**SUPPLEMENTAL DIGITAL CONTENT**

**SDC Figure 1.** Flow chart of the patients included.

**SDC Figure 2.** Distribution of ARDS development during ICU stay

**SDC Table 1.** Differences in outcomes between patients who developed ARDS and those who did not.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | ARDSin the first 28 days(n=65) | No ARDSin the first 28 days (n=1510) | *p* value |
| ICU mortality n(%)[95% CI] |  | 38 (58.6)[45.6-70.6] | 466 (30.9)[28.6-33.3] | <0.001 |
| ICU LOS\*\* |  |  |  |  |
|  | All | 14 (9-24) | 8 (4-14) | <0.001 |
|  | Survivors | 24 (14-31) | 9 (5-15) | <0.001 |
| Hospital mortality n(%)[95% CI]\* |  | 36 (62.1)[48.4-74.5] | 475 (35.9)[33.3-38.5] | <0.001 |
| Hospital LOS\*\* |  |  |  |  |
|  | All | 22 (12-34) | 17 (8-30) | 0.056 |
|  | Survivors | 39 (30-49) | 20 (12-34) | <0.001 |

\*Hospital mortality was only available in 1383 patients.

\*\* LOS data expressed as median (interquartile range).

**SDC Table 2.** Additional sensitivity analyses to assess the effect of driving pressure and ARDS development.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variable | Adjusted ORat day 1 | p-value | Bootstrap | p-value | Adjusted ORat day 2 | p-value |
| ARDS within the first 7 days\* | 1.13(1.07 – 1.19) | <0.001 | 1.12(1.08 – 1.17) | <0.001 | 1.11(1.06 – 1.16) | <0.001 |
| ARDS\*\* | 1.12(1.07 – 1.17) | <0.001 | 1.12(1.07 – 1.16) | <0.001 | 1.11(1.06 – 1.16) | <0.001 |

\*Adjusted by age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2, tidal volume and PEEP. \*\*Adjusted by age, COPD, pneumonia, sepsis, trauma, neurologic disease, postoperative, chronic heart failure, PaO2/FIO2, tidal volume and PEEP. ARDS: acute respiratory distress syndrome; OR: odds ratio; COPD: Chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure. OR and 95% CI are for each cm of water of driving pressure increase.

**SDC Table 3.** Sensitivity analyses to assess the effect of driving pressure and ARDS development in patients with pneumonia and patients with chronic heart failure or postoperative patients.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable |  | OR (95% CI)\* | p-value |
| Patients with pneumonia\*\*  |  |  |
|  | ARDS | 1.21 (1.07 – 1.37) | 0.002 |
|  | ICU mortality | 1.08 (1.01 – 1.15) | 0.037 |
|  | Hospital mortality | 1.06 (0.99 – 1.13) | 0.088 |
| Postoperative patients and patients with neurological disease\*\*\* |  |  |
|  | ARDS | 1.09 (1.02 – 1.19) | 0.019 |
|  | ICU mortality | 1.04 (1.01 – 1.08) | 0.021 |
|  | Hospital mortality | 1.04 (1.00 – 1.08) | 0.043 |

**\***Odds ratio of the driving pressure. \*\*Adjusted by DP, Crs, age, PaO2/FIO2 and tidal volume and PEEP at day 1. COPD, sepsis, trauma, neurologic disease were omitted due to collinearity. \*\*\*Adjusted by DP, Crs, age, PaO2/FIO2 and tidal volume and PEEP at day 1. COPD, pneumonia, sepsis and trauma were omitted due to collinearity. ARDS: acute respiratory distress syndrome; ICU: Intensive Care Unit; OR: odds ratio; DP: Driving pressure; Crs Compliance of the respiratory system; COPD: Chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure. OR and 95% CI are for each cm of water of driving pressure increase.

**SDC Table 4.** Multivariate logistic regression analysis of the effect of static compliance mechanical power of the respiratory system.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable |  | Unadjusted OR of at day 1 | p-value | Adjusted OR at day 1\* | p-value |
| Compliance |  |  |  |  |
|  | ARDS | 0.97 (0.96 – 0.99) | 0.001 | 0.97 (0.95 – 0.99) | 0.002 |
|  | ICU mortality | 0.99 (0.99 – 0.99) | 0.041 | 0.99 (0.99 – 1.00) | 0.141 |
|  | Hospital mortality | 0.99 (0.99 – 0.99) | 0.030 | 0.99 (0.99 – 1.00) | 0.127 |
| Mechanical power |  |  |  |  |
|  | ARDS | 1.03 (1.01 – 1.06) | 0.013 | 1.02 (0.99 – 1.06) | 0.152 |
|  | ICU mortality | 1.01 (0.99 – 1.03) | 0.140 | 1.01 (0.99 – 1.03) | 0.273 |
|  | Hospital mortality | 1.01 (0.99 – 1.02) | 0.287 | 1.01 (0.99 – 1.02) | 0.432 |

**\*** Adjusted by age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2 tidal volume and PEEP at day 1. ARDS: acute respiratory distress syndrome; ICU: Intensive Care Unit; OR: odds ratio; COPD: Chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure. OR and 95% CI are for each cm of water of driving pressure increase.

**SDC Table 5.** Multivariate logistic regression analysis including DP and static compliance of the respiratory system.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable |  | OR (95% CI) | p-value |
| DP at day 1\* |  |  |
|  | ARDS | 1.10 (1.02 – 1.20) | 0.017 |
|  | ICU mortality | 1.05 (1.01 – 1.08) | 0.005 |
|  | Hospital mortality | 1.05 (1.02 – 1.08) | 0.003 |
| Crs at day 1\* |  |  |
|  | ARDS | 0.99 (0.97 – 1.02) | 0.807 |
|  | ICU mortality | 1.00 (0.99 – 1.01) | 0.318 |
|  | Hospital mortality | 1.00 (0.99 – 1.01) | 0.310 |

**\*** Adjusted by DP, Crs, age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2 and tidal volume and PEEP at day 1. ARDS: acute respiratory distress syndrome; ICU: Intensive Care Unit; OR: odds ratio; DP: Driving pressure; Crs Compliance of the respiratory system; COPD: Chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure. OR and 95% CI are for each cm of water of driving pressure increase.

**SDC Table 6.** Multivariate logistic regression analysis including DP and mechanical power of the respiratory system.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable |  | OR (95% CI) | p-value |
| DP at day 1\* |  |  |
|  | ARDS | 1.12 (1.07 – 1.17) | <0.001 |
|  | ICU mortality | 1.03 (1.01 – 1.06) | 0.007 |
|  | Hospital mortality | 1.04 (1.01 – 1.06) | 0.003 |
| PowerRS at day 1\* |  |  |
|  | ARDS | 1.00 (0.97 – 1.05) | 0.709 |
|  | ICU mortality | 1.00 (0.99 – 1.02) | 0.704 |
|  | Hospital mortality | 0.99 (0.98 – 1.02) | 0.956 |

**\*** Adjusted by DP, PowerRS, age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2, tidal volume and PEEP at day 1. ARDS: acute respiratory distress syndrome; ICU: Intensive Care Unit; OR: odds ratio; DP: Driving pressure; Crs Compliance of the respiratory system; COPD: Chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure. OR and 95% CI are for each cm of water of driving pressure increase.

**SDC 7.** Differences in baseline characteristics (within the first 24 hours of inclusion) according to the quartile of driving pressure

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | DP≤9cmH2O(n=497) | DP>9-12 cmH2O(n=385) | DP>12-15 cmH2O(n=331) | DP>15 cmH2O(n=362) | p-value |
| Age (yo) | 60 (18) | 61 (19) | 61 (18) | 60 (17) | 0.609 |
| Sex (male) | 333 (67.0%) | 261 (67.8%) | 208 (62.8%) | 218 (60.2%) | 0.092 |
| Reason for MV |  |  |
|  | COPD | 10 (2.0%) | 13 (3.4%) | 12 (3.6%) | 31 (8.6%) | <0.001 |
|  | Asthma | 1 (0.2%) | 3 (0.8%) | 3 (0.9%) | 6 (1.7%) | 0.127 |
|  | Other CRD | 5 (1.0%) | 2 (0.5%) | 3 (0.9%) | 11 (3.0%) | 0.027 |
|  | Postoperative | 131 (26.4%) | 78 (20.3%) | 55 (16.6%) | 50 (13.8%) | <0.001 |
|  | Chronic heart failure | 15 (3.0%) | 12 (3.1%) | 17 (5.1%) | 32 (8.8%) | <0.001 |
|  | Aspiration | 9 (1.8%) | 5 (1.3%) | 6 (1.8%) | 10 (2.8%) | 0.550 |
|  | Pneumonia | 38 (7.7%) | 38 (9.9%) | 27 (8.2%) | 44 (12.2%) | 0.124 |
|  | Sepsis | 52 (10.5%) | 43 (11.2%) | 40 (12.1%) | 39 (10.8%) | 0.904 |
|  | Trauma | 23 (4.6%) | 22 (5.7%) | 15 (4.5%) | 21 (5.8%) | 0.776 |
|  | Cardiac arrest | 31 (6.2%) | 27 (7.0%) | 23 (7.0%) | 28 (7.7%) | 0.864 |
|  | Other ARF | 18 (3.6%) | 22 (5.7%) | 14 (4.2%) | 11 (3.0%) | 0.276 |
|  | Neurologic disease | 161 (32.4%) | 118 (30.7%) | 109 (32.9%) | 72 (19.9%) | <0.001 |
|  | Neuromuscular disease | 3 (0.6%) | 2 (0.5%) | 7 (2.1%) | 7 (1.9%) | 0.074 |
| Body mass index | 30.0 (5.5) | 26.3 (5.5) | 27.0 (5.2) | 27.2 (6.4) | <0.01 |
| SAPS II | 47.0 (19.7) | 48.7 (19.4) | 50.0 (19.6) | 48.2 (18.8) | 0.170 |
| Fluid balance in the first 24 hours (mL) | 1006 (1772) | 1002 (1831) | 740 (1811) | 884 (1772) | 0.268 |
| Creatinine (mg/dl) | 1.69 (2.11) | 1.59 (1.99) | 1.62 (1.42) | 1.87 (2.77) | 0.329 |
| Bilirubin (mg/dl) | 1.29 (2.49) | 1.39 (2.64) | 1.38 (2.93) | 1.40 (1.74) | 0.936 |
| Platelets (x109/L) | 203 (113) | 208 (111) | 218 (132) | 209 (121) | 0.473 |
| Cardiovascular dysfunction (SOFA>2) | 254 (51.1%) | 200 (51.9%) | 168 (50.8%) | 189 (52.2%) | 0.724 |
| Respiratory variables |  |  |  |  |  |  |
|  | Arterial pH | 7.34 (0.12) | 7.35 (0.12) | 7.34 (0.12) | 7.32 (0.12) | 0.023 |
|  | PaCO2 (mmHg) | 39 (11) | 39 (11) | 40 (12) | 44 (15) | <0.001 |
|  | PaO2/FIO2 (mmHg) | 245 (102) | 244 (100) | 239 (102) | 217 (99) | <0.001 |
|  | RR (bpm) | 17 (4) | 17 (4) | 17 (4) | 18 (4) | <0.01 |
|  | Tidal volume (ml/PBW) | 7.8 (1.4) | 7.9 (1.3) | 8.0 (1.3) | 8.0 (1.5) | 0.079 |
|  | PEEP (cmH2O) | 6.5 (2.1) | 6.3 (2.2) | 6.2 (2.3) | 6.1 (2.3) | 0.035 |
|  | Plateau pressure (cmH2O) | 13 (2) | 17 (2) | 20 (2) | 26 (4) | <0.001 |
|  | Driving pressure (cmH2O) | 7 (2) | 11 (1) | 14 (1) | 20 (4) | <0.001 |
|  | Compliance (ml/cmH2O) | 85 (48) | 43 (8) | 35 (6) | 25 (6) | <0.001 |
|  | Mechanical power (J/min) | 13.8 (6.3) | 15.3 (7.2) | 16.0 (7.0) | 18.5 (7.4) | <0.001 |

ARDS: acute respiratory distress syndrome; MV: mechanical ventilation; COPD: Chronic obstructive pulmonary disease; CRD: chronic respiratory disease; SAPS: Simplified Acute Physiology Score; SOFA: sequential organ failure assessment; RR respiratory rate: PEEP: positive end-expiratory pressure. Variables are expressed as mean (standard deviation) or frequency (percentage).

**SDC Table 8.** Outcomes according to the quartile of driving pressure.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | DP≤9cmH2O(n=497) | DP>9-12 cmH2O(n=385) | DP>12-15 cmH2O(n=331) | DP>15 cmH2O(n=362) | *p* value |
| ARDS n(%) [95% CI] |  | 7 (1.41)[0.57-2.88] | 11(2.86)[1.43-5.05] | 15 (4.53)[2.56-7.36] | 32 (8.84)[6.13-12.25] | <0.001 |
| Duration of MV (days) |  | 4 (2-9) | 4 (2-9) | 5 (3-10) | 6 (3-10) | 0.002 |
| ICU mortality n(%)[95% CI] |  | 138 (27.8)[23.9-31.9] | 125 (32.5)[27.8-37.4] | 111 (33.5)[28.5-38.9] | 130 (35.9)[31.0-41.1] | 0.069 |
| ICU LOS (days)\*\* |  |  |  |  |  |  |
|  | All | 8 (4-14) | 7 (4-13) | 9 (4-16) | 9 (5-16) | 0.103 |
|  | Survivors | 9 (5-14) | 8 (5-15) | 10 (5-16) | 11 (6-17) | 0.209 |
| Hospital mortality n(%)[95% CI]\* |  | 140 (31.7)[27.4-36.6] | 133 (38.8)[33.6-44.2] | 113 (39.6)[34.0-45.6] | 125 (39.8)[34.3-45.5] | 0.052 |
| Hospital LOS (days)\*\* |  |  |  |  |  |  |
|  | All | 18 (9-29) | 16 (7-30) | 18 (8-34) | 17 (8-29) | 0.751 |
|  | Survivors | 21 (12-33) | 19 (12-36) | 23 (12-35) | 20 (14-37) | 0.775 |

\*Hospital mortality was only available in 1383 patients and n value of different quartiles was 441, 343, 285 and 314, respectively.

\*\* LOS data expressed as median (interquartile range)

DP: Driving Pressure; ARDS: acute respiratory distress syndrome; MV: mechanical ventilation; ICU: Intensive Care Unit; LOS: Length of Stay.

**SDC Table 9.** Risk of ARDS between different quartiles of driving pressure taking as a reference the lowest quartile.

|  |  |  |
| --- | --- | --- |
|  | OR (95% CI) | P value |
| DP ≤9 | Reference | - |
| DP >9-12 | 1.80 (0.65-4.96) | 0.256 |
| DP >12-15 | 3.30 (1.27-8.56) | 0.014 |
| DP>15 | 6.72 (2.80-16.15) | <0.001 |

Adjusted by DP, age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2, tidal volume and PEEP at day 1. DP: driving pressure; OR: odds ratio, CI: confidence interval; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure.

**SDC Table 10.** Risk of ICU mortality between different quartiles of driving pressure taking as a reference the lowest quartile.

|  |  |  |
| --- | --- | --- |
|  | OR (95% CI) | P value |
| DP ≤9 | Reference | - |
| DP >9-12 | 1.20 (0.86-1.65) | 0.281 |
| DP >12-15 | 1.20 (0.86-1.68) | 0.284 |
| DP>15 | 1.56 (1.11-2.18) | 0.010 |

Adjusted by DP, age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2, tidal volume and PEEP at day 1. DP: driving pressure; OR: odds ratio, CI: confidence interval; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure.

**SDC Table 11.** Risk of hospital mortality between different quartiles of driving pressure taking as a reference the lowest quartile.

|  |  |  |
| --- | --- | --- |
|  | OR (95% CI) | P value |
| DP ≤9 | Reference | - |
| DP >9-12 | 1.28 (0.92-1.79) | 0.143 |
| DP >12-15 | 1.25 (0.88-1.78) | 0.209 |
| DP>15 | 1.54 (1.08-2.18) | 0.016 |

Adjusted by DP, age, COPD, pneumonia, sepsis, trauma, neurologic disease, PaO2/FIO2, tidal volume and PEEP at day 1. DP: driving pressure; OR: odds ratio, CI: confidence interval; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; PEEP: positive end-expiratory pressure.

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