

e-Appendix 1

Study Design

In this comparative effectiveness study, consecutive patients with severe hypoxemic respiratory failure were included. Data variables were extracted from the institutional electronic medical record database, the METRIC Data Mart,⁶ as well as individual case review. Data extraction was a combination of electronic extraction followed by manual case review. Individual case review was done in all patients who received rescue strategies. Data was verified manually by our research team. The initial screening of 79,846 patients was done from our ICU database (datamart). Then all patients with a PaO₂/FiO₂ ratio under 175 on two consecutive arterial blood gas (ABG) samples were identified as potential severe hypoxemia patients. Positive end-expiratory pressure (PEEP) values and the tidal volume (V_t) and plateau airway pressure (P_{plat}) to determine the static compliance were recorded and within two hours of the first qualifying ABG. The chest radiograph component of the LIS was determined by reviewing the closest digital chest radiograph done within 24 hours of the first qualifying ABG. This data was verified by an independent reviewer (not involved in data extraction or patient care). Twenty percent of the charts were verified in a random fashion. The radiographs of all patients were independently reviewed by a board certified internal medicine physician to determine a quadrant score based on a validated structured assessment. We applied the University of Washington Chest Radiograph Reading Protocol, number of quadrant score was obtained (From 1-4).

Extraction of individual rescue therapies was conducted through respective databases. Each RT was searched electronically via respective databases. HFOV and ECMO were searched through the METRIC ICU Data Mart, and ECMO was also searched through the Mayo Clinic ECMO records. Prone positioning was searched using a query-building tool called the *Data Discovery and Query Builder* through the Mayo Clinic Life Sciences System, which is a sophisticated data warehouse. This has been previously validated.⁶ The Data Discovery and Query Builder was used to form a query for the terms

“prone position” and “rota prone”. The Mayo Clinic Respiratory Care database was used to search for use of inhaled nitric oxide and inhaled prostacyclin.

The following data was electronically extracted:

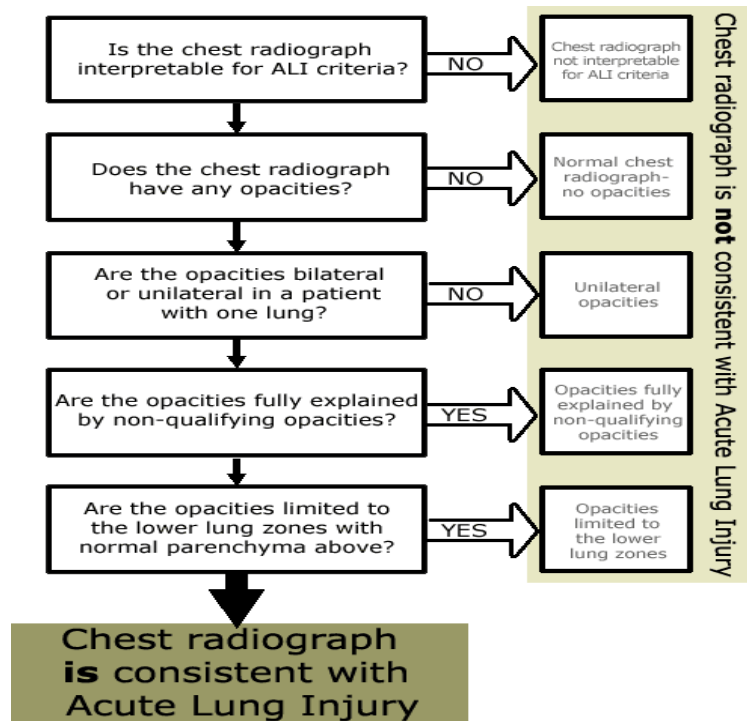
1. Baseline characteristics: date of birth, gender, weight, height, date and time of hospital and ICU admission, admission source (direct admission from the emergency or the operating room vs. transfer admission from another hospital or the hospital floor in the same hospital), ICU admission diagnosis, date/time of onset of mechanical ventilation.
2. Severity of illness at the time of ICU admission: Acute Physiology and
3. Chronic Health Evaluation III scores and predicted mortality
4. Physiologic Variables: Heart rate, Blood pressure, Daily fluid Input/output.
5. Severity of pulmonary dysfunction at day 1 and 3 after development of severe hypoxemia
6. PaO₂/FIO₂, oxygenation index, static and dynamic respiratory system compliances, and minute volume needed to maintain PaCO₂ of 40 mm Hg (V_E 40)
7. Respiratory support: ventilator mode, tidal volume, FiO₂, positive end-expiratory pressure, peak and plateau airway pressure.
8. Laboratory data: ABG: pH, paco₂, pao₂ (median, over 24 hour), Hemoglobin and Hematocrit (nadir), Coagulation studies.

The following data was manually extracted:

1. Advance directives: at admission and during hospital course.
2. Other ICU interventions: use of steroids, neuromuscular blocking agents, NO, iPGI, recruitment maneuvers
3. Etiology for severe hypoxemia

4. Time of initiation of each RS, duration, Sequence of use of RS, complications and reasons for withdrawal/ termination

University of Washington Chest Radiograph Reading Protocol



A 4-component LIS was then calculated and patients with an $LIS \geq 3$ were defined as having severe hypoxemic respiratory failure. Details of Murray LIS follow:

The lung injury score (Murray score)

1. Chest roentgenogram score

No alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrant	2
Alveolar consolidation confined to 3 quadrant	3
Alveolar consolidation in all 4 quadrant	4

2. Hypoxemia score

PaO ₂ /FiO ₂	>300	0
PaO ₂ /FiO ₂	225–299	1
PaO ₂ /FiO ₂	175–224	2
PaO ₂ /FiO ₂	100–174	3
PaO ₂ /FiO ₂	≤ 100	4

3. PEEP score (when ventilated)

PEEP	≤ 5 cm H ₂ O	0
PEEP	6–8 cm H ₂ O	1
PEEP	9–11 cm H ₂ O	2
PEEP	12–14 cm H ₂ O	3
PEEP	> 15 cm H ₂ O	4

4. Respiratory system compliance score (when available)

Compliance	>80 ml/cmH ₂ O	0
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The lung injury score (Murray score)

Compliance	60–79 ml/cmH ₂ O	1
Compliance	40–59 ml/cmH ₂ O	2
Compliance	20–39 ml/cmH ₂ O	3
Compliance	< 19 ml/cmH ₂ O	4

The final score is calculated by the addition of the component parts.

Score 0= no lung injury; 1–2.5 = mild to moderate lung injury

>2.5= severe lung injury