# Temporal Changes in the Epidemiology, Management, and Outcome from Acute Respiratory Distress Syndrome in European Intensive Care Units

TBD..... on behalf of the SOAP and ICON Investigators

**Abstract:**

**Background:** We assessed the temporal changes in the epidemiology and management of acute respiratory distress syndrome (ARDS) in European intensive care units (ICUs) included in two cohorts, the Sepsis Ocurrence in Acutely Ill Patients (SOAP, 2002) Study and the Intensive Care Over Nations (ICON, 2012) audit. We also investigated the association between ventilatory settings and outcome in these patients.

**Methods:** Data were collected prospectively from all ICU adult patients admitted between May 1 and 15, 2002 (SOAP study) and between May 8 and 18, 2012 (ICON audit). For this analysis, we considered only the ICON patients (n=4601) who were admitted to the same 24 European countries as in the SOAP study (n=3147). Patients were followed up for outcome until death, hospital discharge or for 60 days. Patients were identified as having ARDS according to the Berlin definitions.

**Results:** The occurrence of ARDS on admission to the ICU (5.0 vs. 5.3 %, p=0.866) and at any time during the ICU stay (10.4 vs. 10.8%, p=0.793) was similar in SOAP and ICON. In patients with ARDS (n=821), tidal volumes (Vt) were set at lower and positive end-expiratory pressures (PEEP) at higher levels in the later (ICON) than in the earlier (SOAP) cohort. Plateau pressure (Pplat) and driving pressure were higher in the SOAP study than in the ICON audit. ICU and hospital mortality rates were similar in patients with ARDS in the SOAP study (41.1 and 46.7 %) and the ICON audit (36.9 and 44.4 %). In a multivariable logistic regression analysis with in-hospital death as the dependant variable, higher airway pressures on the first day of mechanical ventilation (PEEP > 9 $cmH_2O$, driving pressure >13

$cmH_2O$, Pplat> 22 $cmH_2O$) but not Vt were independently associated with a higher risk of death in these patients. Higher driving pressure (>13 $cmH_2O$) was independently associated with a greater risk of in-hospital death in patients mechanically ventilated with high Vt (> 8.5 mL/Kg PBW) or lower PEEP levels (≤ 9 cm $H_2O$), and those with a greater degree of hypoxia ($PaO_2/FiO_2$ ≤180) and severe ARDS.

**Conclusion:** The frequency of and outcome from ARDS remained relatively stable between 2002 and 2012. Adoption of lower Vt and higher PEEP in ARDS increased overtime. Higher airway pressures on the first day of mechanical ventilation but not Vt were independently associated with a higher risk of death.

**Keywords:** Respiratory failure, ARDS, Airway pressures, Driving pressure.

## Introduction

Despite improvements in respiratory support, acute respiratory distress syndrome (ARDS) is still associated with mortality rates of between 40-60% and represents a high burden on intensive care resources [1-3]. The first definition of ARDS dates back to 1967 [4], however, it was only in 1994 that a broad consensus to define this complex syndrome was achieved [5]. These definitions were widely adopted by clinicians and researchers over the subsequent two decades. In 2012, an expert panel developed a new definition of ARDS, the Berlin Definition, stratifying the severity of ARDS according to the $PaO_2/FiO_2$ ratio at a minimum level of 5 $cmH_2O$ of positive end-expiratory pressure (PEEP) [6]. Several concepts related to the management of patients with ARDS have also changed over the last few decades, including use of a protective lung strategy [7], prone positioning, and extracorporeal membrane oxygenation (ECMO). Although several studies have assessed the epidemiology of, outcome from, and patterns of respiratory support in patients with ARDS [1, 2, 8-10], temporal changes have not been widely reported because of the use of different definitions and the considerable heterogeneity among cohorts. However, assessment of these changes is important to understand the evolution of the burden of the disease over time and to trace possible changes in clinical practice.

Several pulmonary and/or extrapulmonary factors can impact on the prognosis of ARDS [1, 8]. Importantly, mechanical ventilation, the main pillar in the management of patients with ARDS, has been recognized as a possible cause of lung damage or ventilator-induced lung injury (VILI), which may have a negative impact on outcome [11, 12]. Accumulating evidence suggests that adopting a protective lung strategy *per se* [7] does not preclude the development of VILI [13-16]. For example, in an analysis of data from ARDS patients enrolled in nine randomized controlled trials (RCTs), Amato et al., found that driving pressure, calculated as the difference between plateau pressure (Pplat) and PEEP, was the variable that correlated best to better outcome [16]. Assessment of the possible impact of

these ventilatory parameters on outcome may help in developing new concepts that may minimize VILI and improve survival.

The aim of this *post-hoc* analysis was to assess temporal changes in the epidemiology and management of ARDS in European ICUs included in two large observational studies, performed in 2002 (SOAP Study) [17] and 2012 (ICON audit) [18]. We also investigated the possible association between ventilatory settings on the first day of ARDS and outcome. Our hypothesis was that management of ARDS would change over time, especially with respect to ventilator management, and that ventilator settings would have an impact on outcome in these patients.

## Methods

The SOAP study was conducted in 24 European countries and included 3147 patients [17]. The ICON audit included 10,069 patients from 82 countries worldwide [18]. For the purposes of this comparison, we considered only the ICON patients who were admitted to the same 24 European countries as in the SOAP study and had physiologic and ventilation data recorded in the ICU (n=4601) (e-Table 1). For both studies, recruitment for participation was by open invitation, through national scientific societies, national and international meetings, and individual contacts. Participation was entirely voluntary, with no financial incentive. Institutional review board approval for both studies was obtained by the participating institutions according to local ethical regulations.

Participating ICUs (see e-Appendix) were asked to prospectively collect data on all adult patients admitted between May 1 and 15, 2002 for the SOAP study and between May 8 and 18, 2012 for the ICON audit. In both studies, patients who stayed in the ICU for < 24 h for routine postoperative surveillance were not included. Re-admissions of previously included patients were also not included. Data were collected daily during the ICU stay for a

maximum of 28 days. Patients were followed up for outcome data until death, hospital discharge or for 60 days.

Data were collected by the investigators using preprinted (for SOAP) and electronic (for ICON) case report forms. Data collection on admission included demographic data and comorbid diseases as well as source and reason for admission. Clinical and laboratory data for SAPS II [19] scores were reported as the worst values within 24 h after admission. The presence of microbiologically confirmed and clinically suspected infections was reported daily. A daily evaluation of organ function was performed using the sequential organ failure assessment (SOFA) score [20].

Due to the observational nature of the original studies [17, 18], the management of ARDS did not follow a predefined protocol. Values of tidal volume, PEEP, and Pplat corresponding to the most abnormal value of arterial $PO_2$ or arterial $O_2$ saturation were recorded and collected every 24 hours; the mode of mechanical ventilation was not recorded.

***Data management and quality control***

Detailed instructions explaining the aim of the study, instructions for data collection, and definitions were available for all participants before starting data collection and throughout the study periods. Additional queries were answered on a per case basis by the coordinating center during data collection. Data were further reviewed by the coordinating center for plausibility and availability of the outcome parameter, and any doubts were clarified with the center in question. There was no on-site monitoring. Missing data represented < 6% of the data collected for SOAP and 6.1% of the ICON data.

***Definitions***

Patients were identified as having ARDS if they presented all the following: (a) severe hypoxemia, as defined by a $PaO_2/FiO_2$ ratio less than 300 mmHg; (b) presence of bilateral

lung infiltrates on the chest radiograph; (c) no clinical evidence of heart failure; (d) absence of chronic obstructive pulmonary disease (COPD) or other chronic pulmonary disorders; (e) invasive mechanical ventilation. The severity of ARDS was defined according to the Berlin definitions into mild, moderate, and severe [6].

The average predicted body weight of male patients was calculated as equal to 50 + [0.91 (height in centimeters – 152.4)]; and that of female patients as equal to 45.5 + [0.91 (height in centimeters – 152.4)] [7]. We calculated driving pressure as the difference between Pplat and PEEP.

***Organ failure*** was defined as a sequential organ failure assessment (SOFA) score >2 for the organ in question.

***Outcome parameters***

The primary outcome parameter was in-hospital mortality within 60 days of admission to the ICU. Secondary outcome parameters included death in the ICU, ICU and hospital lengths of stay, and organ failure as assessed by the SOFA score.

***Statistical analysis***

All data were processed and analyzed in the Department of Intensive Care of Erasme Hospital, University of Brussels, in collaboration with Jena University Hospital, Jena, Germany. Data were analyzed using IBM® SPSS® Statistics software, v.21 for Windows (IBM, Somers, NY, USA).

Data are summarized using means with standard deviation, medians and interquartile ranges, or numbers and percentages. Difference testing between groups was performed using Student's t test, Mann–Whitney test, Chi square test or Fisher's exact test, as appropriate. The Kolmogorov–Smirnov test was used, and histograms and quantile–quantile plots were

examined to verify whether there were significant deviations from the normality assumption of continuous variables.

To determine the best cutoff point of Vt, PEEP, Pplat, driving pressure, and $PaO_2/FiO_2$ ratio on the first day of ARDS that may be associated with the increased risk of in-hospital death, a robust locally weighted scatter plot smoothing (LOWESS) method was applied (figure 1). The smoothing curves used a bandwidth of 0.7, a polynomial regression with 1 degree of freedom, and a tricubic weight function.

To evaluate the possible association between ventilatory parameters and outcome, we performed a multivariable logistic regression analysis with in-hospital death as the dependent variable in patients with ARDS. Covariates to be included in the final models was based on a univariate logistic regression analysis ($p<0.2$) of demographic variables (age and sex), comorbid conditions, severity scores on admission to the ICU (SAPS II and SOFA scores), mean fluid balance during the ICU stay, severity of respiratory failure according to the $PaO_2/FiO_2$ ratio on the first day of mechanical ventilation, in addition to Vt and respiratory rate and the study to which the patient belonged, i.e., SOAP or ICON. Colinearity between variables was ruled out before covariates were introduced in the model. Goodness of fit was tested using a Hosmer and Lemeshow test, and odds ratios (OR) with 95% confidence interval (CI) were computed. As driving pressure, Pplat, and PEEP are mathematically linked and were confirmed to be colinear ($r^2>0.6$), we constructed separate logistic regression models for each parameter including the previously mentioned parameters. The multivariable models were adjusted to the country of origin and the study period (ICON audit vs. SOAP study).

To further explore the association between driving pressure on outcome, multivariable logistic regression analyses were performed with in-hospital death as the dependent variable within subgroups of patients classified according to best cutoff-points of Pplat, PEEP, Vt and

$PaO_2/FiO_2$ on the first day of ARDS, and according to the severity of ARDS. Covariates considered for these analyses were SAPS II score, age, and the degree of hypoxia as assessed by the $PaO_2/FiO_2$ ratio. Pplat, and PEEP were included separately in the multivariable models for each subgroup.

No statistical adjustments were used for multiple testing. All reported p values are two-sided and a p value <0.05 was considered to indicate statistical significance.

## Results

### *Characteristics of the study groups*

The characteristics of patients included in both cohorts are given in Table 1. Patients included in the ICON audit (2012) were slightly older, more likely to be admitted for medical reasons than after surgical procedures, more likely to have had COPD prior to ICU admission, and had higher SAPS II and SOFA scores on ICU admission than those included in the SOAP study (2002). Shock due to any cause was more frequent on admission to the ICU in the ICON compared to the SOAP study groups (33.8 vs. 24.7, p<0.001), whereas the frequency of other risk factors for ARDS and PaO2/FiO2 was similar between the two cohorts.

### *Temporal differences in the epidemiology and characteristics of ARDS patients*

The occurrence of ARDS on admission to the ICU (5.0 vs. 5.3 %, p=0.866) and at any time during the ICU stay (10.4 vs. 10.8%, p=0.793) was similar in the SOAP and ICON patients. Up to 89% (SOAP) and 86% (ICON) of ARDS cases were reported to be moderate to severe (Table 2).

Patients with ARDS in the later period (ICON audit) were more commonly admitted to the ICU for medical reasons than after surgical interventions (Table 1), had greater SAPS II and SOFA scores on admission to the ICU, and were more likely to have had comorbid conditions prior to ICU admission than those with ARDS included in the earlier (SOAP

study) (Table 1). The degree of hypoxemia in patients with ARDS as assessed by the $PaO_2/FiO_2$ ratio was similar in the two studies (Table 1).
Patients with ARDS were younger, had greater severity of illness as evident from higher SAPS II and SOFA scores on admission to the ICU, and higher prevalence of risk factors for ARDS compared to those without ARDS, irrespective of the inclusion period (Table 1).

***Mechanical ventilation***

Ventilatory settings in patients who required mechanical ventilation in the SOAP study (n=2025) and ICON audit (n=2875) are shown in table 3. Respiratory rates were similar in the two cohorts. Tidal volumes were set at lower and PEEP values at higher levels in the later (ICON) than the earlier (SOAP) cohort, irrespective of the presence of ARDS (Figure 2). Pplat and driving pressure were higher in the SOAP study than in the ICON audit, irrespective of the presence of ARDS (Figure 2). Overall, tidal volumes were similar in patients with and those without ARDS, whereas airway pressures (PEEP, Pplat, and driving pressure) were higher in patients with ARDS than those without (Table 3).

***Morbidity and mortality***

The overall degree of organ dysfunction/failure as assessed by the SOFA scores and the incidence of organ system failures was higher in the ICON audit than in the SOAP study (Table S2). More patients in the SOAP study required mechanical ventilation on admission to the ICU (58.8 vs. 55.8 %, p=0.013) compared to the ICON audit, but the overall rates of mechanical ventilation were similar in the two cohorts throughout the ICU stay (Table S2). The frequency of non-respiratory organ failure and the need for renal replacement therapy was higher in patients with ARDS than in those without ARDS, irrespective of the study cohort. Although the overall infection rates were similar in the two cohorts, ICU-acquired infections were more common in the ICON than the SOAP cohorts, irrespective of the

presence of ARDS. Infections were more prevalent in patients with ARDS than those without, irrespective of the study cohort (Table 2).

The overall ICU and hospital mortality rates were similar in the SOAP study (18.5 and 23.7 %) and ICON audit (16.9 and 23.9%). Patients with ARDS had higher ICU and hospital mortality rates compared to those who did not (Table 2), irrespective of the study cohort. In patients with ARDS, ICU and hospital mortality rates were similar in the SOAP study (41.1 and 46.7 %) and the ICON audit (36.9 and 44.4 %). ICU lengths of stay were similar in the two cohorts. Hospital lengths of stay were longer in the SOAP study than ICON audit, irrespective of the presence of ARDS.

***Predictors of worse outcome in patients with ARDS***

In patients with ARDS, from both cohorts, patients who died in-hospital were older, had greater SAPS II and SOFA scores on admission to the ICU, more likely to have hematologic cancer and admitted after polytrauma, had higher incidence of shock due to any cause, and had lower $PaO_2/FiO_2$ on ICU admission day than survivors (Table S3). Non-respiratory organ system failure occurred more often in non-survivors than survivors (Table S4). The severity of ARDS was higher and the ICU and hospital lengths of stay shorter in non-survivors than in survivors. Airway pressures were higher and fluid balance was more positive in non-survivors than survivors. The initial tidal volume and respiratory rate were similar between survivors and survivors (Table 4).

In a logistic regression analysis with in-hospital death as the dependent variable in patients with ARDS, older age, greater SAPS II score, the presence of coagulation failure on admission to the ICU, higher mean fluid balance during the ICU stay, and lower $PaO_2/FiO_2$ were independently associated with greater risk of in-hospital death. Higher airway pressures on the first day of mechanical ventilation after establishing a diagnosis of ARDS (PEEP > 9 $cmH_2O$, driving pressure> 13 cm $H_2O$, Pplat> 22 cm $H_2O$) but not Vt or respiratory rate were independently associated with the risk of death in these patients (Table 5)

In subgroup analysis, higher driving pressure (> 13 cm $H_2O$) was independently associated with a greater risk of in-hospital death in patients who were mechanically ventilated with high Vt (> 8.5 mL/Kg PBW), patients with lower PEEP levels (≤ 9 cm $H_2O$), those with a greater degree of hypoxia ($PaO_2/FiO_2$ ≤180) and in severe ARDS (Figure 3).

**Discussion**

The main findings of our study are: 1) the incidence of ARDS in European ICUs did not change from 2002 to 2012 and morbidity and mortality rates were comparably high; 2) adherence to a lung protective strategy in mechanically ventilated patients with ARDS increased over time, with lower Vts and lower airway pressures (Pplat and driving pressure); 3) higher airway pressures on the first day of mechanical ventilation but not Vt were independently associated with a higher risk of death in these patients; 4) higher driving pressure (> 13 cm $H_2O$) was independently associated with greater risk of in-hospital death in patients mechanically ventilated with high Vt, lower PEEP levels, and those with a greater degree of hypoxia and severe ARDS.

In these two large European ICU cohorts [17, 18], performed 10 years apart, the incidence of ARDS remained relatively constant over time and ranged from 10.4 to 10.8% during the ICU stay. Similar to our observation, Bellani et al [2] reported that 10.4% of patients admitted to ICUs in 50 countries had ARDS during the ICU stay using the Berlin definitions [6]. Other studies [21-25] have reported the incidence of ARDS to vary largely between 3 and 29% according to the studied population and the applied definitions. Indeed, we previously reported the incidence of ARDS to be 12.6% from the SOAP study database [1] using the earlier European American Consensus criteria [5], which may overestimate the actual incidence of ARDS by including mild cases of respiratory dysfunction. Although we used the Berlin definitions to define ARDS [6], only patients requiring invasive mechanical ventilation were considered in our analysis due to the absence of precise data on non-invasive

mechanical ventilation. Therefore, the overall incidence of ARDS in our study may have been slightly underestimated. Nonetheless, both cohorts [17, 18] collected the same set of data using similar protocols. We also included data from patients admitted to ICUs from the same 24 countries in the two cohorts, so that temporal changes may be reliably investigated. To the best of our knowledge, our analysis is the first study to report temporal changes in the epidemiology and management of ARDS patients receiving mechanical ventilation in the ICU.

Our data confirm the persistently high morbidity and mortality rates in patients with ARDS. Likewise, previous literature has reported mortality rates ranging from 40 to 60 % in these patients [1-3]. ARDS represents a major burden to the health care system, which merits special attention of researchers and clinicians to improve outcome of this potentially lethal syndrome. Despite the increased adherence to a lung protective strategy in mechanically ventilated patients with ARDS observed in the more recent ICON audit [18] compared to the earlier SOAP study [17], mortality rates did not seem to improve accordingly. Other factors may, therefore, have played a role in determining the outcome in these patients. Indeed, we identified several factors such as older age, greater SAPS II score, and the presence of coagulation failure on admission to the ICU as being independently associated with a greater risk of in-hospital death. These factors have been also repeatedly reported in previous studies [1, 8] and reflect the severity of illness and the degree of organ dysfunction in these patients on admission to the ICU.

Fluid balance during the ICU stay was also identified as an independent risk factor of in-hospital death in our analysis. This suggests that fluid overload and the inability to excrete excess fluid intake may be associated with poor outcome in patients with ARDS, likely due to increased tissue edema and worsening of organ function. Fluid therapy may also be associated with several risks related to the type of fluid administered and confounded by the underlying pathophysiology with increased capillary permeability [26, 27] and associated

disorders such as sepsis and cardiovascular failure. In patients with acute lung injury, a randomized controlled study showed that although there was no significant difference in 60-day mortality, a conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation [28].

We found that higher Vt on the first day of mechanical ventilation was not associated with the risk of death in patients with ARDS. This may not be surprising as the increasing use of lower tidal volumes in the ICON audit decreased the median Vt in patients with ARDS included in the analysis (9 mL/Kg PBW), which may have masked the potential deleterious effects of high Vt observed in our previous analysis on the SOAP study database [1]. Airway pressures were also generally low, which may have outweighed the possible deleterious effects of high Vt. Low Vt remains, therefore, a main stay in the ventilator management of these patients as supported by the best available evidence [7].

In our study, higher airway pressures on the first day of mechanical ventilation after establishing the diagnosis of ARDS were independently associated with the risk of death in these patients. Indeed, Pplat is an important determinant of lung overdistention [29], is a good indicator of lung stress, [11] and higher levels are well correlated to the risk of barotrauma [30]. Therefore, limiting Pplat is a crucial component of protective lung ventilation. Excessive PEEP may also be harmful as it may increase static strain on the lung, especially in patients with limited lung recruitability [31]. Higher PEEP levels may also be used in the more severe cases to improve hypoxemia. Therefore, the confounding effect of severity of illness in our analysis cannot be excluded. Due to the extreme variability in the recruitable lung tissue in patients with ARDS [32], individual assessment may be important to optimize PEEP settings.

The potential deleterious influence of higher driving pressure on outcome in this analysis was observed in the subgroups of patients with ARDS who were mechanically ventilated with high Vt, lower PEEP levels, and those suffering from more hypoxia and severe ARDS.

Amato et al. demonstrated that driving pressure was the variable most strongly associated with mortality in a post-hoc analysis of RCTs of mechanically ventilated patients with ARDS [16]. Driving pressure >14 $cmH_2O$ was also reported to be associated with an increased risk of hospital mortality in patients with moderate and severe ARDS [8]. Another study showed that driving pressure was associated with risk of death in hypoxemic patients regardless of the results of the chest radiograph or the presence of ARDS [33]. We may speculate that patients subjected to low PEEP levels may exhibit potentially non-recruited lung areas, so that higher driving pressure may potentiate recruitment-derecruitment lung injury and subsequently aggravate VILI [34]. In ARDS patients subjected to relatively high Vt, driving pressure may lead to alveolar overdistention and potential lung damage. Patients with severe hypoxemia may also be more predisposed to the potential deleterious effects of higher driving pressure levels due to the preexisting severe lung pathology in these cases.

Although the current analysis included a large number of patients with ARDS participating in two similarly designed European cohort studies, 10 years apart, our study has some limitations. First, the multivariable analysis is limited by the variables included and the effect of other non-reported variables cannot be excluded. However, we adjusted for a large number of factors that are known to influence outcomes in patients with ARDS. Second, a cause-effect relationship between the risk factors we have reported and outcome cannot be ascertained due to the observational nature of the study. In this context, our data can be considered as hypothesis-generating that may help guide future RCTs on the subject. Third, colinearity between the various airway pressure parameters due to a mathematical link between these parameters precludes their inclusion in the same multivariable model. Fourth, ventilatory parameters were recorded at a fixed time point and may have changed during the day. Reporting these parameters also did not follow specific instructions to standardize the time of measurements within the respiratory cycle and the possible effect of spontaneous breathing cannot be fully excluded due to the observational nature of the study. Finally, our

observations may be limited by the absence of insensible water loss in our calculation of fluid balance and renal dysfunction and could have contributed to the higher fluid balance observed in non-survivors.

**Conclusion**

The incidence of and outcome from ARDS remained unchanged between 2002 and 2012. The adoption of lower Vt and higher PEEP in ARDS increased over time and lower driving pressure and Pplat were observed in patients with ARDS included in the more recent ICON audit than in the earlier SOAP study. Higher airway pressures on the first day of mechanical ventilation but not Vt were independently associated with a higher risk of death. The potential deleterious influence of higher driving pressure on outcome was observed in patients mechanically ventilated with high Vt, lower PEEP levels, and those suffering from more hypoxia and severe ARDS.

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**Figure Legends**

**Figure 1:** Relationship between initial ventilation parameters and hospital mortality in patients with ARDS. Robust locally weighted regression and smoothing (LOWESS) plot (bandwidth 2/3, 1 degree polynomial regression) of hospital mortality and tidal volume, driving pressure, plateau pressure, and end-expiratory pressure (PEEP).

**Figure 2:** Histograms with normality curves representing the tidal volumes, plateau pressures, and positive end-expiratory pressures (PEEP) during mechanical ventilation in patients with ARDS in the SOAP and ICON studies

**Figure 3:** Adjusted odds ratios of in-hospital death according to driving pressure (DP) > 13 cmH2O in patients with ARDS

Table 1 Basic characteristic of patients on admission to the ICU according to the study cohort and the presence of acute respiratory distress syndrome (ARDS)

| | SOAP Study | | | I | |
|---|---|---|---|---|---|
| | All | ARDS | No ARDS | All | |
| N | 3147 | 327 | 2820 | 4601 | |
| Age, years, mean (SD) | 61 (17) | 59 (17) | 61 (17)∬ | 62 (17)‡ | |
| Male, n (%) | 1820 (61.7) | 194 (59.3) | 1726 (62%) ∬ | 2766 (60.1) | 3 |
| Referring facility, n (%) | | | | | |
| ER/Ambulance | 913 (32.2) | 54 (18.5) | 859 (33.8) | 1644 (35.7) | 1 |
| Hospital floor | 793 (28) | 104 (35.6) | 689 (27.1) | 1328 (28.9) | 1 |
| OR/Recovery room | 784 (27.7) | 77 (26.4) | 707 (27.8) | 882 (19.2) | 7 |
| Other hospital | 345 (12.2) | 57 (19.5) | 288 (11.3) | 430 (9.3) | 6 |
| Other | - | - | - | 317 (6.9) | |
| Type of admission, n (%) | | | ∬ | ‡ | |
| Medical admission | 1759 (55.9) | 178 (54.4) | 1581 (56.1) | 3089 (67.1) | 3 |
| Elective surgery | 778 (24.7) | 58 (17.7) | 720 (25.5) | 758 (16.5) | |
| Emergency surgery | 610 (19.4) | 91 (27.8) | 519 (18.4) | 754 (16.4) | 7 |
| Severity scores, mean (SD) | | | | | |
| SAPS II score | 36.5(17.1) | 47.7 (17.6) | 35.21 (16.6)§§ | 43 (17.7)‡ | 51 |
| SOFA score, total | 5,1 (3.8) | 7.9 (4.4) | 4.8 (3.6)§§ | 6.6 (4.1)‡ | 9 |
| Comorbidities, n (%) | | | | | |
| COPD | 340 (10.8) | - | 340(12.1)§§ | 708 (15.4)‡ | |
| Non metastatic Cancer | 310 (9.9) | 34 (10.4) | 276 (9.8) | 476 (10.3) | |

| | | | | | |
|---|---|---|---|---|---|
| Heart failure, NYHA III-IV | 307 (9.8) | - | 307 (10.9)§§ | 470 (10.2) | |
| Diabetes, insulin dependent | 226 (7.2) | 18 (5.5) | 208 (7.4) | 426 (9.3)† | 4 |
| Cirrhosis | 121 (3.8) | 11 (3.4) | 110 (3.9) | 194 (4.2) | |
| Metastatic Cancer | 105 (3.3) | 9 (2.8) | 96 (3.4) | 158 (3.4) | |
| Hematologic Cancer | 69 (2.2) | 19 (5.8) | 50 (1.8)§§ | 120 ( 2.6) | |
| Chemotherapy | 25 (0.8) | 6 (1.8) | 19 (0.7)§§ | 117 (2.6)‡ | 2 |
| HIV | 8 (0.3) | 0 (0) | 8 (0.3)§§ | 24 (0.5) | |
| Risk factors for ARDS, n (%) | | | | | |
| Shock, any cause | 776 (24.7) | 160 (48.9) | 616 (21.8) §§ | 1557 (33.8) ‡ | 2 |
| Polytrauma | 177 (5.6) | 28 (8.6) | 149 (5.3) ∫∫ | 224 (4.9) | |
| Pancreatitis | 63 (2.0) | 12 (3.7) | 51 (1.8)§ | 80 (1.7) | |
| Near drowning | 6 (0.2) | 2 (0.6) | 4 (0.4) | 3 (0.1) | |
| Burns | 2 (0.1) | 2 (0.3) | 1 (0) | 7 (0.2) | |
| PaO2/FiO2, mean (SD) | 238 (126) | 164 (90) | 250 (127)§§ | 239 (126) | 1 |

ARDS: Acute respiratory distress syndrome, COPD: chronic obstructive pulmonary disease, ER: emergency room, SAPS: Simplified Acute Physiology Score, SOFA: Sequential Organ Failure Assessment, SD: standard deviation

All patients, SOAP vs. ICON: * p=0.05-0.01, † p=0.01-0.001, ‡ p<0.001.
Patients with ARDS, SOAP vs. ICON: ⎪ 0.05-0.01, ‖ p=0.01-0.001, ∫ p<0.001
Patients with ARDS vs. No ARDS (within the same study): ∫∫ 0.05-0.01, § p=0.01-0.001, §§ p<0.001
Patients with no ARDS, SOAP vs. ICON: ¶ 0.05-0.01, ¶¶ p=0.01-0.001, $ p<0.001

Table 2 ARDS and outcome parameters according to the study cohort

| | SOAP study | | | ICON audit | | |
|---|---|---|---|---|---|---|
| | All | ARDS | No ARDS | All | ARDS | |
| N | 3147 | 327 | 2820 | 4601 | 494 | |
| ARDS on ICU admission | | | | | | |
| Any ARDS | 166 (5.3) | 166 (50.8) | 0 (0) | 230 (5) | 230 (46.6) | |
| Mild | 28 ( 0.9) | 28 (8.6) | 0 (0) | 35 (0.8) | 35 (7.1) | |
| Moderate | 72 (7.8) | 72 (22) | 0 (0) | 91 (2) | 91 (18.4) | |
| Severe | 60 (1.9) | 60 (18.3) | 0 (0) | 104 (2.3) | 104 (21.1) | |
| ARDS any time | | | | | | |
| Any ARDS | 327 (10.4) | 327 (100) | 0 (0) | 494 (10.7) | 494 (100) | |
| Mild | 36 (1.1) | 36 (11) | 0 (0)§§ | 79 (1.7) | 79 (16.0) | |
| Moderate | 155 (4.9) | 155 (47.4) | 0 (0)§§ | 201 (4.4) | 201 (40.7) | |
| Severe | 136 (4.3) | 136 (41.6) | 0 (0)§§ | 214 (4.7) | 214 (43.3) | |
| Infection, n (%) | | | | | | |
| Before 48h | 898 (28.5) | 191 (58.4) | 707 (25.1)§§ | 1416 (30.8)* | 250 (50.6) ⌠⌠ | |
| ICU-acquired | 279 (8.9) | 56 (17.1) | 223 (7.9)§§ | 478 (10.4)* | 116 (23.5) ⌠⌠ | |
| Any time | 1177 (37.4) | 247 (75.5) | 930 (33) | 1894 (41.2) | 366 (74.1) | |
| Mortality, n (%) | | | | | | |
| ICU | 583 (18.5) | 134 (41.1) | 449 (15.9)§§ | 768 (16.9) | 179 (36.9) | |
| Hospital | 747 (23.7) | 151 (46.2) | 596 (21.1)§§ | 1058 (23.9) | 212 (44.4) | |
| Length of stay, days, median (IQR) | | | | | | |
| ICU | 3 (2-7) | 10 (4.5-21) | 3 (2-6)§§ | 3 (2-7) | 9 (4-18) | |
| Hospital | 15 (7-32) | 27 (11-55) | 14 (7-29)§§ | 11 (6-22) ‡ | 16 (7-34) ∫ | |

ARDS: *Acute respiratory distress syndrome, ICU: Intensive Care Unit,* SOFA: Sequential Organ Failure Assessment

All patients, SOAP vs. ICON: * p=0.05-0.01, † p=0.01-0.001, ‡ p<0.001.
Patients with ARDS, SOAP vs. ICON: ⎪ 0.05-0.01, ‖ p=0.01-0.001, ∫ p<0.001
Patients with ARDS vs. No ARDS (within the same study): ⌠ ⌠ 0.05-0.01, § p=0.01-0.001, §§ p<0.001
Patients with no ARDS, SOAP vs. ICON: ¶ 0.05-0.01, ¶¶ p=0.01-0.001, $ p<0.001

Table 3 Ventilatory parameters according to the study cohort and the presence of ARDS

| | SOAP Study | | | ICON Audi | |
|---|---|---|---|---|---|
| | All | ARDS | No ARDS | All | ARDS |
| | 2025 | 327 | 1698 | 2875 | 494 |
| Initial settings, mean (SD) | | | | | |
| Respiratory rate | 24 (10) | 26 (15) | 23 (8) | 25 (10) | 27(10) |
| PEEP, cm $H_2O$ | 4.9 (4.0) | 7.2 (4.4) | 4.4 (3.7)§§ | 6.4 (3)‡ | 7.3 (3.3) |
| Plateau pressure, cm $H_2O$ | 20.9 (6.9) | 22.7 (7.6) | 20.5 (6.7)§§ | 18.3 (7.2)‡ | 18.7 (7.7) ∫ |
| Tidal volume, mL/Kg PBW | 9.8 (2.6) | 9.7 (3.1) | 9.8 (2.5) | 8.7 (2.4)‡ | 8.5 (2.2) ∫ |
| Driving pressure, cm $H_2O$ | 14.7 (6.2) | 14.4 (6.5) | 14.8 (6.2) | 12.5 (5.6)‡ | 11.9 (.6) ∫ |
| Overall, mean (SD) | | | | | |
| Respiratory rate | 23 (9) | 25 (17) | 22 (6) | 24 (8) | 25 (7) |
| PEEP, cm $H_2O$ | 5.3 (3.5) | 7.9 (3.1) | 4.8 (3.3)§§ | 6.5 (2.6)‡ | 7.6 (2.6) |
| Plateau pressure, cm $H_2O$ | 23.6 (6.5) | 27 (6.3) | 20.5 (6.7)§§ | 20.7 (6.6)‡ | 23 (6.5) ∫ |
| Tidal volume, mL/Kg PBW | 10.3 (2.4) | 10.5 (2.7) | 10.2 (2.3) | 9.2 (2.2)‡ | 9.1 (1.9) ∫ |
| Driving pressure, cm $H_2O$ | 17.6 (5.8) | 18.9 (5.9) | 17.3 (17.3)§§ | 14.8 (5.4)‡ | 15.7 (5.2) ∫ |

PBW: Predicted body weight, PEEP: Positive end-expiratory pressure; SD: Standard Deviation,
Missing values: Respiratory rate SOAP 53 ICON 29; PEEP 167; 168; Plateau pressure 598; 818; Tidal volume IBW 309;459; Driving pressure 598; 868; PEEP mean167; 168; Plateau pressure mean 598; 818; Tidal volume mean IBW 309;459; Driving pressure mean 598; 868

All patients, SOAP vs. ICON: * p=0.05-0.01, † p=0.01-0.001, ‡ p<0.001.
Patients with ARDS, SOAP vs. ICON: ⎪0.05-0.01, ‖ p=0.01-0.001, ∫ p<0.001
Patients with ARDS vs. No ARDS (within the same study): ⌈ ⌈0.05-0.01, § p=0.01-0.001, §§ p<0.001
Patients with no ARDS, SOAP vs. ICON: ¶ 0.05-0.01, ¶¶ p=0.01-0.001, $ p<0.001

Table 4: Ventilatory settings and fluid balance in patients with ARDS according to in-hospital outcome

| | | In-hospital outcome | |
|---|---|---|---|
| | All | Alive | Dead |
| N | 811 | 439 | 363 |
| Initial settings, mean (SD) | | | |
| Respiratory rate | 26 ( 12) | 27 (9) | 26 (15) |
| PEEP, cm $H_20$ | 7.3 (3.8) | 6.7 (3.4) | 8 (4.1) |
| Plateau pressure, cm $H_2O$ | 20.4 (7.9) | 18.9 (7.2) | 22 (8.4) |
| Tidal volume, mL/Kg PBW | 9 (2.6) | 9.1 (2.9) | 8.8 (2.3) |
| Driving pressure, cm $H_2O$ | 13 (6.1) | 12.1 (2.9) | 14 (6.5) |
| Overall, mean (SD) | | | |
| Respiratory rate | 25 (12.1) | 25 (7) | 25 (17) |
| PEEP, cm $H_2O$ | 7.8 (2.8) | 7.3 (2.5) | 8.3 (3.1) |
| Plateau pressure, cm $H_2O$ | 24.6 (6.7) | 24 (6) | 26 (7.4) |
| Tidal volume, mL/Kg PBW | 9.7 (2.3) | 9.9 (2.4) | 9.5 (2.2) |
| Driving pressure, cm $H_2O$ | 17.1 (5.7) | 16.3 (5.4) | 18 (6) |

| | | | |
|---|---|---|---|
| Fluid balance, median (IQR) | | | |
| Admission day fluid balance | 1064 ([-200]-2721) | 850 ( [-394]-2356) | 1344([-290]-7275) |
| Fluid balance (72h) | 2046 ([-1373]-5989) | 1203 ([-2217]-4882) | 2870 ([-1845]-11704 |
| Fluid balance (96h) | 1790 ([-2821]-6684) | 499 ([-4099]-4882) | 3155 ([-822)-8105) |
| Total fluid balance | 1051 ([-5919]-7749) | -1185 ([-8822]-3841) | 3545 (-1845]-11704 |
| Median fluid balance/day | 113 ([-587]-970) | -128 ([-781]-415) | 605 ([-250]-1701) |

IQR: Interquartile range; PEEP: positive end-expiratory pressure; SD: standard deviation
Missing: Plateau pressure: 136; Tidal Volume: 34; Driving pressure: 138.

Table 5 Logistic regression analysis with in-hospital death as the dependent variable in patients with ARDS*

| | Odds Ratio (95% CI) | p-value |
|---|---|---|
| Age (per year) | 1.03 (1.01-1.04) | <0.001 |
| Male | 0.75 (0.51-1.11) | 0.148 |
| SAPS II (per point) | 1.04 (1.02-1.06) | <0.001 |
| Referring facility | - | - |
| ER/Ambulance | R | NA |
| Hospital Floor | 0,86 (0.52-1.40) | 0.538 |
| OR/Recovery Room | 0,78 (0.44-1.39) | 0.403 |
| Other Hospital | 0,77 (0.48-3.14) | 0.408 |
| Others | 1,23 (0.48-3.14) | 0.671 |
| Comorbidities | - | - |
| Solid cancer | | |
| No cancer | R | NA |
| Cancer, non-metastatic | 0.98 (0.53-1.184) | 0.963 |
| Cancer, metastatic | 2.04 (0.75-5.53) | 0.160 |
| Cirrhosis | 1.59 ( 0.63-4.03) | 0.321 |
| Hematologic cancer | 1.18 (0.46-3.03) | 0.732 |
| Steroids | 1.33 (0.61-2.90) | 0.472 |
| Polytrauma | 0.45 ( 0.19-1.08) | 0.073 |
| Organ failure on admission to the ICU | - | - |
| Coagulation failure | 3.98 (1.88-8.39) | <0.001 |
| Hepatic | 1.04 (0.54-2.02) | 0.900 |
| CNS | 0.85 (0.50-1.42) | 0.528 |
| Renal | 1.17 (0.74-1.84) | 0.508 |
| CVS | 0.84 (0.56-1.25) | 0.379 |
| $PaO_2/FiO_2$ (per 20 mmHg) | 0.99 (0.98-0.99) | 0.003 |
| Infection within 48 hours | 1.04 (0.66-1.64) | 0.862 |
| ICU acquired infections | 1.65 (0.96-2.85) | 0.072 |
| Fluid balance, mean (per 100 mL) | 1.04 (1.02-1.05) | <0.001 |

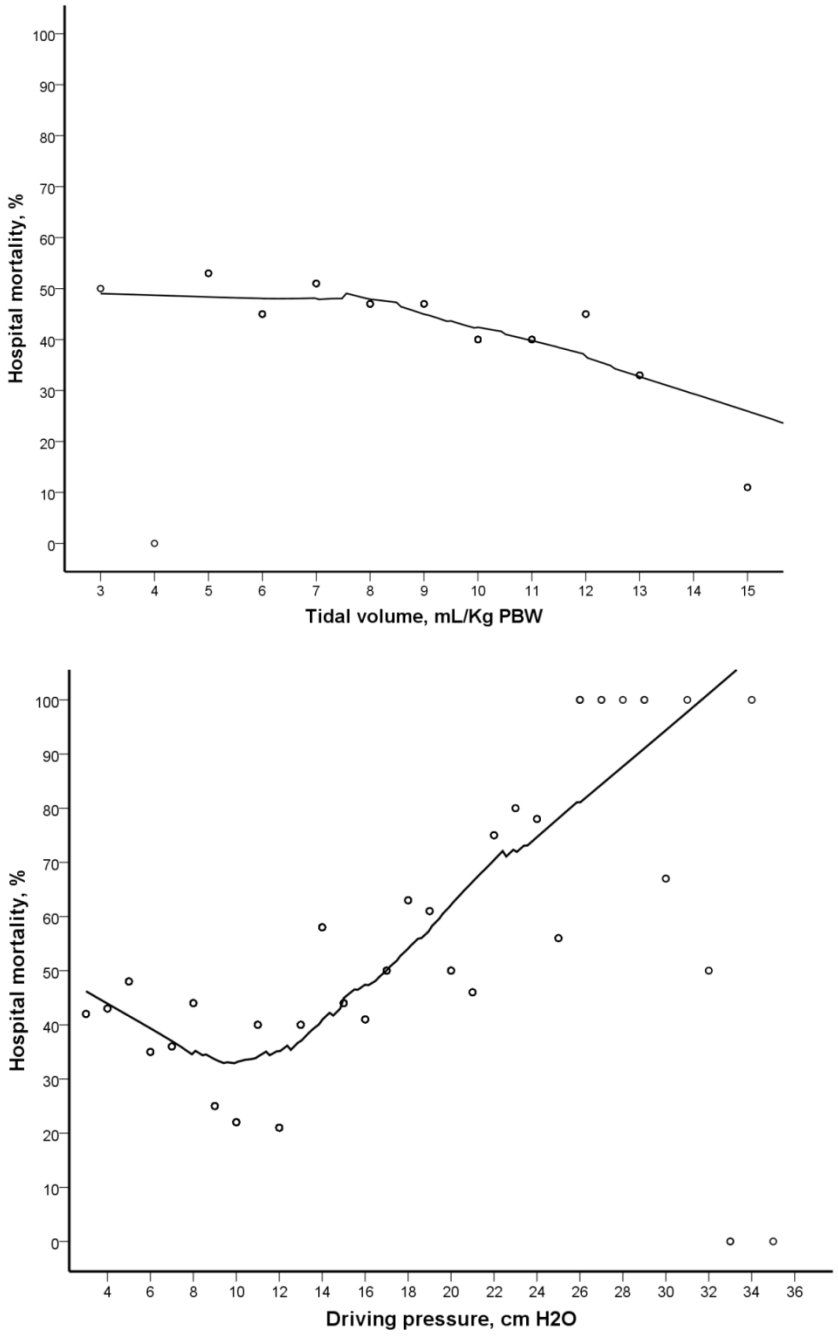
| | | |
|---|---|---|
| Initial ventilatory settings | - | - |
| Respiratory rate | 1.00 (0.99-1.02) | 0.685 |
| Tidal volume > 8.5 mL/kg PBW | 0.93 (0.64-1.35) | 0.687 |
| PEEP > 9 $cmH_2O$ † | 2.38 (1.54-3.67) | <0.001 |
| Driving pressure> 13 cm $H_2O$ † | 1.75 (1.14-2.68) | 0.010 |
| Plateau pressure> 22 cm $H_2O$ † | 2.21 (1.42-3.45) | <0.001 |

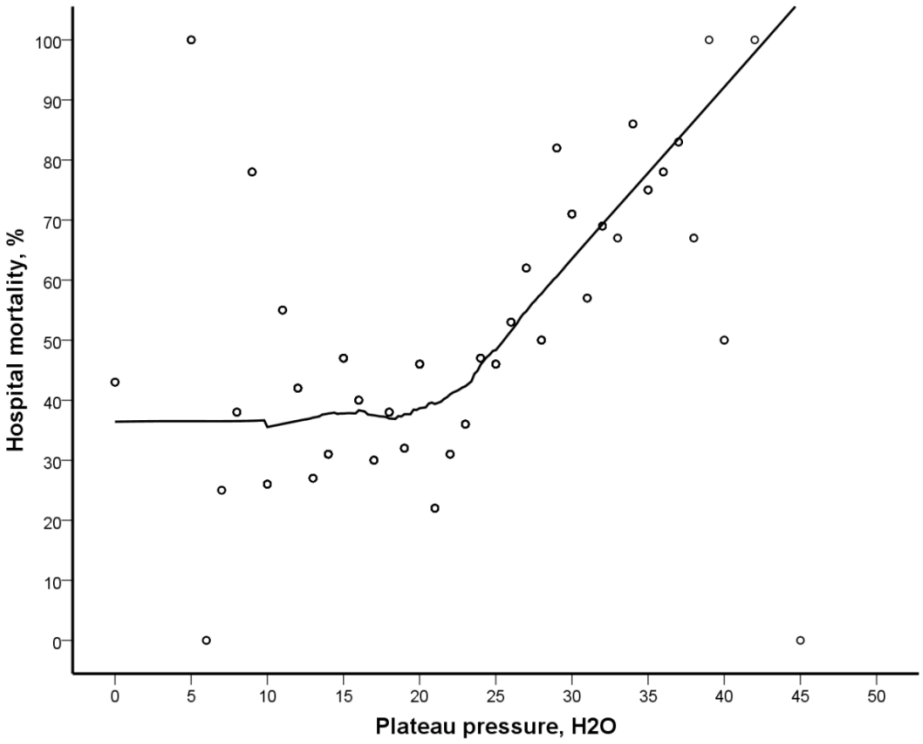
CI: Confidence interval, CNS: central nervous system, ER: emergency room, ICU: intensive care unit, PEEP: positive end-expiratory pressure, SAPS: Simplified Acute Physiology Score

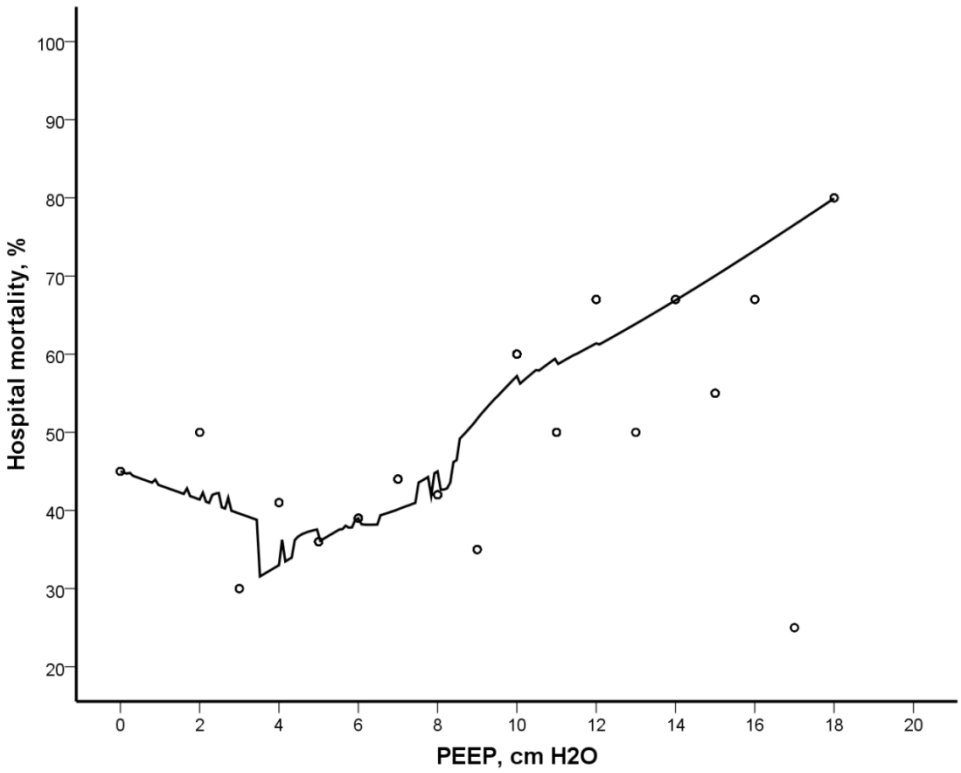
* Excluding 96 patients with missing values and adjusted for country and study cohort (SOAP vs. ICON). Covariate inclusion in the final models was based on a univariate logistic regression analysis ($p<0.2$) within the categories demographic variables (age and sex), comorbid conditions, severity of respiratory failure according to the $PaO_2/FiO_2$ ratio on the first day of mechanical ventilation, in addition to tidal volume and respiratory rate (Hosmer & Lemeshow goodness of fit Chi square: 9.93, $p=0.27$; Nagelkerke's $R^2 = 0.392$). Patients who were excluded from the multivariable analysis due to missing variables (n=69) had similar severity of respiratory failure as assessed by the $PaO_2/FiO_2$ ratio on the first day of mechanical ventilation and similar mortality rates compared to those who were included in the analysis.

† Introduced alternately in the different models due to colinearity. The displayed values refer to those considered in the model which includes the driving pressure as a covariate. Changes in the pressure parameters did not influence the significant p-values of the other covariates.

**Figure 1**


Hospital mortality, %
Tidal volume, mL/Kg PBW
Hospital mortality, %
Driving pressure, cm H2O


Hospital mortality, %
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
Plateau pressure, H2O


Hospital mortality, %
100
90
80
70
60
50
40
30
20
0
2
4
6
8
10
12
14
16
18
20
PEEP, cm H2O

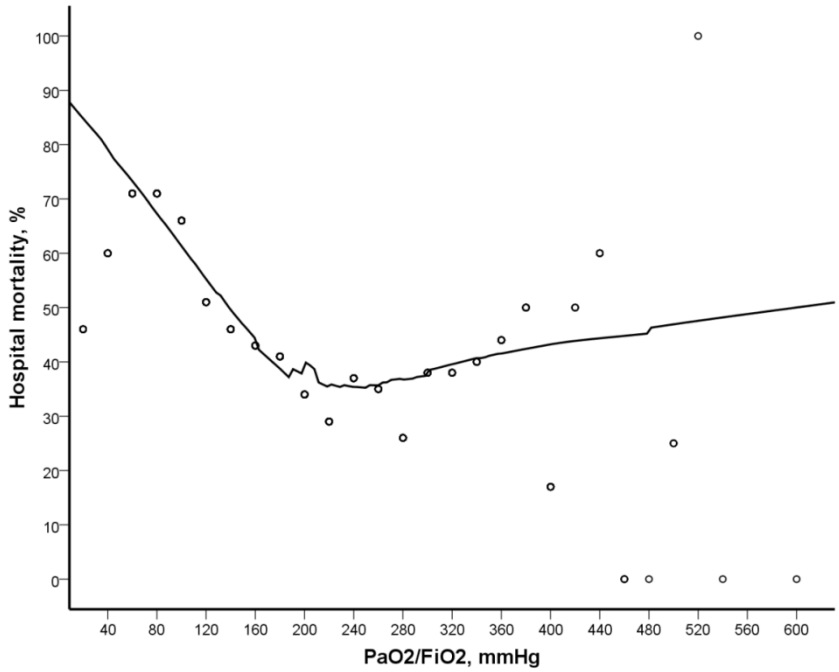
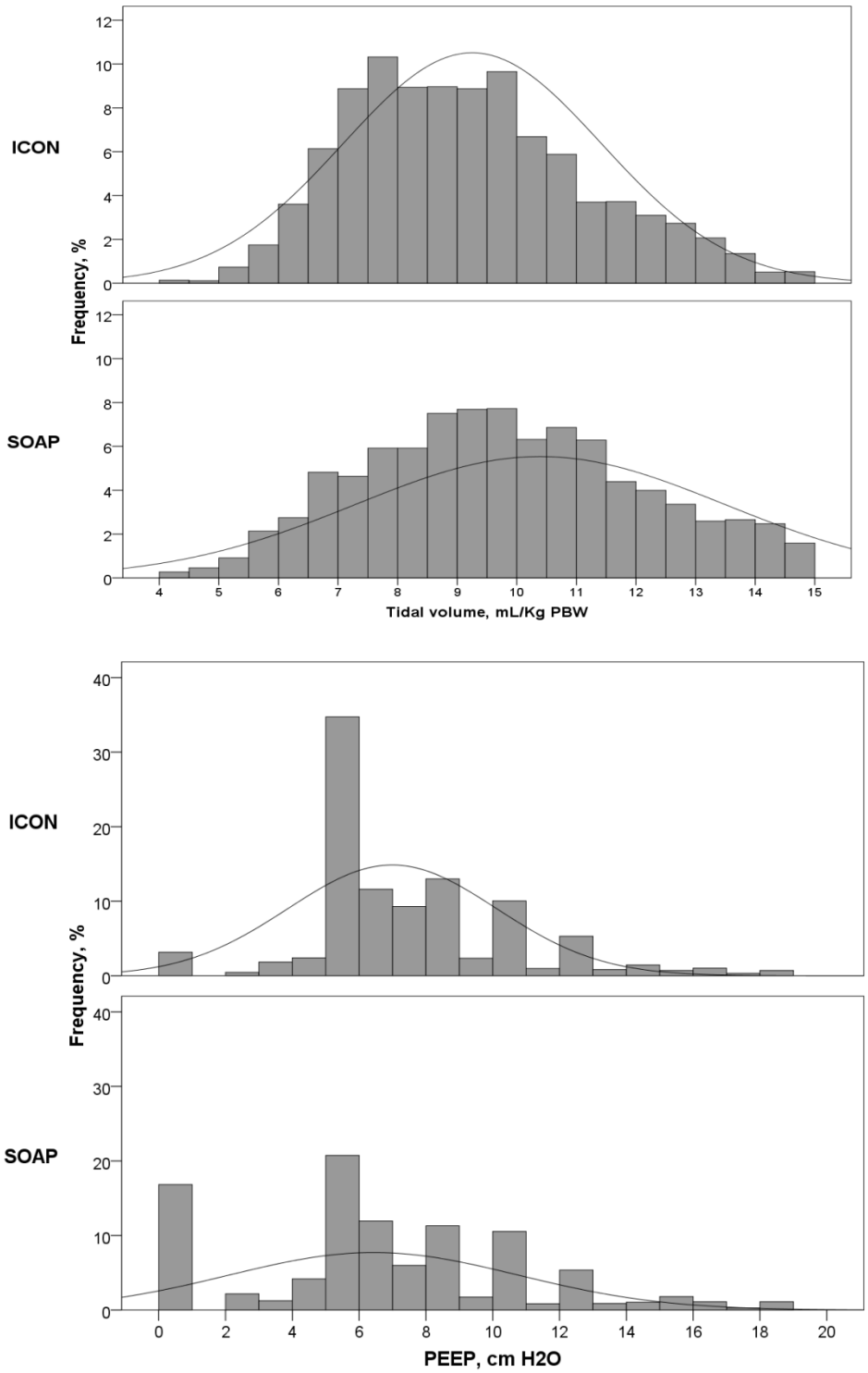

Hospital mortality, %
100
90
80
70
60
50
40
30
20
10
0
40
80
120
160
200
240
280
320
360
400
440
480
520
560
600
PaO2/FiO2, mmHg

Figure 2


ICON
SOAP
Frequency, %
Tidal volume, mL/Kg PBW
ICON
SOAP
Frequency, %
PEEP, cm H2O

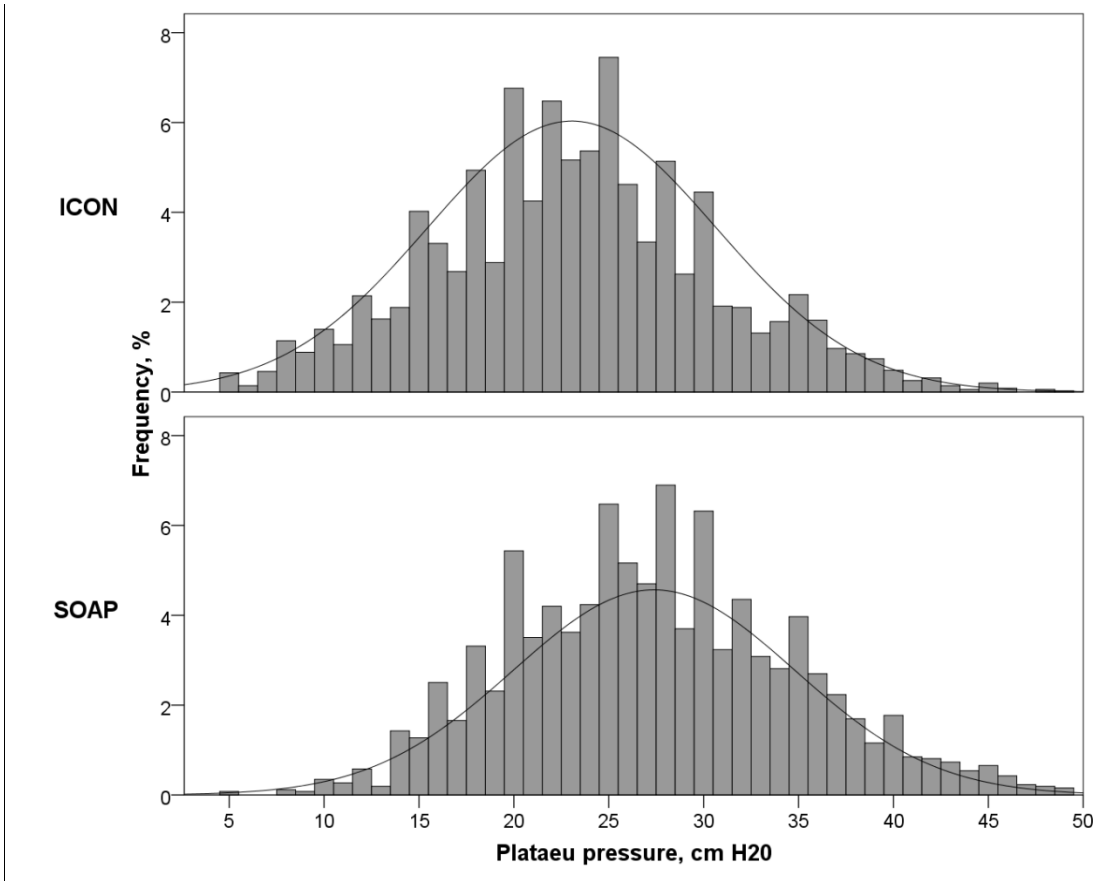
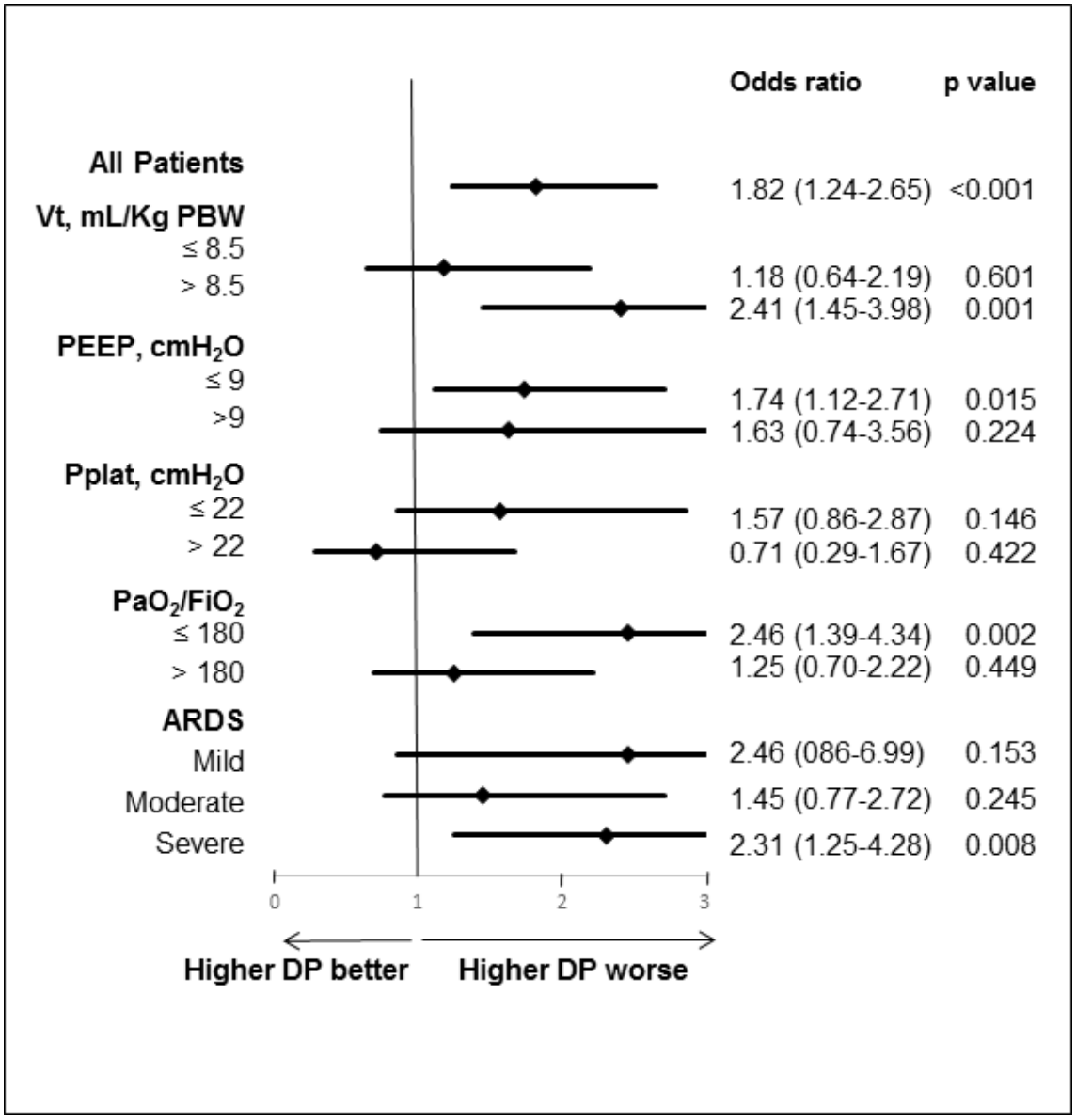

ICON
SOAP
Frequency, %
0
2
4
6
8
5
10
15
20
25
30
35
40
45
50
Plataeu pressure, cm H20

Figure 3.


Odds ratio
p value
All Patients
1.82 (1.24-2.65)
<0.001
Vt, mL/Kg PBW
≤ 8.5
1.18 (0.64-2.19)
0.601
> 8.5
2.41 (1.45-3.98)
0.001
PEEP, cmH2O
≤ 9
1.74 (1.12-2.71)
0.015
>9
1.63 (0.74-3.56)
0.224
Pplat, cmH2O
≤ 22
1.57 (0.86-2.87)
0.146
> 22
0.71 (0.29-1.67)
0.422
PaO2/FiO2
≤ 180
2.46 (1.39-4.34)
0.002
> 180
1.25 (0.70-2.22)
0.449
ARDS
Mild
2.46 (086-6.99)
0.153
Moderate
1.45 (0.77-2.72)
0.245
Severe
2.31 (1.25-4.28)
0.008
0
1
2
3
Higher DP better
Higher DP worse

# Temporal Changes in the Epidemiology , Management, and Outcome from Acute Respiratory Distress Syndrome in European Intensive Care Units

Sakr/Ranieri ..... on behalf of the SOAP and ICON Investigators

## Electronic Supplementary Material

## e-Appendix: List of SOAP and ICON investigators

**Alphabetical list of SOAP participating centers by country**

*Austria:* University Hospital of Vienna (G. Delle Karth); LKH Steyr (V. Draxler); LKH-Deutschlandsberg (G. Filzwieser); Otto Wagner Spital of Vienna (W. Heindl); Krems of Donau (G. Kellner, T. Bauer); Barmherzige Bruede of Linz (K. Lenz); KH Floridsdorf of Vienna (E. Rossmann); University Hospital of Innsbruck (C. Wiedermann)
*Belgium:* CHU of Charleroi (P. Biston); Hôpitaux Iris Sud of Brussels (D. Chochrad); Clinique Europe Site St Michel of Brussels (V. Collin); C.H.U. of Liège (P. Damas); University Hospital Ghent (J. Decruyenaere, E. Hoste); CHU Brugmann of Brussels (J. Devriendt); Centre Hospitalier Jolimont-Lobbes of Haine St Paul (B. Espeel); CHR Citadelle of Liege (V. Fraipont); UCL Mont-Godinne of Yvoir (E. Installe); ACZA Campus Stuivenberg (M. Malbrain); OLV Ziekenhuis Aalst (G. Nollet); RHMS Ath-Baudour-Tournai (J.C. Preiser); AZ St Augustinus of Wilrijk (J. Raemaekers); CHU Saint-Pierre of Brussels (A. Roman); Cliniques du Sud-Luxembourg of Arlon (M. Simon); Academic Hospital Vrije Universiteit Brussels (H. Spapen); AZ Sint-Blasius of Dendermonde (W. Swinnen); Clinique Notre-Dame of Tournai (F. Vallot); Erasme University Hospital of Brussels (J.L. Vincent)
*Czech Republic:* University Hospital of Plzen (I. Chytra); U SV.Anny of Brno (L. Dadak); Klaudians of Mlada Boleslav (I. Herold); General Faculty Hospital of Prague (F. Polak); City Hospital of Ostrava (M. Sterba); *Denmark :* Gentofte Hospital, University of Copenhagen (M. Bestle); Rigshospitalet of Copenhagen (K. Espersen); Amager Hospital of Copenhagen (H. Guldager); Rigshospitalet, University of Copenhagen (K-L. Welling)
*Finland:* Aland Central Hospital of Mariehamn (D. Nyman); Kuopio University Hospital (E. Ruokonen); Seinajoki Central Hospital (K. Saarinen)
*France:* Raymond Poincare of Garches (D. Annane); Institut Gustave Roussy of Villejuif (P. Catogni); Jacques Monod of Le Havre (G. Colas); CH Victor Jousselin of Dreux (F. Coulomb); Hôpital St Joseph & St Luc of Lyon (R. Dorne); Saint Joseph of Paris (M. Garrouste); Hôpital Pasteur of Nice (C. Isetta); CHU Brabois of Vandoeuvre Les Nancy (J. Larché); Saint Louis of Paris (J-R. LeGall); CHU de Grenoble (H. Lessire); CHU Pontchaillou of Rennes (Y. Malledant); Hôpital des Hauts Clos of Troyes (P. Mateu); CHU of Amiens (M. Ossart); Hôpital Lariboisière of Paris (D. Payen); CHD Félix Gyuon of Saint Denis La Reunion (P. Schlossmacher); Hôpital Bichat of Paris (J-F. Timsit); Hôpital Saint Andre of Bordeaux (S. Winnock); Hôpital Victor Dupouy of Argentueil (J-P. Sollet); CH Auch (L. Mallet); CHU Nancy-Brabois of Vandoeuvre (P. Maurer); CH William Morey of Chalon (JM. Sab); Victor Dupouy of Argenteuil (JP. Sollet)
*Germany:* University Hospital Heidelberg (G. Aykut); Friedrich Schiller University Jena (F. Brunkhorst); University Clinic Hamburg-Eppendorf (A. Nierhaus); University Hospital Mainz (M. Lauterbach); University Hospital Carl Gustav Carus of Dresden (M. Ragaller); Hans Sushemihl Krankenhaus of Emden (R. Gatz); Vivantes-Klinikum Neukoelln of Berlin (H. Gerlach); University Hospital RWTH Aachen (D. Henzler); Kreisklinik Langen-

Seligenstadt (H-B Hopf**);** GKH Bonn (H. Hueneburg); Zentralklinik Bad Berka (W. Karzai); Neuwerk of Moenchengladbach (A. Keller); Philipps University of Marburg (U. Kuhlmann); University Hospital Regensburg (J. Langgartner); ZKH Links der Weser of Bremen (C. Manhold); University Hospital of Dresden (M. Ragaller); Universtiy of Wuerzburg (B. Reith); Hannover Medical School (T. Schuerholz); Universitätsklinikum Charité Campus Mitte of Berlin (C. Spies); Bethanien Hospital of Moers (R. Stögbauer); KhgmbH Schongau (J. Unterburger)
*Greece:* Thriassio Hospital of Athens (P-M. Clouva-Molyvdas); Sismanoglion General Hospital of Athens (G. Giokas); KAT General Hospital of Athens (E. Ioannidou); G. Papanikolaou General Hospital of Thessaloniki (A. Lahana); Agios Demetrios of Thessaloniki (A. Liolios); Onassis Cardiac Surgery Center of Athens (K. Marathias); University Hospital of Ioannina (G. Nakos); Tzanio Hospital of Athens (A. Tasiou); Athens General Hospital Gennimatas (H. Tsangaris)
*Hungary:* Peterfy Hospital of Budapest (P. Tamasi)
*Ireland:* Mater Hospital of Dublin (B. Marsh); Beaumont Hospital of Dublin (M. Power)
*Israel:* Hadassah Hebrew University Medical Center (C. Sprung)
*Italy:* Azienda Ospedaliera Senese o Siena (B. Biagioli); S. Martino of Genova (F. Bobbio Pallavicini); Azienda Ospedaliera S. Gerardo dei Tintori of Monza (A. Pesenti); Osp Regionale of Saronno (C. Capra); Ospedale Maggiore - University A. Avogadro of Novara (F. Della Corte); Osp. Molinette of Torino (P. P. Donadio); A.O. Umberto I Ancona, Rianimazione Clinica (A. Donati); Azienda Ospedaliera Universitaria Policlinico of Palermo (A. Giarratano); San Giovanni Di Dio of Florence (T. Giorgio); H San Raffaele IRCCS of Milano (D. Giudici); Ospedale Di Busto Arsizio (S. Greco); Civile Di Massa (A. Guadagnucci); San Paolo of Milano (G. Lapichino); S.Giovanni Bosco Torino (S. Livigni); Osp. San Giovanni of Sesto (G. Moise); S Camillo of Roma (G. Nardi); Vittorio Emanuele of Catania (E. Panascia); Hospital of Piacenza (M. Pizzamiglio); Universita di Torino-Ospedale S. Giovanni Battista (V. M. Ranieri); Policlinico Le Scotte of Siena (R. Rosi); Ospedale Maggiore Policlinico IRCCS of Milano (A. Sicignano); A. Uboldo of Cernusco Sul Naviglio (M. Solca); P.O. Civile Carrara of Massa (G. Vignali); San Giovanni of Roma (I. Volpe Rinonapoli)
*Netherlands:* Boven IJ Ziekenhuis of Amsterdam (M. Barnas); UMC St Radboud of Nijmegen (E.E. De Bel); Academic Medical Center of Amsterdam (A-C. De Pont); VUMC of Amsterdam (J. Groeneveld); Groningen University Hospital (M Nijsten); Waterlandziekenhuis of Purmerend (L Sie); OLVG of Amsterdam (D. F. Zandstra)
*Norway:* Sentralsjukehuset i Rogaland of Stavanger (S. Harboe); Sykehuset Østfold of Fredrikstad (S. Lindén); Aker University Hospital of Oslo (R. Z. Lovstad); Ulleval University Hospitalof Oslo (H. Moen); Akershus University Hospital of Nordbyhagen (N. Smith-Erichsen)
*Poland:* Paediatric University Hospital of Lodz (A. Piotrowski); Central Clinic Hospital SLAM of Katowice (E. Karpel)
*Portugal :* Garcia de Orta of Almada (E. Almeida); Hospital de St. António dos Capuchos of Lisboa (R. Moreno); Hospital de Santa Maria of Lisboa (A. Pais-De-Lacerda); Hospital S.Joao of Porto (J. A. Paiva); Fernado Fonseca of Masama (I. Serra); São Teotonio Viseu (A. Pimentel)
*Romania:* Inst of Cardiovascular Diseases of Bucharest (D. Filipescu)
*Serbia:* Military Medical Academy of Belgrade (K. Jovanovic)
*Slovakia:* SUSCH of Bratislava (P. Malik)
*Slovenia:* General Hospital of Novo Mesto (K. Lucka); General Hospital of Celje (G. Voga)
*Spain:* Hospital Universitario Rio Hortega of Valladolid (C. Aldecoa Alvarez-Santullano); Sabadell Hospital (A. Artigas); Hospital Clinic of Barcelona (E.

Zavala, A. Escorsell, J. Nicolas); Virgen del Camino of Pamplona (J. J. Izura Cea); Virgen de la Salud of Toledo (L. Marina); 12 de Octubre of Madrid (J. Montejo); Gregorio Maranon of Madrid (E. Palencia); General Universitario de Elche (F. Santos); Puerta del Mar of Cadiz (R. Sierra-Camerino); Fundación Jiménez Díaz of Madrid (F. Sipmann); Hospital Clinic of Barcelona (E. Zavala)
*Sweden:* Central Hospital of Kristianstad (K. Brodersen); Stockholm Soder Hospital (J. Haggqvist); Sunderby Hospital of Luleå (D. Hermansson); Huddinge University Hospital of Stockholm (H. Hjelmqvist)
*Switzerland:* Kantonsspital Luzern (K. Heer); Hirslanden Klinik Beau-Site of Bern (G. Loderer); University Hospital of Zurich (M. Maggiorini); Hôpital de la ville of La Chaux-de-Fonds (H. Zender)
*United Kingdom:* Edinburgh Western General Hospital (P. Andrews); Peterborough Hospitals NHS Trust of Peterborough (B. Appadu); University Hospital Lewisham, London (C. Barrera Groba); Bristol Royal Infirmary (J. Bewley); Queen Elizabeth Hospital Kings Lynn (K. Burchett); Milton Keynes General (P. Chambers); Homerton University Hospital of London (J. Coakley); Charing Cross Hospital of London (D. Doberenz); North Staffordshire Hospital of Stoke On Trent (N. Eastwood); Antrim Area Hospital (A. Ferguson); Royal Berkshire Hospital of Reading (J. Fielden); The James Cook University Hospital of Middlesbrough (J. Gedney); Addenbrookes of Cambridge (K. Gunning); Rotherham DGH (D. Harling); St.Helier of Carshalton (S. Jankowski); Southport & Formby (D. Jayson); Freeman of Newcastle Upon Tyne (A. Kilner); University Hospital of North Tees at Stockton on Tees (V. Krishna-Kumar); St. Thomas Hospital of London (K. Lei); Royal Infirmary of Edinburgh (S. Mackenzie); Derriford of Plymouth (P. Macnaughton); Royal Liverpool University Hospital (G. Marx); Stirling Royal Infirmary (C. McCulloch); University Hospital of Wales, Cardiff (P. Morgan); St George's Hospital of London (A. Rhodes); Gloucestershire Royal Hospital (C. Roberts); St Peters of Chertsey (M. Russell); James Paget Hospital of Great Yarmouth (D. Tupper-Carey, M. Wright); Kettering General Hospital (L. Twohey); Burnley DGH (J. Watts); Northampton General Hospital (R. Webster); Dumfries Royal Infirmary (D. Williams)

**Alphabetical list of ICON participating centers by country (for the same countries as were included in SOAP)**

*Austria*: Akh Wien (P Urbanek); Allgemeines Und Orthopädisches Landeskrankenhaus Stolzalpe (J Schlieber); Barmherzige Schwestern Linz (J Reisinger); General Hospital Braunau (J Auer); Krankenhaus D. Barmherzigen Schwestern Ried I.I. (A Hartjes); Krankenhaus Floridsdorf (A Lerche); LK Gmünd-Waidhofen/Thaya-Zwettl, Standort Zwettl (T Janous); LKH Hörgas-Enzenbach (E Kink); LKH West (W Krahulec); University Hospital (K Smolle)
*Belgium*: AZ Groeninge Kortrijk (M Van Der Schueren); AZ Jan Palfijn Gent (P Thibo); AZ Turnhout (M Vanhoof); Bracops Anderlecht (I Ahmet); Centre Hospitalier Mouscron (G Philippe); CH Peltzer La Tourelle (P Dufaye); Chirec Edith Cavell (O Jacobs); CHR Citadelle (V Fraipont); CHU Charleroi (P Biston); Chu Mont-Godinne (A Dive); CHU Tivoli (Y Bouckaert); Chwapi (E Gilbert); Clinique Saint-Pierre Ottignies (B Gressens); Clinique-Maternité Sainte Elisabeth (E Pinck); Cliniques De L'Europe - St-Michel (V Collin); Erasme University Hospital (JL Vincent); Ghent University Hospital (J De Waele); Moliere Hospital (R Rimachi); Notre Dame (D Gusu); Onze Lieve Vrouw Ziekenhuis, Aalst (K De Decker); Ixelles Hospital (K Mandianga); Sint-

Augustinus (L Heytens); St Luc University Hospital (UCL) (X Wittebole); UZ Brussel (S Herbert); Vivalia Site De Libramont (V Olivier); VZW Gezondheidszorg Oostkust Knokke-Heist (W Vandenheede); ZNA Middelheim (P Rogiers)
*Czech Republic*: Centre of Cardiovascular and Transplant Surgery (P Pavlik); Charles University Hospital (J Manak); IKEM, Prague (E Kieslichova); KNTB Zlín A.S. (R Turek); Krajska Nemocnice Liberec (M Fischer); Masarykova Nemocnice V Usti Nad Labem (R Valkova); St. Anne's University Hospital Brno (L Dadak); University Hospital Haradec Králové (P Dostal); University Hospital Brno (J Malaska); University Hospital Olomouc (R Hajek); University Hospital Plzen (A Židková); Charles University Hospital Plzen (P Lavicka)
*Denmark:* Herning Hospital (P Kolodzeike); Hjoerring Hospital (M Kruse); Vejle Hospital (T Andersen)
*Finland*: Helsinki University Central Hospital (V Harjola); Seinäjoki Central Hospital (K Saarinen)
*France*: Aix Marseille Univ, Hôpital Nord (M Leone); Calmette Hospital, Lille (A Durocher); Centre Hospitalier de Dunkerque (S Moulront); Centre Hospitalier Lyon Sud (A Lepape); Centre Hospitalo-Universitaire Nancy-Brabois (M Losser); CH Saint Philibert, Ghicl, Lille (P Cabaret); CHR De Dax (E Kalaitzis); CHU Amiens (E Zogheib); CHU Dijon (P Charve); CHU Dupuytren (B Francois); CHU Nîmes (JY Lefrant); Centre Hospitalier De Troyes (B Beilouny); Groupe Hospitalier Est Francilien-Centre Hospitalier De Meaux (X Forceville); Groupe Hospitalier Paris Saint Joseph (B Misset); Hopital Antoine Béclère (F Jacobs); Hopital Edouard Herriot (F Bernard); Hôpital Lariboisère, APHP, Paris France (D Payen); Hopital Maison Blanche, Reims (A Wynckel); Hopitaux Universitaires de Strasbourg (V Castelain); Hospices Civils de Lyon (A Faure); CHU-Grenoble (P Lavagne); CHU-Nantes (L Thierry); Réanimation Chirurgical Cardiovasculaire, CHRU Lille (M Moussa); University Hospital Ambroise Paré (A Vieillard-Baron); University Hospital Grenoble (M Durand); University Hospital of Marseille (M Gainnier); University of Nice (C Ichai)
*Germany*: Alexianer Krefeld Gmbh (S Arens); Charite Hochschulmedizin Berlin (C Hoffmann); Charite-University-Hospital, Berlin (M Kaffarnik); Diakoniekrankenhaus Henriettenstiftung Gmbh (C Scharnofske); Elisabeth-Krankenhaus Essen (I Voigt); Harlaching Hospital, Munich Municipal Hospital Group (C Peckelsen); Helios St. Johannes Klinik (M Weber); Hospital St. Georg Leipzig (J Gille); Klinik Hennigsdorf Der Oberhavel Kliniken Gmbh (A Lange); Klinik Tettnang (G Schoser); Klinikum "St. Georg" Leipzig (A Sablotzki); Klinikum Augsburg (U Jaschinski); Klinikum Augsburg (A Bluethgen); Klinikum Bremen-Mitte (F Vogel); Klinikum Bremen-Ost (A Tscheu); Klinikum Heidenheim (T Fuchs); Klinikum Links Der Weser Gmbh (M Wattenberg); Klinikum Luedenscheid (T Helmes); Krankenhaus Neuwerk (S Scieszka); Marienkrankenhaus Schwerte (M Heintz); Medical Centre Cologne Merheim (S Sakka); Schwarzwald-Baar Klinikum Villingen-Schwenningen (J Kohler); St. Elisabeth Krankenhaus Köln-Hohenlind (F Fiedler); St. Martinus Hospital Olpe (M Danz); Uniklinikum Jena (Y Sakr); Universitätsklinikum Tübingen (R Riessen); Universitätsmedizin Mainz (T Kerz); University Hospital Aachen, CPACC (A Kersten); University Hospital Aachen, DMIII (F Tacke); University Hospital Aachen, OIC (G Marx); University Hospital Muenster (T Volkert); University Medical Centre Freiburg (A Schmutz); University Medical Centre Hamburg-Eppendorf (A

Nierhaus); University Medical Centre Hamburg-Eppendorf (S Kluge); University Medicine Greifswald (P Abel); University of Duisburg-Essen (R Janosi); University of Freiburg (S Utzolino); University clinic Ulm (H Bracht); Vivantes Klinikum Neukoelln (S Toussaint)
*Greece*: Ahepa University Hospital (M Giannakou Peftoulidou); Athens University (P Myrianthefs); Athens University Medical School (A Armaganidis); Evangelismos Hospital (C Routsi); General Hospital of Chania, Crete (A Xini); Hippokration General Hospital, Thessaloniki (E Mouloudi); General hospital of Velos (I Kokoris); Lamia General Hospital (G Kyriazopoulos); Naval and Veterans Hospital (S Vlachos); Papanikolaou General Hospital (A Lavrentieva); University Hospital Alexandroupolis (P Partala); University of Ioannina (G Nakos)

*Hungary*: Dr. Kenessey Albert Hospital (L Medve); Fejér County St George Teaching Hospital (A Sarkany); Flor Ferenc County Hospital (I Kremer); Jávorszky Ödön Hospital (Z Marjanek); Peterfy Hospital Budapest (P Tamasi)
*Ireland*: Cork University Hospital (J Barry); Mercy University Hospital (R O'Leary); Mid Western Regional Hospital Complex (C Motherway); Midland Regional Hospital Mullingar, Co Westmeath (M Faheem); St. Vincent's University Hospital (E Dunne); Tallaght Hospital (M Donnelly); University Hospital Galway (T Konrad)
*Israel*: Rabin Medical Centre (J Cohen); Sourasky Tel Aviv Medical Centre (O Sold)
*Italy*: Anesthesiology and Intensive Care (E Bonora); AO Ospedale Niguarda Ca' Granda (C Achilli); Azienda Ospedaliera Di Padova (S Rossi); Azienda Ospedaliero Universitaria Policlinico Vittorio Emanuele (G Castiglione); Careggi Teaching Hospital (A Peris); Clinicized Hospital Ss Annunziata - Chieti (D Albanese); Fondazione Irccs Ca' Granda Ospedale Maggiore Policlinico, Milano; University of Milan (N Stocchetti); H San Gerardo - Monza (G Citerio); Icu "Ceccarini" Hospital Riccione (L Mozzoni); Irccs Centro Cardiologico Monzino (E Sisillo); Irccs Centro Di Riferimento Oncologico Della Basilicata (P De Negri); Irccs Fondazione Ca' Granda - Ospedale Maggiore Policlinico (M Savioli); Ospedale Belcolle Viterbo (P Vecchiarelli); Ospedale Civile Maggiore - A.O.U.I Verona (F Puflea); Ospedale Civile Maggiore - A.O.U.I Verona (V Stankovic); Ospedale Di Circolo E Fondazione Macchi - Varese (G Minoja); Ospedale Di Trento - Azienda Provinciale Per I Servizi Sanitari Della Provincia Autonoma Di Trento (S Montibeller); Ospedale Orlandi (P Calligaro); Ospedale Regionale U.Parini-Aosta (R Sorrentino); Ospedale San Donato Arezzo (M Feri); Ospedale San Raffaele (M Zambon); Policlinico G.B. Rossi - A.O.U.I Verona (E Colombaroli); Policlinico University of Palermo (A Giarratano); Santa Maria Degli Angeli Hospital (T Pellis); Saronno Hospital (C Capra); Università Cattolica Del Sacro Cuore (M Antonelli); University Catania, Italy (A Gullo); University of Florence, Florence (C Chelazzi); University of Foggia (A De Capraris); University of Milano-Bicocca, San Gerardo Hospital (N Patroniti); University of Modena (M Girardis); University of Siena (F Franchi); University of Trieste (G Berlot)
*Netherlands*: Albert Schweitzer Hospital (H Ponssen); Antoni Van Leeuwenhoek Ziekenhuis (J Ten Cate); Atrium Medisch Centrum Parkstad (L Bormans); Bovenij Hospital (S Husada); Catharina Hospital Eindhoven (M Buise); Erasmus University Medical Centre (B Van Der Hoven);

Martiniziekenhuis Groningen (A Reidinga); Medical Centre Leeuwarden (M Kuiper); Radboud University Nijmegen Medical Centre (P Pickkers); Slotervaart Ziekenhuis Amsterdam (G Kluge); Spaarne Ziekenhuis (S Den Boer); University Medical Centre Utrecht (J Kesecioglu); Ziekenhuis Rijnstate (H Van Leeuwen)
*Norway*: Haukeland University Hospital (H Flaatten); St Olavs Hospital, Trondheim University Hospital (S Mo)
*Poland*: Csk Mswia (J Kolbusz); Medical University (A Kübler); Medical University Of Wroclaw (B Mielczarek); Medical University Warsaw (M Mikaszewska-Sokolewicz); Pomeranian Medical University (K Kotfis); Regional Hospital in Poznan (B Tamowicz); Szpital Powiatowy W Ostrowi Mazowieckiej (W Sulkowski); University Hospital, Poznam (P Smuszkiewicz); Wojewódzki Szpital Zakazny (A Pihowicz); Wojewódzkie Centrum Medyczne (E Trejnowska)
*Portugal*: Centro Hospitalar Cova Da Beira (V Branco); Centro Hospitalar Do Porto (F Rua); Centro Hospitalar Do Tâmega E Sousa (E Lafuente); Centro Hospitalar Gaia/Espinho, Epe (M Sousa); Centro Hospitalar Médio Tejo (N Catorze); Centro Hospitalar Tondela-Viseu (M Barros); Faro Hospital (L Pereira); Hospital Curry Cabral (A Vintém De Oliveira); Hospital Da Luz (J Gomes); Hospital De Egas Moniz - Chlo (I Gaspar); Hospital De Santo António, Centro Hospitalar Do Porto (M Pereira); Hospital Divino Espírito Santo, Epe (M Cymbron); Hospital Espirito Santo - Évora Epe (A Dias); Hospital Garcia Orta (E Almeida); Hospital Geral Centro Hospitalar E Universitario Coimbra (S Beirao); Hospital Prof. Doutor Fernando Fonseca Epe (I Serra); Hospital São Bernardo (R Ribeiro); Hospital Sao Francisco Xavier, Chlo (P Povoa); Instituto Portugues De Oncologia Francisco Gentil, Porto (F Faria); Santa Maria Hospital (Z Costa-E-Silva); Serviço De Saúde Da Região Autonóma Da Madeira (J Nóbrega); UCIP (F Fernandes); ULS - Castelo Branco (J Gabriel)
*Romania*: Emergency County Hospital Cluj (N Hagau); Emergency Institute for Cardiovascular Diseases (D Filipescu); Fundeni Clinical Institute (G Droc); Galati Hospital (M Lupu); Inbi "Prof. Dr. Matei Bals" (A Nica); Institute of Pulmonology Marius Nasta (R Stoica); Institutul Clinic Fundeni (D Tomescu); Sfantul Pantelimon Hospital (D Constantinescu); Spitalul Cf 2 Bucuresti (G Valcoreanu Zbaganu); “Luliu Hatieganu” University of Medicine and Pharmacy, Teaching Hospital of Infectious Diseases, Cluj-Napoca (A Slavcovici)
*Serbia*: Clinic for Cardiac Surgery, Clinical Centre of Serbia (L Soskic); Clinic for Digestive Surgery, Clinical Centre Serbia (I Palibrk); Clinic for Vascular Surgery, Clinical Centre Nis (R Jankovic); Clinical Centre of Serbia (B Jovanovic); Clinical Centre of Serbia (M Pandurovic); Emergency Centre, Clinical Centre of Belgrade (V Bumbasirevic); General University Hospital (B Uljarevic); Military Medical Academy (M Surbatovic); Urology Hospital (N Ladjevic)
*Slovakia*: District Hospital (G Slobodianiuk); Faculty Hospital (V Sobona); University Hospital Bratislava-Hospital Ruzinov ICU (A Cikova); University Hospital Ruzinov Bratislava (A Gebhardtova)
*Slovenia*: General Hospital Celje (G Voga); General Hospital Izola (E Rupnik); General Hospital Novo Mesto (L Kosec); Oncological Institute (M Kerin Povšic); Ukc Maribor (I Osojnik); University Clinic of Respiratory and Allergic Diseases (V Tomic); University Clinical Centre Maribor (A Sinkovic)
*Spain*: CH Salamanca (J González); Clinic Hospital (E Zavala); Complejo

Hospitalario De Jaén (J Pérez Valenzuela); Complejo Hospitalario De Toledo (L Marina); Complexo Hospitalario Universitario De Ourense (P Vidal-Cortés); Complexo Hospitalario Universitario De Vigo (P Posada); Corporación Sanitaria Parc Tauli (A Ignacio Martin-Loeches); Cruz Roja Hospital (N Muñoz Guillén); H Vall Hebron (M Palomar); HGGC Dr Negrín (J Sole-Violan); Hospital Clinic (A Torres); Hospital Clinico San Carlos (M Gonzalez Gallego); Hospital Clínico Universitario De Valencia (G Aguilar); Hospital Clínico Universitario Lozano Blesa (R Montoiro Allué); Hospital Clinico Valencia (M Argüeso); Hospital De La Ribera (M Parejo); Hospital De Sagunto (M Palomo Navarro); Hospital De San Juan De Alicante (A Jose); Hospital De Torrejon De Ardoz (N Nin); Hospital Del Mar (F Alvarez Lerma); Hospital Del Tajo (O Martinez); Hospital General Universitario De Elche (E Tenza Lozano); Hospital General Universitario Gregorio Marañon (S Arenal López); Hospital General Universitario Gregorio Marañon (M Perez Granda); Hospital General Universitario Santa Lucía (S Moreno); Hospital Germans Trias I Pujol (C Llubia); Hospital Infanta Margarita (C De La Fuente Martos); Hospital Infanta Sofia (P Gonzalez-Arenas); Hospital J.M. Morales Meseguer (N Llamas Fernández); Hospital J.M. Morales Meseguer (B Gil Rueda ); Hospital Marina Salu. Denia. Alicante. (I Estruch Pons); Hospital Nuestra Señora Del Prado, Talavera De La Reina, Toledo. España (N Cruza); Hospital San Juan De Dios Aljarafe (F Maroto); Hospital Sas of Jerez (A Estella); Hospital Son Llatzer (A Ferrer); Hospital Universitario Central De Asturias (L Iglesias Fraile); Hospital Universitario Central De Asturias (B Quindos); Hospital Universitario De Alava, Santiago (A Quintano); Hospital Universitario De Basurto, Bilbao (M Tebar); Hospital Universitario de Getafe (P Cardinal); Hospital Universitario De La Princesa (A Reyes); Hospital Universitario de Tarragona Joan Xxiii (A Rodríguez); Hospital Universitario Del Henares (A Abella); Hospital Universitario Fundación Alcorcón (S García Del Valle); Hospital Universitario La Paz (S Yus); Hospital Universitario La Paz (E Maseda); Hospital Universitario Rio Hortega (J Berezo); Hospital Universitario San Cecilio (Granada) (A Tejero Pedregosa); Hospital Virgen Del Camino (C Laplaza); Mutua Terrassa University Hospital (R Ferrer); Rão Hortega University Hospital (J Rico-Feijoo); Servicio Andaluz De Salud. Spain. (M Rodríguez); University Opf Navarra (P Monedero)
*Sweden*: Karolinska University Hospital And Karolinska Institute (K Eriksson); Sunderby Hospital, Luleå (D Lind)
*Switzerland*: Hôpital Intercantonal De La Broye (D Chabanel); Hôpital Neuchâtelois - La Chaux-De-Fonds (H Zender); Lindenhofspital (K Heer); Regionalspital Surselva Ilanz (Gr) Schweiz (B Frankenberger); University Hospital Bern (S Jakob); Zentrum Für Intensivmedizin (A Haller)
*United Kingdom*: Alexandra Hospital Redditch (S Mathew); Blackpool Teaching Hospitals (R Downes); Brighton And Sussex University Hospitals (C Barrera Groba); Cambridge University Hospitals NHS Foundation Trust (A Johnston); Charing Cross Hospital (R Meacher); Chelsea & Westminster Hospital (R Keays); Christie Foundation Trust (P Haji-Michael); County Hospital, Lincoln (C Tyler); Craigavon Area Hospital (A Ferguson); Cumberland Infirmary (S Jones); Darent Valley Hospital (D Tyl); Dorset County Hospital (A Ball); Ealing Hospital NHS Trust (J Vogel); Glasgow Royal Infirmary (M Booth); Gloucester Royal Hospital (P Downie); The Great Western Hospital, Swindon (M Watters); Imperial College Healthcare NHS Trust (S Brett); Ipswich Hospital Nhs Trust (M Garfield); James Paget University Hospital NHS Foundation Trust (L Everett); King's College

Hospital (S Heenen); King's Mill Hospital (S Dhir); Leeds Teaching Hospitals NHS Trust (Z Beardow); Lewisham Healthcare NHS Trust (M Mostert); Luton and Dunstable Hospital NHS Trust (S Brosnan); Medway Maritime Hospital (N Pinto); Musgrove Park Hospital (S Harris); Nevill Hall Hospital (A Summors); Pilgrim Hospital (N Andrew); Pinderfields Hospital, Mid Yorkshire NHS Trust (A Rose); Plymouth Hospitals Nhs Trust (R Appelboam); Princess Royal Hospital Telford (O Davies); Royal Bournemouth Hospital (E Vickers); Royal Free Hampstead NHS Foundation Trust (B Agarwal); Royal Glamorgan Hospital (T Szakmany); Royal Hampshire County Hospital (S Wimbush); Royal Liverpool University Hospital (I Welters); Royal London Hospital, Barts Health NHS Trust (R Pearse); Royal Shrewsbury Hospital (R Hollands); Royal Surrey County Hospital (J Kirk-Bayley); St Georges Healthcare (N Fletcher); Surrey & Sussex Healthcare Trust (B Bray); University College Hospital (D Brealey)

Table S1 Countries contributing to the SOAP study and ICON audit with the corresponding number of total patients and patients with ARDS

| | SOAP study | | ICON audit | |
|---|---|---|---|---|
| | All, n | ARDS, n (%) | All, n | ARDS, n (%) |
| Austria | 68 | 5 (7.4) | 61 | 0 (0) |
| Belgium | 703 | 31 (4.4) | 481 | 48 (10) |
| Czech Republic | 45 | 3 (6,7) | 106 | 12 (11.2) |
| Denmark | 29 | 8 (27.6) | 49 | 3 (6.1) |
| Finland | 51 | 3 (5.9) | 32 | 3 (9.4) |
| France | 332 | 35 (10.5) | 327 | 34 (10.4) |
| Germany | 329 | 21 (6.4) | 659 | 43 (6.5) |
| Greece | 109 | 23 (21.1) | 45 | 14 (31.1) |
| Hungary | 8 | 0 (0) | 55 | 4 (7.3) |
| Ireland | 33 | 11 (33.3) | 75 | 15 (20) |
| Israel | 13 | 2 (15.4) | 23 | 6 (26.1) |
| Italy | 237 | 25 ( 10.5) | 299 | 46 (15.4) |
| Netherlands | 144 | 9 (6.3) | 219 | 15 (6.8) |
| Norway | 61 | 6 (9.8) | 29 | 7 (24.1) |
| Poland | 13 | 0 (0) | 54 | 16 (29.6) |
| Portugal | 69 | 13 (18.8) | 188 | 32 (17) |
| Romania | 44 | 4 (9,1) | 189 | 13 (6.9) |
| Serbia | 2 | 2 (100) | 126 | 14 (11.1) |
| Slovakia | 3 | 0 (0) | 17 | 3 (17.6) |
| Slovenia | 46 | 1 (2.2) | 78 | 6 (7.7) |
| Spain | 202 | 24 (11.9) | 574 | 45 (7.8) |
| Sweden | 68 | 1 (1.5) | 37 | 3 (8.1) |
| Switzerland | 114 | 3 (2.6) | 151 | 10 (6.6) |
| United Kingdom | 424 | 97 (22.9) | 727 | 102 (14) |
| All patients | 3147 | 327 ( 10.4) | 4601 | 494 ( 10.7) |

Table S2 Organ failure as assessed by the sequential organ failure score

| | SOAP Study | | | |
|---|---|---|---|---|
| | All | ARDS | No ARDS | All |
| N | 3147 | 327 | 2820 | 4601 |
| Organ failure on admission, n (%) | | | | |
| Any organ failure | 1809 (57.5) | 266 (81.3) | 1543 (54.7) §§ | 3017 (65.6) ‡ |
| Respiratory | 696 (22.1) | 140 (42.8) | 556 (19.7) §§ | 1198 (26) ‡ |
| Coagulation | 149 (4.7) | 36 (11) | 113 (4) §§ | 196 (4.3) |
| Hepatic | 85 (2.7) | 19 (5.8) | 66 (2.3) § | 440 (9.6) ‡ |
| CNS | 683 (21.7) | 107 (32.7) | 576 (20.4) §§ | 1094 (23.8) † |
| Renal | 575 (18.3) | 91 (27.8) | 484 (17.2) §§ | 898 (19.5) |
| Cardiovascular | 776 (24.7) | 160 (48.9) | 616 (21.8) | 1557 (33.8) ‡ |
| Organ failure at any time, n (%) | | | | |
| Any organ failure | 2244 (71.3) | 327 (100) | 1917 (68.0) §§ | 3732 (81.1) ‡ |
| Respiratory | 1331 (42.3) | 327 (100) | 1004 (35.6) §§ | 1823 (39.6)* |
| Coagulation | 309 (9.8) | 87 (26.6) | 222 (7.9) §§ | 451 (9.8) |
| Hepatic | 168 (5.3) | 43 (13.1) | 125 (4.4) §§ | 944 (20.5) ‡ |
| CNS | 839 (26.7) | 149 (45.6) | 690 (24.5) §§ | 1374 (29.9) † |
| Renal | 1120 (35.6) | 168 (51.4) | 952 (33.8) §§ | 2280 (49.6) ‡ |
| Cardiovascular | 1052 (33.4) | 238 (72.8) | 814 (28.9) §§ | 1978 (43) ‡ |
| Organ supporting therapy on admission, n (%) | | | | |
| Renal replacement therapy | 115 (3.7) | 23 (7) | 92 (3.3) § | 242 (5.3) † |
| Mechanical ventilation | 1850 (58.8) | 290 (88.7) | 1560 (55.3) §§ | 2572 (55.9)* |
| Organ supporting therapy, any time, n (%) | | | | |
| Renal replacememt therapy | 306 (9.7) | 79 (24.2) | 227 (8) §§ | 615 (13.4) |
| Mechanical ventilation | 2025 (64.3) | 327 (100) | 1698 (60.2) §§ | 2875 (62.5) |
| SOFA Score in the ICU, mean (SD) | | | | |
| SOFA score, ICU admission | 5.1 (3.8) | 7.9 (4.4) | 4.8 (3.6)§§ | 6.6 (4.1)‡ |
| SOFA non-respiratory, ICU admission | 4.2 (3.3) | 8.6 (3.9) | 3.9 (3.1)§§ | 4.8 (3.6)‡ |
| SOFAmean | 4.5 (3.5) | 7.1 (3.9) | 4.2 (3.3) §§ | 6.1 (3.8) ‡ |
| SOFAmax | 6.6 (4.4) | 11.2 (4.3) | 6 (4.1) §§ | 8.3 (4.6) ‡ |
| SOFAmean (non-respiratory) | 3.6 (3.1) | 5.6 (3.6) | 3.4 (2.9) §§ | 4.5 (3.3) ‡ |
| SOFAmax (non respiratory) | 5.3 (3.8) | 8.6 (3.9) | 4.9 (3.5) §§ | 6.4 (4.0) ‡ |

CNS: central nervous system, ICU: intensive care unit, SOFA: sequential organ failure assessment.
SOFAmean: mean SOFA score during the ICU stay, SOFAmax: maximum SOFA score in the ICU
All patients, SOAP vs. ICON: * p=0.05-0.01, † p=0.01-0.001, ‡ p<0.001.
Patients with ARDS, SOAP vs. ICON: ⎮ 0.05-0.01, ‖ p=0.01-0.001, ∫ p<0.001
Patients with ARDS vs. No ARDS (within the same study): ⌠ ⌠ 0.05-0.01, § p=0.01-0.001, §§ p<0.001
Patients with no ARDS, SOAP vs. ICON: ¶ 0.05-0.01, ¶¶ p=0.01-0.001, $ p<0.001

Table S3 Basic characteristics of patients with ARDS on admission to the ICU according to in-hospital outcome

| | All | In hospital outcome | | |
|---|---|---|---|---|
| | | Alive | Dead | p-value |
| N | 821 | 439 | 363 | |
| Age, yeasrs, mean (SD) | 60 (16.6) | 56 (17) | 64 (56,5) | <0.001 |
| Male, n (%) | 513 (63) | 286 (65.1) | 213 (58.7) | 0.055 |
| SAPS II score, mean (SD) | 49.8(17.4) | 44.2 (15.1) | 56.5 (17.6) | <0.001 |
| Referring facility, n (%) | | | | 0.106 |
| ER/Ambulance | 224 (28.5) | 119 (28.5) | 98 (28.1) | |
| Hospital floor | 260 (33.1) | 120 (28.7) | 132 (37.8) | |
| OR/Recovery room | 149 (19) | 86 (20.6) | 61 (17.5) | |
| Other hospital | 118 (15) | 75 (17.9) | 42 (12) | |
| Others | 35 ( 4.5) | 18 (4.3) | 16 (4.6) | |
| Type of admission, n (%) | | | | 0.313 |
| Medical admission | 547 (66.6) | 284 (64.7) | 250 (68.9) | |
| Elective surgery | 106 (12.9) | 62 (14.1) | 42 (11.6) | |
| Emergency surgery | 168 (20.5) | 93 (21.2) | 71 (19.6) | |
| SOFA score, mean (SD) | | | | <0.001 |
| Total | 8,9 (4.3) | 8 (3.9) | 9.9 (4.5) | |
| Non-respiratory | 6.6 (3.7) | 5.8 (3.5) | 7.5 (3.8) | |
| Comorbidities, n (%) | | | | |
| Non-metastatic cancer | 83 (10.1) | 47 (10.7) | 33 (9.1) | 0.144 |
| Diabetes | 61 (7.4) | 33 (7.5) | 28 (7.7) | 0.917 |
| Hematologic cancer | 44 (5.4) | 12 (2.7) | 31 (8.5) | <0.001 |
| Cirrhosis | 37 (4.5) | 15 (3.4) | 21 (5.8) | 0.107 |
| Chemotherapy | 31 (3.8) | 13 (3) | 17 (4.7) | 0.201 |
| Metastatic cancer | 30 (3.7) | 10 (2.3) | 20 (5.5) | 0.144 |
| HIV | 8 (1) | 3 (0.7) | 5 (1.4) | 0.479 |
| Risk factors for ARDS, n (%) | | | | |
| Shock, any cause | 432 (52.6) | 212 (48.3) | 209 (57.6) | 0.009 |
| Polytrauma | 63 (7.7) | 48 (10.9) | 11 (3) | <0.001 |
| Drug overdose | 12 (1.5) | 8 (1.8) | 3 (0.8) | 0.361 |
| Pancreatitis | 29 (3.5) | 15 (3.4) | 14 (3.9) | 0.740 |
| Near drowning | 2 (0.2) | 2 (0.5) | - | 0.198 |
| Burns | 1 (0.1) | 1 (0.2) | - | 1 |
| $PaO_2/FiO_2$, mean (SD) | 169.1 (101.4) | 174.5 (97.1) | 160.9 (104.4) | 0.002 |

ARDS: Acute respiratory distress syndrome, ER: emergency room, SAPS: Simplified Acute Physiology Score, SOFA: Sequential Organ Failure Assessment, SD: standard deviation

Missing values: Age: 4; sex: 3.

Table S4 Organ failure as assessed by SOFA score, severity of ARDS, and length of stay in patients with ARDS according to in-hospital outcome

| | All | In-hospital outcome | | |
|---|---|---|---|---|
| | | Alive | Dead | p-value |
| N | 811 | 439 | 363 | |
| Organ failure on admission, n (%) | | | | |
| Respiratory | 437 (53.2) | 227 (51.7) | 200 (55.1) | 0.339 |
| Coagulation | 83 (10.1) | 18 (4.1) | 61 (16.8) | <0.001 |
| Hepatic | 86 (10.5) | 45 (10.3) | 39 (10.7) | 0.820 |
| CNS | 279 (34) | 138 (31.4) | 130 (35.8) | 0.202 |
| Renal | 198 (24.1) | 79 (18) | 116 (32) | <0.001 |
| Cardiovascular | 432 (52.6) | 212 (48.3) | 209 (57.6) | 0.009 |
| Organ failure at any time, n (%) | | | | |
| Coagulation | 193 (23.5) | 49 (11.2) | 140 (38.6) | <0.001 |
| Hepatic | 204 (24.8) | 98 (22.3) | 99 (27.3) | 0.105 |
| CNS | 406 (49.5) | 174 (39.6) | 217 (59.8) | <0.001 |
| Renal | 464 (56.5) | 206 (46.9) | 247 (68) | <0.001 |
| Cardiovascular | 637 (77.6) | 308 (70.2) | 314 (86.5) | <0.001 |
| Organ supporting therapy on admission, n (%) | | | | |
| Renal replacement therapy | 63 (7.7) | 27 (6.2) | 35 (9.6) | 0.066 |
| Mechanical ventilation | 701 (85.4) | 377 (85.9) | 307 (84.6) | 0.604 |
| Organ supporting therapy, any time, n (%) | | | | |
| Renal replacememt therapy | 219 (26.7) | 85 (19.4) | 129 (35.5) | <0.001 |
| SOFA Scores in the ICU, mean (SD) | | | | |
| SOFAmean | 8.2 (4.1) | 6.3 (2.9) | 10.5 (4) | <0.001 |
| SOFAmax | 12 (4.2) | 10.3 (3.7) | 14.1 (3.9) | <0.001 |
| SOFAmean (non-respiratory) | 6.1 (3.6) | 4.4 (2.7) | 8.2 (3.5) | <0.001 |
| SOFAmax (non respiratory) | 9.2 (3.9) | 7.6 (3.5) | 11.1 (3.6) | <0.001 |
| ARDS on ICU admission | | | | |
| Any ARDS | 390 (47.5) | 204 (46.5) | 178 (49) | 0.478 |
| Severity of ARDS | | | | 0.011 |
| Mild | 63 (7.7) | 39 (8.9) | 23 (6.3) | |
| Moderate | 163 (19.9) | 95(21.6) | 65 (17.9) | |
| Severe | 164 (20) | 70 (15.9) | 60 (24.8) | |
| ARDS worst category any time | | | | <0.001 |
| Mild | 115 (14) | 70 (15.9) | 42 (11.6) | |
| Moderate | 356 (43.4) | 225 (51.3) | 125 (34.4) | |
| Severe | 350 (42.6) | 144 (32.8) | 196 (54) | |
| Infection, n (%) | | | | |
| Before 48h | 441 (53.7) | 230 (52.4) | 202 (55.6) | 0.358 |
| ICU acquired | 172 (21) | 96 (21.9) | 73 (20.1) | 0.544 |
| Any time | 613 (74.7) | 326 (74.3) | 275 (75.8) | 0.626 |
| Length of stay, days, median (IQR) | | | | |
| ICU | 9.5 (4.2-18) | 10 (5.6-20.6) | 8 (3-16) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Hospital | 20 (9-41) | 29 (15-20.6) | 11 (4-25) | <0.001 |

CNS: central nervous system, ICU: intensive care unit, SOFA: sequential organ failure assessment. SOFAmean: mean SOFA score during the ICU stay, SOFAmax: maximum SOFA score in the ICU

Missing: ICU stay: 12 Hospital stay: 24

Figure S1. Bar chart representing hospital mortality rates according to the study cohort and the severity of ARDS