**Supplementary Digital Content**

**Implementation of Protocolized Care in Acute Respiratory Distress Syndrome Improves Outcomes**

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**Fig. S4** Left: The proportion of missing data of patients with PaO2:FiO2 < 150 that were used for matching. Right: The matrix plot represents pattern of missing (red rectangles) and available data (green rectangles) of patients with PaO2:FiO2 < 150 that were used for matching.

**Fig. S5** The summary plot of covariate balance before (red) and after (green) propensity score matching of patients with PaO2:FiO2 < 150 across 50 imputations. The red circles represent standardized mean difference for continuous covariates and raw differences for binary covariates before implementation of the protocol. After matching, standardized mean and raw differences are between -0.1 and 0.1 (vertical dashed lines) that indicated sufficient balance.

**Fig. S6** Smoothed histogram (density estimate) of average tidal volume on day 1 to day 3 of acute respiratory distress syndrome (ARDS) before (red) and after (green) ARDS implementation protocol are shown. The dashed vertical red line represents median tidal volume before implementation of ARDS protocol and the dashed vertical green line represents median tidal volume after implementation.

**Fig. S7** Smoothed histogram (density estimate) of average tidal volume on day 1 to day 3 of acute respiratory distress syndrome (ARDS) before (red) and after (green) ARDS implementation protocol are shown. The population are patients who had PaO2:FiO2 < 150. The dashed vertical red line represents median tidal volume before implementation of ARDS protocol and the dashed vertical green line represents median tidal volume after implementation.

**Appendix 1: Data collection and patient selection**

The highest daily settings for PEEP, mean airway pressure, spontaneous tidal volume, plateau pressures, FiO2 were recorded for days 1, 2, 3, 7, and 14. PEEP discrepancy was defined as PEEP that the patient received subtracted by PEEP recommendation from ARDSnet PEEP-FiO2 table 1 (A negative value indicated that the patient’s PEEP was set below the recommendation from the PEEP-FiO2 table). Arterial blood gases closest to the time of recorded mechanical ventilation parameters was chosen when available.

Clinical characteristics including the patient demographic, ARDS risk factors, echocardiographic findings, time from intubation to hospital admission. Severity of illness including the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology, Age, Chronic Health Evaluation (APACHE) III were recorded based on the worst clinical data on day 1 of the diagnosis of ARDS. For patients who were transferred from outside the Cleveland Clinic, SOFA and APACHE III score were recorded in the first 24 hours of hospital admission.

We defined acute kidney injury and septic shock according to guidelines from The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines 2 and Sepsis-3 consensus definition 3, respectively. Need for renal replacement therapy was recorded until 28 days after the diagnosis of ARDS or hospital discharge. Intake, output, cumulative fluid balance and percentage of fluid overload 4 were collected for the first three days, day 7, and day 14 from the onset of ARDS. Percentage of fluid overload was calculated using the following formula: Percentage of fluid overload (%) = [fluid intake (L) – total output (L)]/body weight at ICU admission (kg.) x 100. Serum lactate, serum creatinine, bicarbonate and complete blood count (CBC) were collected on day 1, 2, 3, 7, and 14 from the diagnosis of ARDS. Presence of Septic shock, and need for administration of vasopressors were recorded daily until day 28 of ARDS.

Continuous analgesia and sedative drugs that were intravenously dispensed for more than 48 hours and use of antipsychotic drugs were collected. Rescue therapies including prone positioning ventilation, high frequency ventilation, inhaled vasodilators, extracorporeal membrane oxygenation (ECMO), continuous neuromuscular blockade, and recruitment maneuvers were recorded until intensive care unit discharge. Actual body weight and height were recorded at the first day of ARDS.

**Appendix 2: Definitions**

**Acute kidney injury (AKI):** AKI was defined as any of the following (1) Increase in serum creatinine (Scr) by greater than or equal 0.3 mg/dL within 48 hours. (2) Increase in SCr to greater than or equal 1.5 times baseline. (3) Urine output less than 0.5 mL/kg/h for 6 hours.

**Acute respiratory distress syndrome (ARDS):** ARDS was defined as all of the following (1) Lung injury onset within 1 week of a known clinical insult or new or worsening respiratory symptoms. (2) Bilateral opacities on chest imaging that not fully explained by effusions, atelectasis or nodules. (3) Respiratory failure not fully explained by cardiac failure or volume overload. (4) Arterial PaO2/FiO2 ratio less than or equal 300 mmHg (5) Minimum PEEP of 5 cmH2O

**Driving pressure:** plateau pressure minus PEEP

**PEEP discrepancy:** actual PEEP minus PEEP recommendation from ARDSnet PEEP-FiO2 table

**Septic shock:** sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate > 2 mmol/L despite adequate volume resuscitation.

**Ventilator free days to day 28:** Ventilator free days to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

**Unassisted breathing (UAB):** Spontaneously breathing with face mask, nasal prong oxygen, or room air, T-tube breathing, tracheostomy collar breathing, or CPAP ≤ 5 without PSV or IMV assistance, or use of noninvasive ventilation solely for sleep disordered breathing, or use of nasal high flow oxygen.

**Appendix 3: Cleveland Clinic ARDS Management Protocol**

1. Initial overall Ventilator management for ANY patient initiated on mechanical ventilation
2. Establishing ARDS diagnosis
3. ARDS basic management
   1. Ventilator settings and management goals
   2. FACTT lite fluid management
4. Adjunctive Options for Severe ARDS
   1. Prone
   2. Neuromuscular blockers for 48 hrs
   3. Recruitment maneuvers
5. ARDS rescue treatments
   1. Inhaled vasodilators
   2. Proning
   3. Inverse ratio ventilation
   4. HFOV
   5. ECMO

**Initial Ventilator Management**

All patients that are initiated on mechanical ventilation should start on the following settings. The goal is to attempt to minimize injurious tidal volumes. According to the patient condition, there may be deviations of these guidelines.

* The initial mode of ventilation for ***all patients*** on mechanical ventilation is:
  + *A/C Volume Control* on PB 840
  + *Volume Control* on Servo-i
    - * *Mode failure criteria:* High tidal volume alarm (on Servo-i) or double triggering (either ventilator)
* *If mode failure criteria met (assuming all efforts have been made to optimize settings):*
  + Respiratory therapist will chart type of failure
  + Respiratory therapist calls attending physician or fellow in charge or on call
  + Alternative mode is chosen or patient treatment initiated (eg, sedation/paralysis, treatment of metabolic acidosis, etc) and documented
* **Overall Ventilator Goals:**
  + Goal tidal volume is 6-8 mL/Kg/IBW, exceptions exist.
  + Set alarms for tidal volume at 3 to 9 mL/kg IBW
  + Titrate FiO2 to a SpO2 of 90-95%
  + Use ARDSnet table (low PEEP) to adjust PEEP/FiO2
  + Adjust ventilator settings per routine care

**ARDS diagnosis**

The caregiver must be vigilant to recognize features of ARDS.

**If SpO2 is at 90-95% and FiO2 is ≥ 40% then** **the patient MAY have ARDS, use the Berlin definition**

* If ARDS is suspected, **a fellow or staff *must* be informed**,
* If ARDS is diagnosed then follow the ARDS ventilator management protocol until ARDS resolved.

**ARDS Basic Management**

If ARDS is identified, then our initial goal of ventilation is safety; that is to ensure minimum minute ventilation and minimize injurious lung volumes.

**ARDS ventilator management goals**

* Adjust the goals to enhance lung protective lung strategies 5:
  + Goal tidal volume is 6 mL/kg, acceptable range VT 4-8 mL/kg
  + Goal SpO2 is 88 -95%
  + Set PEEP and FiO2 using the ARDSnet PEEP/FiO2 table 1 *unless* staff/fellow enter order otherwise
  + Tolerate hypercapnia, only correct if needed
* Baseline arterial blood gas and as needed per respiratory therapy department protocol
* Measure Pplat on every ventilator check and document

**ARDS Conservative Fluid Management**

* Minimize all unnecessary fluids (If not essential, stop KVOs)
* The table depicts the FACTT lite protocol as a guide for fluid management 6

***Furosemide dosing according to FACCT lite***

**Withhold if:**

* Vasopressor or a ﬂuid bolus given last 12 hours
* ESRD on RRT
* oliguria with Cr > 3
* oliguria with Cr 0-3 and urinary studies indicative of AKI.

**Dose**

* Give 20 mg IV bolus OR 3mg/hr infusion or last known eﬀective dose.
* Reassess urine output in 1 hour.
* Double each subsequent dose until :
  + Oliguria reversal or intravascular pressure target met
  + Maximum infusion rate of 24 mg/hr or 160 mg bolus reached.
  + Do not exceed 620 mg/day.
* Discontinue furosemide if no response to maximum dose after 1 hour.

**Adjunctive Treatment for ARDS**

**If a patient has a SpO2 88-95% and the FiO2 is ≥ 0.6 the patient is likely to have Severe ARDS and may be candidate for adjunctive therapy (Prone position and neuromuscular blockers).**

**The Basic ARDS management (ventilation, PEEP, goals) will continue as usual. Although, may want to consider higher PEEP table.**

*An ABG is needed only if trying to implement any of these strategies (prone or NMB).*

* ***Criteria for implementing adjuntive therapies:***
  + PaO2/FiO2 < 150 and FiO2 ≥ 0.60

**AND**

* + *Onset of ARDS ≤ 36 hrs and ≥* 12 hours of basic ARDS management

**Prone positioning 7**

* Record the last ABG, the FiO2, PaO2/FiO2, Pplat and compliance
* Repeat ventilator checks every 4 hours and as needed
* Alternate positions ever y 2 hours
* The patients should be placed in supine position after at least 16 hrs of proning
* Maintain supine for 4-6 hours, with the timing to match their nursing, radiology and procedural needs.
* The ABG, the FiO2, PaO2/FiO2, Pplat and compliance should be again checked after 4 hours of supine position
* **Stop proning if**:
  + PaO2/FiO2 ≥150 mm Hg with a PEEP of ≤10 cm H2O **and** an FiO2 of ≤0.6 in the supine position at least 4 hours after the end of the last prone session
  + A decrease in the PaO2/FiO2 > 20% relative to the ratio in the supine position, in two consecutive prone sessions
  + Complications occurring during a prone session and leading to its immediate
* Contraindications
  + Absolute:
    - Spine (spinal instability)or pelvic fractures
    - Abdominal compartment syndrome
    - Increased Intracranial pressure
  + Relative
    - Hemodynamic instability
    - thoracic or abdominal surgery
    - Chronic respiratory failure

**Neuromuscular blockade for 48 hrs 8**

* Ensure the patient is on continuous sedation or analgesia
* Target RASS of -5
* Consider application of a **BIS** monitor (titrate sedation to 40-60)
* Check **train of four** using peripheral nerve stimulation, to look at the baseline before initiation of NMBs
* Use appropriate drug:
  + Atracurium
    - Initial bolus of 0.4-0.5 mg/kg
    - Maintenance 4-20 mcg/kg/minute
  + or
  + Cis-atracurium
    - Initial: 0.15-0.2 mg/kg
    - Maintenance dose of 1-3 mcg/kg/minute (0.06-0.18 mg/kg/hour)
* Titrate for a 2/4 in the train of fours
* Stop after 48 hrs

**Recruitment Maneuvers:**

These maneuvers are done at request of attending physician or fellow. The goal is to recruit lung fast. There is no evidence to suggest better outcomes with its use, however, clinical situations may indicate them.

**Maneuver**

1. Ensure cuff is well inflated and patient is hemodynamically stable
2. Make sure PEEP has been set according to ARDSnet table
3. Switch to CPAP at 40 cm H2O for 10 – 15 seconds 9
4. Return to original settings and PEEP

**STOP** if hypotension, arrhytmias or desaturation < 85%

**Recruitability criteria**

* SpO2 increase > 5% or
* PaCO2 decrease or
* Compliance increase > 10%

**Contraindications**

* Obstructive lung disease (bullous disease, COPD, Asthma)
* Unilateral disease
* Hemodynamic instability
* Pneumothorax
* Increased intracranial pressure

**ARDS Rescue Treatments**

**If patient fails Basic ARDS management then Rescue therapy may be used**. *Evidence supporting the use of rescue treatments is incomplete, conflicting or absent. Thus, we use them when basic management has failed (persistent hypoxia) or is injurious.*

***CRITERIA FOR FAILURE TO BASIC ARDS MANAGEMENT:***

* Treatment with basic therapy and stable settings for > 1 hour

**and**

* Pplat > 30 cm H2O **and** FiO2 > 0.80

**or**

* pH < 7.20 (respiratory acidosis)

**Rescue Treatment Options**

* + 1. **Flolan/NO**

Indication in ARDS is failure to oxygenate. Improve V/Q matching. Other indications may exist (right heart failure, pulmonary hypertension etc., which are not covered in this document)

* Positive response is defined as:
  + - * 30 minutes after reaching maximum dose there is a 20% increase in PaO2

Reassess in 12 hours for weaning

* + 1. **Inverse ratio PC-IMV**

Indication in ARDS is to increase mean airway pressure without increasing VT. However, if patient is not paralyzed, VT due to patient inspiratory efforts may be injurious, PEEP difficult to estimate, and work of breathing too high.

* + - * Use BiLevel (PB 840) or BiVent (Servo-i)
    1. **High Frequency Oscillatory Ventilation**

Indication in ARDS is to increase mean airway pressure and minimize tidal volume. However, it requires high levels of sedation/paralysis and staff involvement to titrate settings. Use the MICU HFO protocol and algorithm.

* + 1. **Proning**

Indication is failure to oxygenate. Goal is to enhance V/Q matching and decrease lung injury.

* + 1. **Neuromuscular blockade:**

Indications are usually failure to oxygenate/ventilate, asynchrony or decrease oxygen demand.

* + 1. **ECMO**

See next

**ECMO**

Patients that have failed basic ARDS management and are being placed on rescue therapy should have an ECMO consult. Medical ECMO staff to be notified and ECMO evaluation note to be finished before discussion with the ECMO team.



Fig. S1 Cleveland Clinic MICU ARDS Management Protocol

**Appendix 4: Education Curriculum for the ARDS Protocol**

We developed the learning and education modules for dissemination of our ARDS protocol modeled on the learning theory of education. The ARDS protocol decision points were matched to core concepts of experiential learning and instructional theory. This theory divides instructional interventions into nine steps. These steps include

* + - Gaining Attention
    - Informing the learners of the objective
    - Stimulating recall of prior learning
    - Presenting the content
    - Providing learning guidance
    - Eliciting performance
    - Providing feedback
    - Assessing performance
    - Enhancing retention and transfer

When any new educational intervention is initiated it needs to gain attention of the learners, there needs to be clear objectives and learners should be able to recall prior knowledge related to the subject. As the educational theory is applied, the content that needs to be taught needs to be presented to the learners with appropriate guidance related to its use or application. As the new concepts are taught the learners should be able to perform the new tasks. A key components of the sequence of instruction is reflections and there needs to be mechanisms to provide feedback, assess performance and have mechanism to enhance reflections. As we implemented the protocol we realized that even though this model gives clears objectives and guidance for independent practice, it lacked a mechanism to promote reflection on practice through feedback. We modified our model to incorporate feedback over the first six months of the launch of the protocol. The components of the protocol were tailored towards the different bedside provides based on their roles in the care of these patients, but we implemented concepts of interprofessional education and communication so that there was cross talk amongst the different caregivers. We gained attention for the protocol by designating champions amongst physicians, respiratory therapists and nurses. Education modules were developed to present the specific content to the bedside providers and these modules were presented to the different providers through multiple mediums. There were didactic lectures, simulation, online content and bedside teaching that provided guidance to the bedside providers regarding the specific domains of the protocol. Each specialty was given clear objectives that lined with the protocol. The teaching modules for the physicians focused on the early and appropriate identification of ARDS patients, and awareness regarding the best available evidence in the management of these patients and the physiologic rationale behind those management decisions. The ventilator management including compliance with low tidal volume strategies, measurements of Plateau pressures and titration of PEEP was the responsibility of the bedside respiratory therapists. Nursing teaching modules focused on the appropriate use of sedation and analgesia protocols, initiation and continued use of neuromuscular blocking agents and care for patients undergoing prone position ventilation. The protocol was developed in May 2014, and concurrent education was initiated at the same time. Over the next 6 months the protocol was modified based on feedback from key stakeholders and the finalized version was implemented 12/2014.

**Table S1 Baseline characteristic before propensity score matching by ARDS implementation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristics\*** | **Entire cohort (450)** | | | | | |
| **Before implementation (118)** | | **After implementation (332)** | | **P-value** | |
| Age, years | 55 | (44-66) | 58 | (44-67) |  | 0.16 |
| Male sex, n (%) | 58 | (49.2) | 179 | (53.9) |  | 0.37 |
| Body mass index, kg/m2 | 31.6 | (27.1-39.7) | 30.2 | (25.2-36.4) |  | 0.06 |
| Race, n (%)  White  Black or African American | 90  20 | (76.3)  (16.9) | 243  75 | (73.2)  (22.6) |  | 0.51  0.20 |
| SOFA, points | 11 | (8-15) | 13 | (10-16) |  | 0.01 |
| Non-pulmonary SOFA | 7 | (5-11) | 9 | (7-12) |  | 0.002 |
| APACHE III | 110 | (90-131) | 117 | (98-142) |  | 0.04 |
| Charlson comorbidities index, points | 3 | (1-6) | 4 | (2-6) |  | 0.33 |
| Comorbidities, n (%)  Diabetes mellitus  Active malignancy  Liver disease  Chronic kidney disease  Heart failure  Recent surgery (within 3 months) | 46  21  12  13  14  1 | (39)  (17.8)  (10.2)  (11)  (11.9)  (0.8) | 88  69  49  48  35  16 | (26.5)  (20.8)  (14.8)  (14.5)  (10.5)  (4.8) |  | 0.01  0.49  0.21  0.35  0.69  0.05 |
| Chronic lung disease, n (%)  Chronic obstructive pulmonary disease  Idiopathic pulmonary fibrosis  Other | 19  1  14 | (16.1)  (0.8)  (11.9) | 44  7  52 | (13.3)  (2.1)  (15.7) |  | 0.44  0.69  0.32 |
| Cause of ARDS, n (%)  Pneumonia  Aspiration  Non-pulmonary sepsis  Pancreatitis | 91  14  15  6 | (77.1)  (11.9)  (12.7)  (5.1) | 253  65  38  17 | (76.2)  (19.6)  (11.4)  (5.1) |  | 0.84  0.06  0.71  0.99 |
| Echocardiography  Ejection fraction, %  Right ventricular systolic pressure (mmHg) | 58.2  37 | (55-64.3)  (30-47) | 60  40 | (55-65)  (32-50) |  | 0.17  0.15 |
| Septic shock, n (%) | 63 | (53.4) | 189 | (57.1) |  | 0.49 |
| Outside hospital transfer, n (%) | 76 | (64.4) | 173 | (52.1) |  | 0.02 |
| Time from intubation to hospital admission, days | 0 | (-3 to 1) | 0 | (-1 to 3) |  | 0.01 |
| PaO2:FiO2 on day 1 | 106 | (75-153) | 128 | (88-178) |  | 0.02 |
| Oxygenation index on day 1 | 15.9 | (10.3-26) | 13.3 | (8-22.7) |  | 0.03 |

APACHE, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen in arterial blood; SOFA, sequential organ failure assessment.

\*Continuous data were presented as median (interquartile range)

**Table S2 Baseline characteristic before propensity score matching in ARDS patients with PaO2:FiO2 < 150 by ARDS implementation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristics\***  **(Patients with PaO2:FiO2 < 150)** | **Entire cohort (249)** | | | | | |
| **Before implementation (71)** | | **After implementation (178)** | | **P-value** | |
| Age, years | 54 | (44-65) | 57 | (42-65) |  | 0.76 |
| Male sex, n (%) | 30 | (42.3) | 95 | (53.4) |  | 0.11 |
| Body mass index, kg/m2 | 32 | (28.6-39.2) | 30.9 | (25.3-37.4) |  | 0.21 |
| Race, n (%)  White  Black or African American | 51  15 | (71.8)  (21.1) | 122  45 | (68.5)  (25.3) |  | 0.61  0.49 |
| SOFA, points | 11 | (8-14) | 13 | (10-16) | < | 0.001 |
| Non-pulmonary SOFA | 7 | (5-10) | 9 | (7-12) | < | 0.001 |
| APACHE III | 108 | (91-125) | 124 | (101-143) |  | 0.01 |
| Charlson comorbidities index, points | 3 | (1-5) | 3 | (1-5) |  | 0.61 |
| Comorbidities, n (%)  Diabetes mellitus  Active malignancy  Liver disease  Chronic kidney disease  Heart failure  Recent surgery (within 3 months) | 31  12  5  6  8  1 | (43.7)  (16.9)  (7)  (8.5)  (11.3)  (1.4) | 46  34  22  27  18  9 | (25.8)  (19.1)  (12.4)  (15.2)  (10.1)  (5.1) |  | 0.01  0.69  0.22  0.16  0.79  0.29 |
| Chronic lung disease, n (%)  Chronic obstructive pulmonary disease  Idiopathic pulmonary fibrosis  Other | 11  1  9 | (15.5)  (1.4)  (12.7) | 23  3  30 | (12.9)  (1.7)  (16.9) |  | 0.59  0.99  0.41 |
| Cause of ARDS, n (%)  Pneumonia  Aspiration  Non-pulmonary sepsis  Pancreatitis | 57  9  9  4 | (80.3)  (12.7)  (12.7)  (5.6) | 137  35  17  9 | (77)  (19.7)  (9.6)  (5.1) |  | 0.57  0.19  0.47  0.99 |
| Echocardiography  Ejection fraction, %  Right ventricular systolic pressure (mm Hg) | 60  38 | (55-65)  (30-48) | 60  40 | (55-65)  (31-50) |  | 0.54  0.50 |
| Septic shock, n (%) | 37 | (52.1) | 106 | (59.6) |  | 0.28 |
| Outside hospital transfer, n (%) | 45 | (63.4) | 91 | (51.1) |  | 0.08 |
| Time from intubation to hospital admission, days | 0 | (-2 to 1) | 0 | (-1 to 4) |  | 0.01 |
| PaO2:FiO2 on day 1 | 88 | (69-117) | 94 | (72-120) |  | 0.25 |
| Oxygenation index on day 1 | 19.9 | (13.4-30) | 19.3 | (13-27.9) |  | 0.41 |

APACHE, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen in arterial blood; SOFA, sequential organ failure assessment.

\*Continuous data were presented as median (interquartile range)

**Table S3 Baseline characteristic after propensity score matching in ARDS patients with PaO2:FiO2 < 150 by ARDS implementation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristics\***  **(Patients with PaO2:FiO2 < 150)** | **Matching cohort (216)** | | | | | |
| **Before implementation (55)** | | **After implementation (161)** | | **P-value** | |
| Age, years | 54 | (45-63.5) | 57 | (42-65) |  | 0.81 |
| Male sex, n (%) | 22 | (40) | 86 | (53.4) |  | 0.09 |
| Body mass index, kg/m2 | 32.0 | (27.8-39.2) | 30.9 | (25.2-37.9) |  | 0.35 |
| Race, n (%)  White  Black or African American | 38  13 | (69.1)  (23.6) | 109  42 | (67.7)  (26.1) |  | 0.85  0.72 |
| SOFA, points | 11 | (8-14) | 13 | (10-15) |  | 0.03 |
| Non-pulmonary SOFA | 7 | (4.5-11) | 9 | (7.0-12) |  | 0.01 |
| APACHE III | 113.0 | (91-126.5) | 120.5 | (100-139.0) |  | 0.08 |
| Charlson comorbidities index, points | 3 | (1-5.5) | 3 | (1-5.0) |  | 0.46 |
| Comorbidities, n (%)  Diabetes mellitus  Active malignancy  Liver disease  Chronic kidney disease  Heart failure  Recent surgery (within 3 months) | 18  8  5  6  8  1 | (32.7)  (14.5)  (9.1)  (10.9)  (14.5)  (1.8) | 44  32  19  20  17  9 | (27.3)  (19.9)  (11.8)  (12.4)  (10.6)  (5.6) |  | 0.44  0.38  0.58  0.77  0.43  0.46 |
| Chronic lung disease, n (%)  Chronic obstructive pulmonary disease  Idiopathic pulmonary fibrosis  Other | 8  1  7 | (14.5)  (1.8)  (12.7) | 22  3  29 | (13.7)  (1.9)  (18) |  | 0.87  0.99  0.36 |
| Cause of ARDS, n (%)  Pneumonia  Aspiration  Non-pulmonary sepsis  Pancreatitis | 44  8  8  3 | (80)  (14.5)  (14.5)  (5.5) | 121  27  16  8 | (75.2)  (16.8)  (9.9)  (5) |  | 0.47  0.70  0.35  0.99 |
| Echocardiography  Ejection fraction, %  Right ventricular systolic pressure (mm Hg) | 60  36 | (55-65)  (29.0-46.8) | 60  40 | (55-65)  (31.2-50.8) |  | 0.71  0.15 |
| Septic shock, n (%) | 31 | (56.4) | 91 | (56.5) |  | 0.98 |
| Outside hospital transfer, n (%) | 36 | (65.5) | 87 | (54) |  | 0.14 |
| Time from intubation to hospital admission, days | 0 | (-2 to 1) | 0 | (-1 to 3) |  | 0.11 |
| PaO2:FiO2 on day 1 | 89 | (71-117) | 93 | (71-120) |  | 0.60 |
| Oxygenation index on day 1 | 18.0 | (12.5-26.3) | 20.5 | (13.8-28.7) |  | 0.86 |

APACHE, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen in arterial blood; SOFA, sequential organ failure assessment.

\*Continuous data were presented as median (interquartile range)

**Table S4 Percentage of missing data of variables that used for matching**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Percent of missing data (%)** | | | |
|  | **Entire cohort** | | **Patients with PaO2:FiO2 on day 1 < 150** | |
|  | **Before implementation (118)** | **After implementation (332)** | **Before implementation (71)** | **After implementation (178)** |
| Mean airway pressure on day 1 | 32.2 | 23.2 | 18.3 | 12.9 |
| PaO2:FiO2 on day 1 | 19.5 | 13.3 | 0 | 0 |
| APACHE III | 0.85 | 1.51 | 0 | 1.7 |
| SOFA | 0.85 | 1.51 | 0 | 1.7 |
| Septic shock | 0 | 0.30 | 0 | 0 |
| Age | 0 | 0 | 0 | 0 |
| Charlson comorbidities index | 0 | 0 | 0 | 0 |
| Aspiration as a cause of ARDS | 0 | 0 | 0 | 0 |
| Time to intubation to hospital admission | 0 | 0 | 0 | 0 |
| Mortality at day 28 | 0 | 0 | 0 | 0 |
| Mortality at day 90 | 0 | 0 | 0 | 0 |
| Body mass index | 0 | 0 | 0 | 0 |
| History of diabetes mellitus | 0 | 0 | 0 | 0 |
| History of chronic kidney disease | 0 | 0 | 0 | 0 |
| History of liver disease | 0 | 0 | 0 | 0 |
| History of active malignancy | 0 | 0 | 0 | 0 |
| ARDS implementation | 0 | 0 | 0 | 0 |

APACHE, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen in arterial blood; SOFA, sequential organ failure assessment

**Table S5 Baseline characteristics of selected and excluded patients from match analysis by ARDS implementation**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristics\*** | **Before implementation** | | | | **After implementation** | | | |
| **Not selected for matching (16)** | | **Selected for matching (102)** | | **Not selected for matching (2)** | | **Selected for matching (330)** | |
| Age, years | 47.5 | (43.5-55.2) | 55.5 | (45.2-66) | 66.5 | (62.2-70.8) | 58 | (44-67) |
| Male sex, n (%) | 5 | (31.2) | 53 | (52) | 1 | (50) | 178 | (53.9) |
| BMI, kg/m2 | 32.8 | (30.2-39.4) | 31.4 | (27.0-39.7) | 24.3 | (19.8-28.8) | 30.2 | (25.2-36.4) |
| Race, n (%)  White  Black or African American | 14  2 | (87.5)  (12.5) | 76  18 | (74.5)  (17.6) | 2  0 | (100)  (0) | 241  75 | (73)  (22.7) |
| SOFA, points | 9 | (7-12) | 11 | (8-15) | 18.5 | (17.2-19.8) | 13.0 | (10.0-16.0) |
| Non-pulmonary SOFA, points | 5 | (3.8-8.2) | 8 | (5.0-12.0) | 16.5 | (15.2-17.8) | 9.0 | (7.0-12.0) |
| APACHE III, points | 90 | (77-113) | 112 | (92-139) | 146 | (140-153) | 117 | (98-142) |
| Charlson comorbidities index, points | 2.5 | (1-4) | 3.0 | (2-6) | 5.5 | (4.8-6.2) | 4.0 | (2.0-6.0) |
| Comorbidities, n (%)  Diabetes mellitus  Active malignancy  Liver disease  Chronic kidney disease  Heart failure  Recent surgery within 3 months | 12  2  0  1  1  0 | (75)  (12.5)  (0)  (6.2)  (6.2)  (0) | 34  19  12  12  13  1 | (33.3)  (18.6)  (11.8)  (11.8)  (12.7)  (1) | 0  1  1  0  0  0 | (0)  (50)  (50)  (0)  (0)  (0) | 88  68  48  48  35  16 | (26.7)  (20.6)  (14.5)  (14.5)  (10.6)  (4.8) |
| Chronic lung disease, n (%)  COPD  IPF  Other | 2  0  2 | (12.5)  (0)  (12.5) | 17  1  12 | (16.7)  (1)  (11.8) | 0  0  0 | (0)  (0)  (0) | 44  7  52 | (13.3)  (2.1)  (15.8) |
| Cause of ARDS, n (%)  Pneumonia  Aspiration  Non-pulmonary sepsis  Pancreatitis | 11  1  4  1 | (68.8)  (6.2)  (25)  (6.2) | 80  13  11  5 | (78.4)  (12.7)  (10.8)  (4.9) | 2  1  0  0 | (100)  (50)  (0)  (0) | 251  64  38  17 | (76.1)  (19.4)  (11.5)  (5.2) |
| Echocardiography  EF, %  RVSP (mm Hg) | 57.0  30.0 | (55-65)  (24-46.0) | 58.3  37.5 | (55-64)  (31-47.2) | 57  32.5 | (55-59)  (31.2-33.8) | 60  41.0 | (55-65)  (32.0-50.0) |
| Septic shock, n (%) | 7 | (43.8) | 56 | (54.9) | 1 | (50) | 188 | (57.1) |
| Outside hospital transfer, n (%) | 13 | (81.2) | 63 | (61.8) | 0 | (0) | 173 | (52.4) |
| Time from intubation to hospital admission, days | -1 | (-6.8 to 0.5) | 0 | (-3 to 1) | 18 | (9 to 27) | 0 | (-1 to 3) |
| PaO2:FiO2 on day 1 | 97 | (73-114) | 107 | (76-165) | 250 | (247-253) | 128 | ( 87-178) |
| Oxygenation index on day 1 | 21.8 | (14-26.4) | 15.6 | (10-25.2) | 4.5 | (3.9-5.0) | 13.4 | (8.1-22.8) |

APACHE, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; FiO2, fraction of inspired oxygen; IPF, idiopathic pulmonary fibrosis; PaO2, partial pressure of oxygen in arterial blood; RVSP, right ventricular systolic pressure; SOFA, sequential organ failure assessment.

\*Continuous data were presented as median (interquartile range)

**Table S6 Baseline characteristics of selected and excluded patients from match analysis in patients with PaO2:FiO2 < 150 by ARDS implementation**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristics\***  **(Patients with PaO2:FiO2 < 150)** | **Before implementation** | | | | **After implementation** | | | |
| **Not selected for matching (16)** | | **Selected for matching (55)** | | **Not selected for matching (17)** | | **Selected for matching (161)** | |
| Age, years | 56.5 | (43.5-67) | 54.0 | (45-63.5) | 62 | (55-71) | 57 | (42-65) |
| Male sex, n (%) | 8 | (50) | 22 | (40) | 9 | (52.9) | 86 | (53.4) |
| BMI, kg/m2 | 31.9 | (29.6-39.5) | 32.0 | (27.8-39.2) | 30.9 | (26.1-35.2) | 30.9 | (25.2-37.9) |
| Race, n (%)  White  Black or African American | 13  2 | (81.2)  (12.5) | 38  13 | (69.1)  (23.6) | 13  3 | (76.5)  (17.6) | 109  42 | (67.7)  (26.1) |
| SOFA, points | 10 | (8.8-11.2) | 11 | (8.0-14.0) | 16 | (15-17) | 13 | (10-15) |
| Non-pulmonary SOFA, points | 6 | (5.0-7.5) | 7 | (4.5-11.0) | 12 | (12-14) | 9 | (7-12) |
| APACHE III, points | 97 | (71-113) | 113 | (91-126) | 149 | (136-166) | 121 | (100-139) |
| Charlson comorbidities index, points | 4 | (2.8-5.0) | 3 | (1.0-5.5) | 4 | (2-6) | 3 | (1-5) |
| Comorbidities, n (%)  Diabetes mellitus  Active malignancy  Liver disease  Chronic kidney disease  Heart failure  Recent surgery within 3 months | 13  4  0  0  0  0 | (81.2)  (25)  (0)  (0)  (0)  (0) | 18  8  5  6  8  1 | (32.7)  (14.5)  (9.1)  (10.9)  (14.5)  (1.8) | 2  2  3  7  1  0 | (11.8)  (11.8)  (17.6)  (41.2)  (5.9)  (0) | 44  32  19  20  17  9 | (27.3)  (19.9)  (11.8)  (12.4)  (10.6)  (5.6) |
| Chronic lung disease, n (%)  COPD  IPF  Other | 3  0  2 | (18.8)  (0)  (12.5) | 8  1  7 | (14.5)  (1.8)  (12.7) | 1  0  1 | (5.9)  (0)  (5.9) | 22  3  29 | (13.7)  (1.9)  (18) |
| Cause of ARDS, n (%)  Pneumonia  Aspiration  Non-pulmonary sepsis  Pancreatitis | 13  1  1  1 | (81.2)  (6.2)  (6.2)  (6.2) | 44  8  8  3 | (80)  (14.5)  (14.5)  (5.5) | 16  8  1  1 | (94.1)  (47.1)  (5.9)  (5.9) | 121  27  16  8 | (75.2)  (16.8)  (9.9)  (5) |
| Echocardiography  EF, %  RVSP (mm Hg) | 57  45.5 | (55-63)  (40-53) | 60  36 | (55-65)  (29-46.8) | 60  36 | (55-66)  (28.0-40.0) | 60  40 | (55-65)  (31.2-50.8) |
| Septic shock, n (%) | 6 | (37.5) | 31 | (56.4) | 15 | (88.2) | 91 | (56.5) |
| Outside hospital transfer, n (%) | 9 | (56.2) | 36 | (65.5) | 4 | (23.5) | 87 | (54) |
| Time from intubation to hospital admission, days | 0 | (-6.2 to 1) | 0 | (-2.0 to 1) | 5 | (0 to 13) | 0 | (-1 to 3) |
| PaO2:FiO2 on day 1 | 86 | ( 60-118) | 89 | (71-117) | 110 | (95-134) | 93 | (71-120) |
| Oxygenation index on day 1 | 27 | (17.2-36.4) | 18 | (12.5-26.3) | 16.2 | (10.6-20.0) | 20.5 | (13.8- 28.7) |

APACHE, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; FiO2, fraction of inspired oxygen; IPF, idiopathic pulmonary fibrosis; PaO2, partial pressure of oxygen in arterial blood; RVSP, right ventricular systolic pressure; SOFA, sequential organ failure assessment.

\*Continuous data were presented as median (interquartile range)

**Table S7 Ventilator settings, gas exchange, acute kidney injury, and fluid overload of matched patients with PaO2:FiO2 < 150 by ARDS implementation protocol**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable\*** | **Matched patients with PaO2:FiO2 < 150 (216)** | | | | | |
| **Before implementation (55)** | | **After implementation (161)** | | **P-value** | |
| **Average ventilator settings on day 1 to 3, median (IQR)** | | |  | |  |  |
| FiO2 | 0.80 | (0.7-0.93) | 0.68 | (0.6-0.86) |  | 0.002 |
| Tidal volume, mL/kg PBW | 7.9 | (7.1-8.8) | 7.4 | (6.7-8.4) |  | 0.03 |
| PEEP, cm H2O | 11.3 | (8.7-14.5) | 12.0 | (9.3-14.7) |  | 0.45 |
| Plateau pressure, cm H2O | 30.8 | (25.9-33.2) | 27.3 | (24.0-31.2) |  | 0.08 |
| Peak airway pressure, cm H2O | 31.8 | (27.8-35.7) | 31.7 | (27.7-35.3) |  | 0.67 |
| Mean airway pressure, cm H2O | 19.7 | (16.3-23.0) | 18.3 | (15.7-21.7) |  | 0.08 |
| Minute ventilation, L/min | 11.6 | (10.5-13.9) | 11.0 | (8.6-12.6) |  | 0.01 |
| Driving pressure, cm H2O† | 15.2 | (14.0-17.1) | 14.0 | (11.8-17.4) |  | 0.04 |
| **Average gas exchange on day 1 to 3 , median (IQR)** | |  |  |  |  |  |
| PaO2:FiO2 | 105 | (86-119) | 125 | (96-162) | < | 0.001 |
| Oxygenation index | 19.3 | (14.0-28.3) | 15.7 | (11.4-23.1) |  | 0.04 |
| PaCO2, mm Hg | 44.0 | (37.2-50.7) | 44.3 | (38.3-49.7) |  | 0.96 |
| pH | 7.35 | (7.29-7.42) | 7.34 | (7.29-7.39) |  | 0.32 |
| **Acute kidney injury** | |  |  |  |  |  |
| Acute kidney injury, n (%) | 43 | (78.2) | 116 | (72) |  | 0.37 |

FiO2, fraction of inspired oxygen; IQR, interquartile range; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood; PBW, predicted body weight; PEEP; positive end expiratory pressure.

\* Continuous data were presented as median (interquartile range)

† Driving pressure = Plateau pressure – PEEP

**Table S8 Compliances of ventilator settings, fluid overload and ICU interventions in matched patients with PaO2:FiO2 <150 by ARDS implementation protocol**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable\*** | **Matched patients with PaO2:FiO2 < 150 (216)** | | | | | |
| **Before implementation (55)** | | **After implementation (161)** | | **P-value** | |
| **Average ventilator settings on day 1 to 3** | | |  | |  |  |
| Tidal volume, n (%)  < 8 mL/kg PBW  8-10 mL/kg PBW  > 10 mL/kg PBW | 28  16  9 | (52.8)  (30.2)  (17) | 108  41  10 | (67.9)  (25.8)  (6.3) |  | 0.04 |
| Plateau pressure ≤ 30 cm H2O, n (%) | 10 | (41.7) | 86 | (67.7) |  | 0.02 |
| Driving pressure† < 15 cm H2O, n (%) | 7 | (29.2) | 74 | (58.3) |  | 0.01 |
| PEEP discrepancy, cm H2O‡ | -8.7 | (-11.5 to -6.4) | -7 | (-8.7 to -4) |  | 0.003 |
| **Other measures and ICU interventions** | |  |  |  |  |  |
| Percent of fluid overload§  Day 1  Day 2  Day 3  Day 7  Day 14 | 0.7  2.3  4.4  9.3  7.9 | (-0.2 to 3.3)  (0.2 to 7.7)  (0.5 to 10.8)  (1.2 to 12.8)  (3.9 to 15.4) | 0.9  2.8  4.1  5.3  5.2 | (-0.5 to 3.3)  (0.5 to 5.8)  (1.2 to 7.6)  (0.7 to 9.0)  (-1.2 to 13.3) |  | 0.89  0.93  0.78  0.07  0.14 |
| Rescue therapies, n (%) |  |  |  |  |  |  |
| Neuromuscular blocking agents | 22 | (40) | 79 | (49.1) |  | 0.24 |
| Inhaled vasodilators | 26 | (47.3) | 40 | (24.8) |  | 0.002 |
| Prone positioning | 13 | (23.6) | 20 | (12.4) |  | 0.046 |
| Recruitment maneuvers | 8 | (14.5) | 11 | (6.8) |  | 0.10 |
| Extracorporeal membrane oxygenation | 2 | (3.6) | 5 | (3.1) |  | 0.99 |
| High frequency oscillatory ventilation | 1 | (1.8) | 1 | (0.6) |  | 0.45 |
| Sedation, n (%) | 43 | (78.2) | 132 | (82) |  | 0.53 |
| Analgesia, n (%) | 35 | (63.6) | 139 | (86.3) | < | 0.001 |
| Antipsychotic drugs, n (%) | 22 | (40) | 83 | (51.6) |  | 0.14 |
| Furosemide, n (%) | 30 | (54.5) | 93 | (57.8) |  | 0.68 |

ICU, intensive care unit; PBW, predicted body weight; PEEP; positive end expiratory pressure.

\* Continuous data were presented as median (interquartile range)

† Driving pressure = Plateau pressure – PEEP

‡ PEEP discrepancy is a difference between set PEEP and PEEP-FiO2 table by NIH-NHLBI ARDS Network. The negative value means set PEEP below PEEP-FiO2 table.

§ Fluid overload (%) = [fluid intake (L) – total output (L)]/body weight at time of ICU admission (kg.) x 100

**Table S9 Ventilator settings and gas exchange of all matched patients with ARDS by before and after implementation protocol**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable\*** | **All matched cohort** | | | | | |
| **Before implementation (102)** | | **After implementation (330)** | | **P-value** | |
| **Ventilator settings, median (IQR)** | | |  |  |  |  |
| FiO2  Day 1  Day 2  Day 3 | 1.0  0.7  0.65 | (0.66-1.0)  (0.5-1.0)  (0.46-0.89) | 0.8  0.5  0.5 | (0.6-1.0)  (0.4-0.76)  (0.4-0.7) | <  < | 0.09  0.001  0.001 |
| Tidal volume, mL/kg PBW  Day 1  Day 2  Day 3 | 7.8  7.8  7.7 | (6.7-8.8)  (7.0-8.5)  (6.9-8.8) | 7.4  7.3  7.4 | (6.7-8.5)  (6.4-8.2)  (6.5-8.4) |  | 0.19  0.01  0.02 |
| PEEP, cm H2O  Day 1  Day 2  Day 3 | 10  10  10 | (8-12)  (8-15)  (8-15) | 10  10  10 | (8-14)  (8-14)  (8-13) |  | 0.19  0.27  0.03 |
| Plateau pressure, cm H2O  Day 1  Day 2  Day 3 | 27.5  27  32 | (23.8-31.5)  (23-31.5)  (26-34.5) | 27  26  26 | (21.8-31)  (22-30)  (21-30) |  | 0.39  0.44  0.001 |
| Peak airway pressure, cm H2O  Day 1  Day 2  Day 3 | 31.5  30  30 | (27-35.2)  (26-35.5)  (26-35) | 30  29  29 | (26-35)  (25-34)  (24-34) |  | 0.27  0.26  0.10 |
| Mean airway pressure, cm H2O  Day 1  Day 2  Day 3 | 18  17.6  18 | (15-22)  (14.9-23)  (16-25) | 17  17  16 | (14-21)  (14-20)  (13-20) | < | 0.31  0.02  0.001 |
| Minute ventilation, L/min  Day 1  Day 2  Day 3 | 12  11.9  12 | (9.9-15.3)  (10.4-14.6)  (9.3-14) | 10.9  10.5  10.3 | (9.0-13.5)  (8.3-12.6)  (8.5-12.5) | < | 0.01  0.001  0.003 |
| Driving pressure, cm H2O†  Day 1  Day 2  Day 3 | 17.5  13  16.5 | (13.8-19.2)  (11-15)  (13-17.8) | 13  14  14 | (11-19)  (11-18)  (11-18) |  | 0.15  0.16  0.09 |
| PEEP discrepancy, cm H2O‡  Day 1  Day 2  Day 3 | -10  -7  -6 | (-12 to -6)  (-10 to -2)  (-10 to -2) | -8  -6  -5 | (-12 to -5)  (-10 to 0)  (-8 to 0) |  | 0.10  0.19  0.01 |
| **Gas exchange , median (IQR)** | |  |  |  |  |  |
| PaO2:FiO2  Day 1  Day 2  Day 3 | 107  114  133 | (76-165)  (85-170)  (87-168) | 128  147  170 | (87-178)  (107-214)  (112-236) | <  < | 0.08  0.001  0.001 |
| Oxygenation index  Day 1  Day 2  Day 3 | 15.6  14.9  17.5 | (10-25.2)  (9.6-24.3)  (11.1-25.8) | 13.4  11.6  10.0 | (8.1-22.8)  (7.1-17.8)  (6.7-17.5) | < | 0.14  0.003  0.001 |
| PaCO2, mm Hg  Day 1  Day 2  Day 3 | 41  42  42.5 | (35-49)  (37-47)  (36.2-49.8) | 41.3  41.5  42 | (35.8-50)  (35-48.2)  (35-49) |  | 0.99  0.94  0.28 |
| pH  Day 1  Day 2  Day 3 | 7.35  7.35  7.35 | (7.27-7.41)  (7.27-7.42)  (7.29-7.42) | 7.34  7.35  7.36 | (7.26-7.40)  (7.28-7.41)  (7.30-7.41) |  | 0.60  0.79  0.61 |

ARDS, acute respiratory distress syndrome; FiO2, fraction of inspired oxygen; IQR, interquartile range; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood; PBW, predicted body weight; PEEP; positive end expiratory pressure

\* Continuous data were presented as median (interquartile range)

† Driving pressure = Plateau pressure – PEEP

‡ PEEP discrepancy is a difference between set PEEP and PEEP-FiO2 table by NIH-NHLBI ARDS Network. The negative value means set PEEP below PEEP-FiO2 table.

**Table S10 Ventilator settings and gas exchange of all matched patients with PaO2:FiO2 < 150 by before and after implementation protocol**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable\*** | **Matched patients with PaO2:fiO2 < 150** | | | | | |
| **Before implementation (55)** | | **After implementation (161)** | | **P-value** | |
| **Ventilator settings, median (IQR)** | | |  |  |  |  |
| FiO2  Day 1  Day 2  Day 3 | 1  0.8  0.7 | (0.8-1)  (0.6-1)  (0.6-0.9) | 1  0.6  0.5 | (0.7-1)  (0.5-0.9)  (0.4-0.8) | < | 0.27  0.02  0.001 |
| Tidal volume, mL/kg PBW  Day 1  Day 2  Day 3 | 7.9  7.8  7.8 | (6.6-9.2)  (7.0-8.5)  (6.9-9.2) | 7.4  7.2  7.2 | (6.7-8.8)  (6.4-8.2)  (6.5-8.2) |  | 0.30  0.01  0.003 |
| PEEP, cm H2O  Day 1  Day 2  Day 3 | 10  10  12 | (8-12)  (8-14.2)  (8-15) | 12  12  12 | (10-15)  (10-15)  (8-14) |  | 0.03  0.11  0.67 |
| Plateau pressure, cm H2O  Day 1  Day 2  Day 3 | 30  31  30.5 | (26-31)  (28-34)  (26.8-33.8) | 28  27  28 | (25-33)  (23.5-31.5)  (23.2-32) |  | 0.79  0.20  0.06 |
| Peak airway pressure, cm H2O  Day 1  Day 2  Day 3 | 33  32  31.5 | (28-37)  (27-36)  (27-36.5) | 32  32  31 | (28-37)  (27-35)  (26-37) |  | 0.71  0.89  0.93 |
| Mean airway pressure, cm H2O  Day 1  Day 2  Day 3 | 18  18  20 | (15-22)  (15.8-23)  (16-25) | 19  18  18 | (16-23)  (16-22)  (14-22) |  | 0.76  0.59  0.02 |
| Minute ventilation, L/min  Day 1  Day 2  Day 3 | 11.8  11.5  12.3 | (9.1-14.6)  (10.4-14.7)  (9.4-13.2) | 11.3  10.4  10.3 | (9.0-13.5)  (8.2-12.8)  (8.4-12.8) |  | 0.19  0.004  0.02 |
| Driving pressure, cm H2O†  Day 1  Day 2  Day 3 | 19  15  16 | (16-22)  (12-16)  (13-17) | 14  14  14 | (11-19.8)  (11-18)  (11-18) |  | 0.03  0.83  0.16 |
| PEEP discrepancy, cm H2O‡  Day 1  Day 2  Day 3 | -11  -8  -6 | (-12 to -7.8)  (-12 to -5.2)  (-11 to -4) | -8  -6  -5.5 | (-12 to -6)  (-10 to -2)  (-8 to 0) |  | 0.01  0.01  0.01 |
| **Gas exchange , median (IQR)** | |  |  |  |  |  |
| PaO2:FiO2  Day 1  Day 2  Day 3 | 89  98  115 | (71-117)  (83-128)  (82-155) | 93  130  152 | (71-120)  (91-175)  (102-216) | < | 0.60  0.004  0.001 |
| Oxygenation index  Day 1  Day 2  Day 3 | 18  15.4  18.8 | (12.5-26.3)  (12.0-24.6)  (13.8-28.6) | 20.5  14.1  12.0 | (13.8-28.7)  (9.3-21.6)  (7.5-20.2) | < | 0.86  0.09  0.001 |
| PaCO2, mm Hg  Day 1  Day 2  Day 3 | 43.1  41.5  43.5 | (37-51.5)  (36-48.5)  (36-50.2) | 43  43  43 | (37-51)  (37-50)  (37-50) |  | 0.72  0.31  0.96 |
| pH  Day 1  Day 2  Day 3 | 7.36  7.36  7.36 | (7.27-7.41)  (7.28-7.43)  (7.30-7.42) | 7.33  7.34  7.36 | (7.26-7.39)  (7.27-7.41)  (7.29-7.41) |  | 0.31  0.18  0.53 |

ARDS, acute respiratory distress syndrome; FiO2, fraction of inspired oxygen; IQR, interquartile range; PaCO2, partial pressure of carbon dioxide in arterial blood; PaO2, partial pressure of oxygen in arterial blood; PBW, predicted body weight; PEEP; positive end expiratory pressure

\* Continuous data were presented as median (interquartile range)

† Driving pressure = Plateau pressure – PEEP

‡ PEEP discrepancy is a difference between set PEEP and PEEP-FiO2 table by NIH-NHLBI ARDS Network. The negative value means set PEEP below PEEP-FiO2 table.

**Table S11 28-day and 90-day survival in non-imputed data**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes\*** | **Multivariable logistic regression for non-imputed data\*** | | | | | |
| **Entire cohort** | | | **Patient with PaO2:FiO2 <150** | | |
| **Odds ratio (95%CI)** | **P value** | | **Odds (95%CI)** | **P value** | |
| 28-day survival | 0.49 (0.28-0.85) |  | 0.01 | 0.52 (0.26-1.00) |  | 0.05 |
| 90-day survival | 0.44 (0.25-0.75) |  | 0.003 | 0.40 (0.20-0.76) |  | 0.01 |

CI; confidence interval, FiO2, fraction of inspired oxygen; PaO2, partial pressure of oxygen in arterial blood.

\* Adjustment for confounding factors including age, APACHE III score, Charlson comorbidity index, septic shock, time from intubation to hospital admission, and PaO2:FiO2 on day 1.



**Fig. S2** Left: The proportion of missing data of all entire cohort that were used for matching. Right: The matrix plot represents pattern of missing (red rectangles) and available data (green rectangles) of all entire cohort that were used for matching.



**Fig. S3** The summary plot of covariate balance before (red) and after (green) propensity score matching of all entire cohort across 50 imputations. The red circles represent standardized mean difference for continuous covariates and raw differences for binary covariates before implementation of the protocol. After matching, standardized mean and raw differences are between -0.1 and 0.1 (vertical dashed lines) that indicated sufficient balance.



**Fig. S4** Left: The proportion of missing data of patients with PaO2:FiO2 < 150 that were used for matching. Right: The matrix plot represents pattern of missing (red rectangles) and available data (green rectangles) of patients with PaO2:FiO2 < 150 that were used for matching.



**Fig. S5** The summary plot of covariate balance before (red) and after (green) propensity score matching of patients with PaO2:FiO2 < 150 across 50 imputations. The red circles represent standardized mean difference for continuous covariates and raw differences for binary covariates before implementation of the protocol. After matching, standardized mean and raw differences are between -0.1 and 0.1 (vertical dashed lines) that indicated sufficient balance.



**Fig. S6** Smoothed histogram (density estimate) of average tidal volume on day 1 to day 3 of acute respiratory distress syndrome (ARDS) before (red) and after (green) ARDS implementation protocol are shown. The dashed vertical red line represents median tidal volume before implementation of ARDS protocol and the dashed vertical green line represents median tidal volume after implementation.



**Fig. S7** Smoothed histogram (density estimate) of average tidal volume on day 1 to day 3 of acute respiratory distress syndrome (ARDS) before (red) and after (green) ARDS implementation protocol are shown. The population are patients who had PaO2:FiO2 < 150. The dashed vertical red line represents median tidal volume before implementation of ARDS protocol and the dashed vertical green line represents median tidal volume after implementation.

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