
100
125
150
PaCO2 (mmHg) at day 1 of ARDS
B
All patients
P/F ratio (day 2) < 150 mmHg
P/F ratio (day 2) ≥ 150 mmHg
Probability density function
PaCO2 (mmHg) at day 2 of ARDS
C
Non-Invasive MV (day 1)
Invase MV (day 1)
Probability density function
PaCO2 (mmHg) at day 1 of ARDS
D
Non-Invasive MV (day 2)
Invase MV (day 2)
Probability density function
PaCO2 (mmHg) at day 2 of ARDS




A
B
C
D
P/F ratio (day 1) < 150 mmHg
P/F ratio (day 1) ≥ 150 mmHg
Hospital mortality (90 days) (%)
PaCO2 (mmHg) at day 1
Base excess (mEq/l) at day 1
pH at day 1
MInute ventilation (l/min) at day 1



# at risk					
Sust. Hypercapnia	268	126	56	27	13
Sust. Normocapnia	271	118	52	28	13



# at risk					
Sust. Normocapnia	183	82	34	19	10
Sust. Hypocapnia	181	81	27	13	6