ARDS: Which rescue firstly in ARDS, prone positioning vs. ECMO?
- ECMO -

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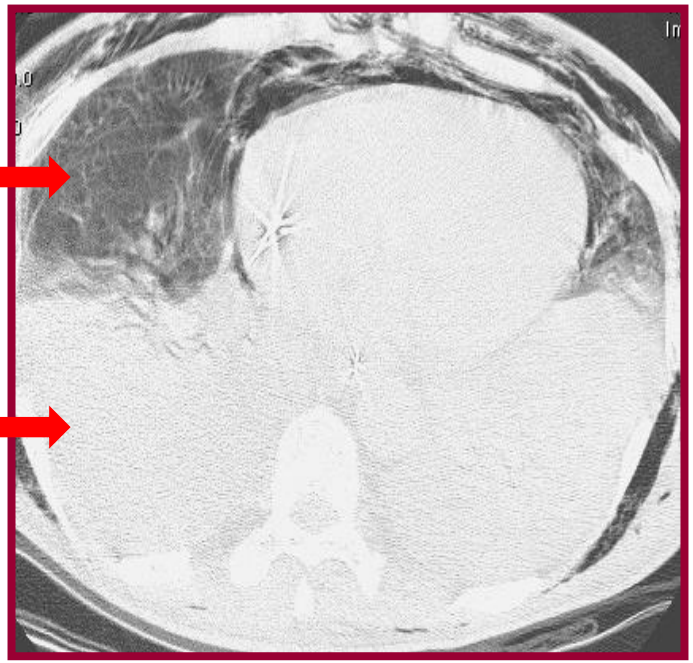
Lung-protective ventilation

- Low tidal volume (≈6ml/kg)
- "Sufficient" PEEP
- Permissive hypercapnia
- Pressure limitation (Pplat ≤ 30 cmH_2O)

Overdistention

Repeated closing and opening of alveoli

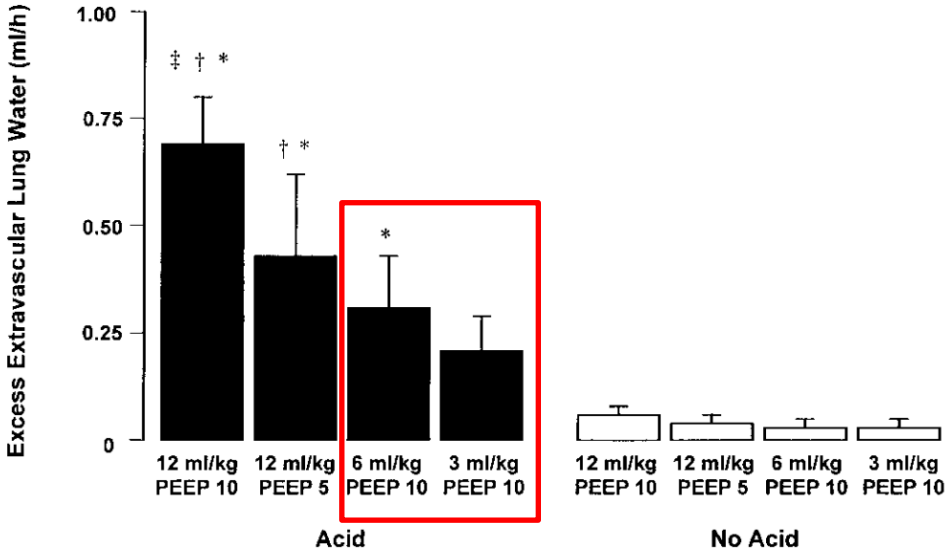


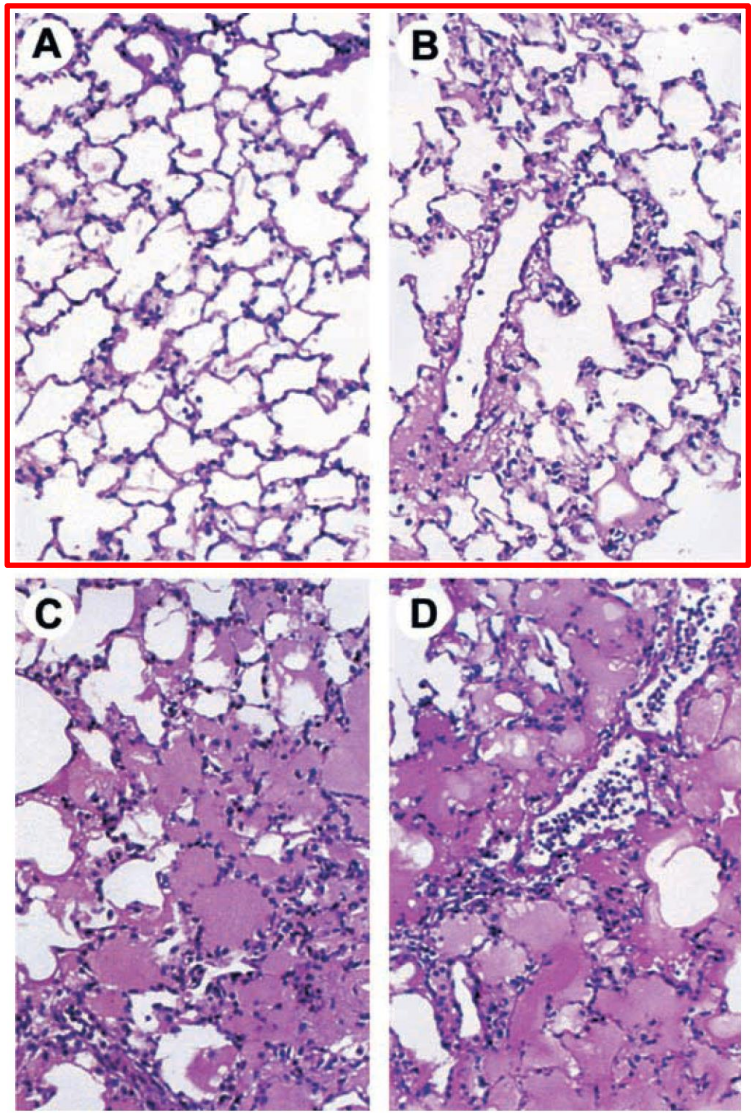
"Baby lung"

Ventilator-induced lung injury (VILI)

- Barotrauma: Pplat, driving pressure (ΔP)
- Volutrauma: Vt
- Atelectrauma: respiratory rate (RR), mechanical power
- Ergotrauma: vascular
- Myotrauma: ventilator-induced diaphragmatic dysfunction (VIDD)
- Biotrauma

VILI despite lung-protective ventilation

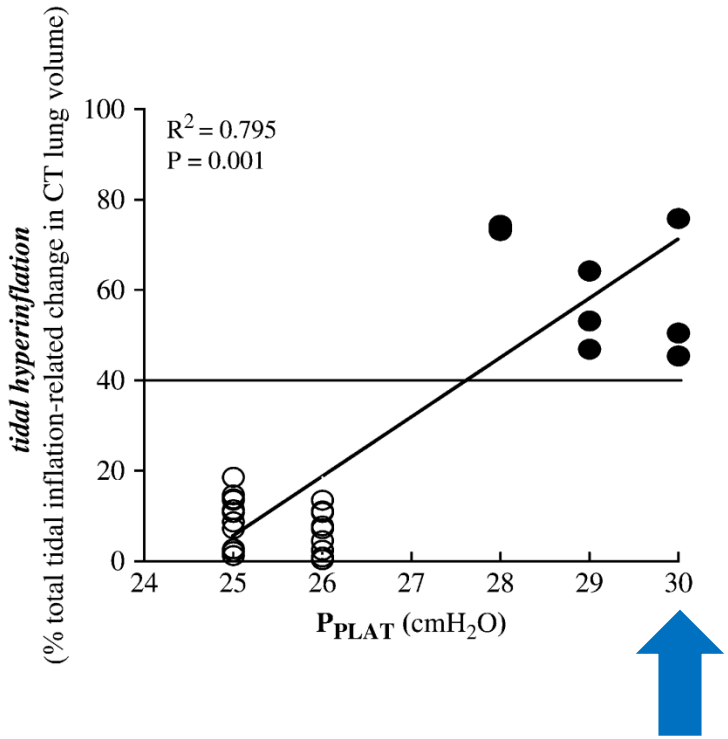


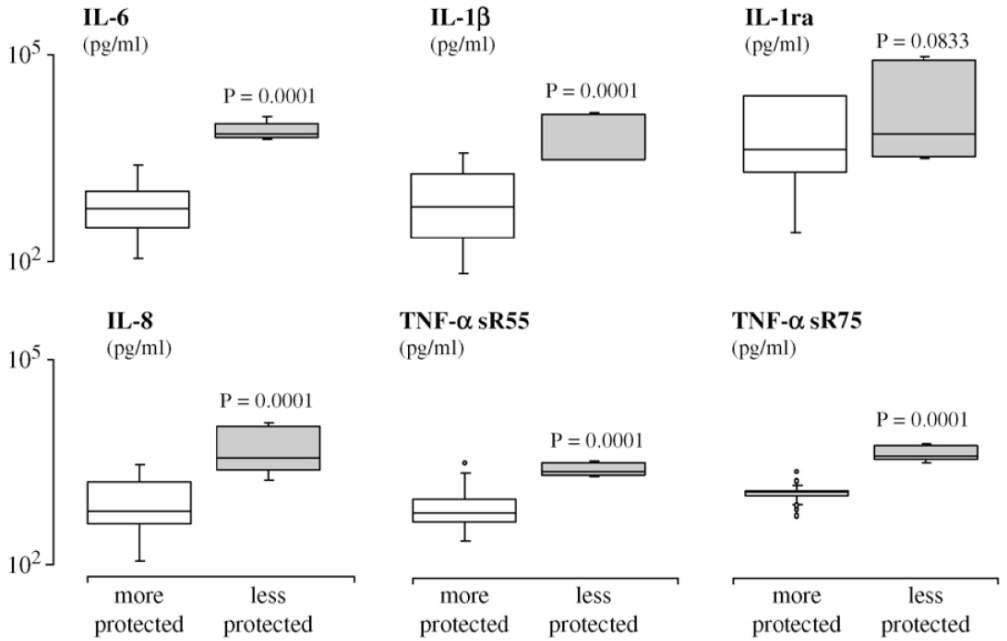


Am J Respir Crit Care Med 2002;165:242-9

VILI despite lung-protective ventilation

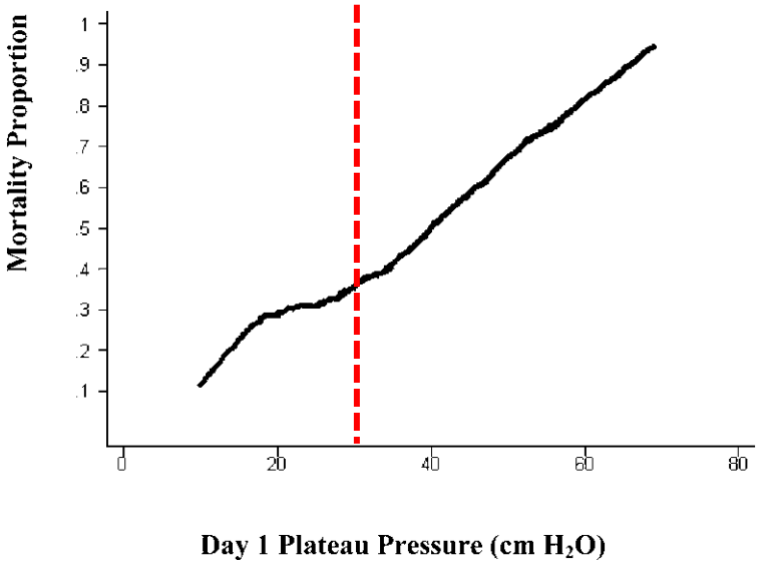
10/30 (33%) of ARDS pts: tidal hyperinflation and elevated cytokine levels despite traditional lung protection strategy



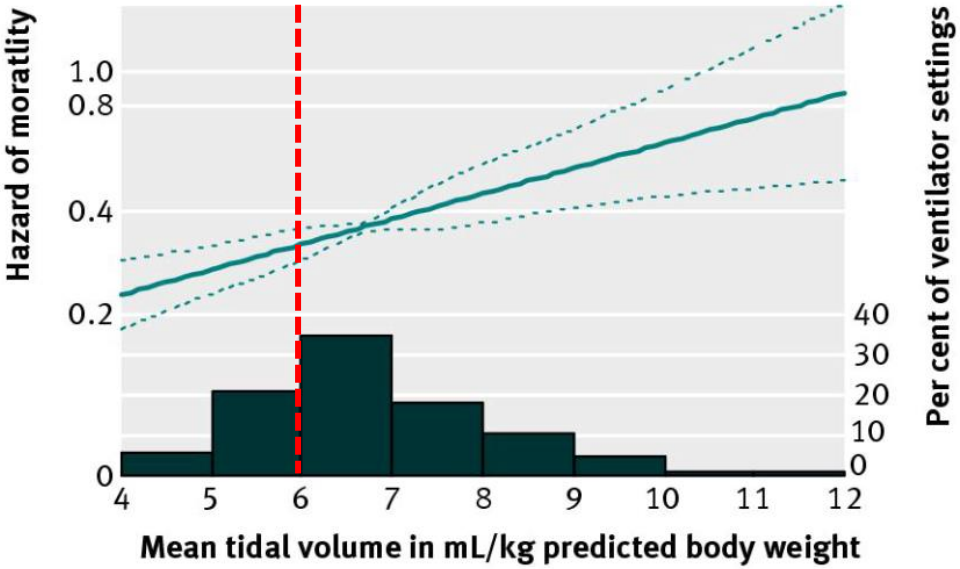


Am J Respir Crit Care Med 2007;175:160-6

VILI despite lung-protective ventilation



ARDSNet ARMA data set
(n = 787)

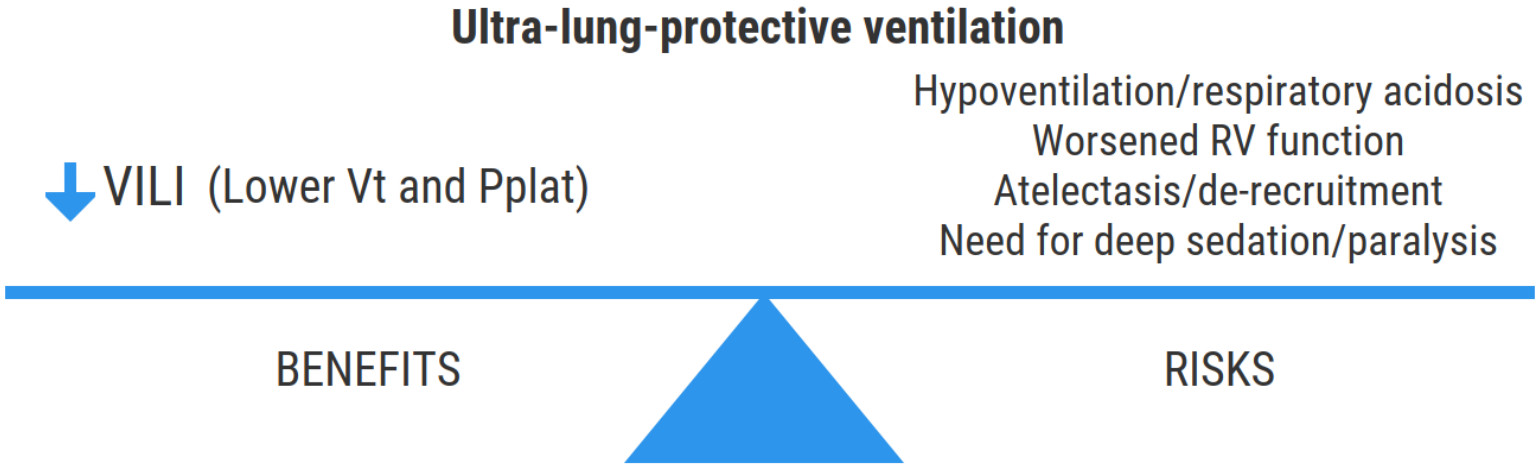


485 pts with acute lung injury

Am J Respir Crit Care Med 2005;172:1241-5
BMJ 2012;344:e2124

Ultra-lung-protective ventilation

- Below current standard of care with lower Vt and pressures
- ≤4 mL/kg PBW
- Pplat ≤25 cmH_2O



Increasing respiratory rate

- May produce dynamic hyperinflation
- Impair right ventricular dysfunction (acute cor pulmonale)
- Require deep sedation and paralysis
- Increases mechanical power
- Mortality: ↑ RR of 4 breaths/min ≈ ↑ ΔP of 1 cmH_2O (Costa et al.)

Am J Respir Crit Care Med 2021;204:303-11

ECMO

- Membrane oxygenators designed to replace lungs' gas exchange by supplying oxygen and removing CO_2 from blood

- Venovenous: venous blood from IVC through femoral v. and reinjected to jugular v. (Vf-Vj) or contralateral femoral v. (Vf-Vf)

- High blood flow (4-8 L/min) and diffusion of gases between blood and "sweep gas" flow

  → provide oxygen and remove CO_2 directly from blood

  → lower intensity of mechanical ventilation

ECMO

The NEW ENGLAND JOURNAL of MEDICINE

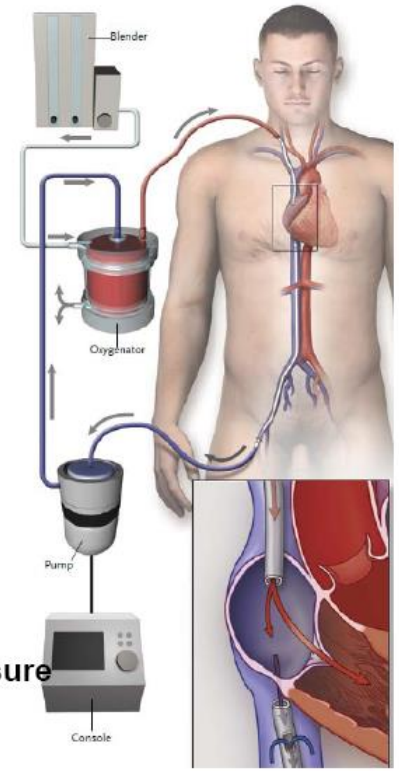
CLINICAL THERAPEUTICS

Extracorporeal Membrane Oxygenation for ARDS in Adults

Daniel Brodie, M.D., and Matthew Bacchetta, M.D.

N Engl J Med 2011;365:1905-14.

Arbitrary !!!



Indications:

- severe hypoxemia (PaO_2/FIO_2 < 80) despite high PEEP (15 – 20 cm H_2O) for at least 6 hrs
- uncompensated hypercapnia with acidemia (pH<7.15) despite best standard care
- excessively high end-inspiratory plateau pressure > 35 cm H_2O

ECMO

- Minimizing hypoxemia decreases tissue hypoxia → reduce organ dysfunction
- Decreases respiratory acidosis and RV afterload → increase cardiac output
- May reduce diaphragmatic myotrauma + controlling CO_2 elimination → decreasing respiratory drive
- Avoid need for paralysis and reduce sedation requirements
- Keeping pts ambulatory (bridge to lung transplantation)

ECMO

12 influenza A(H1N1) ECMO-treated pts

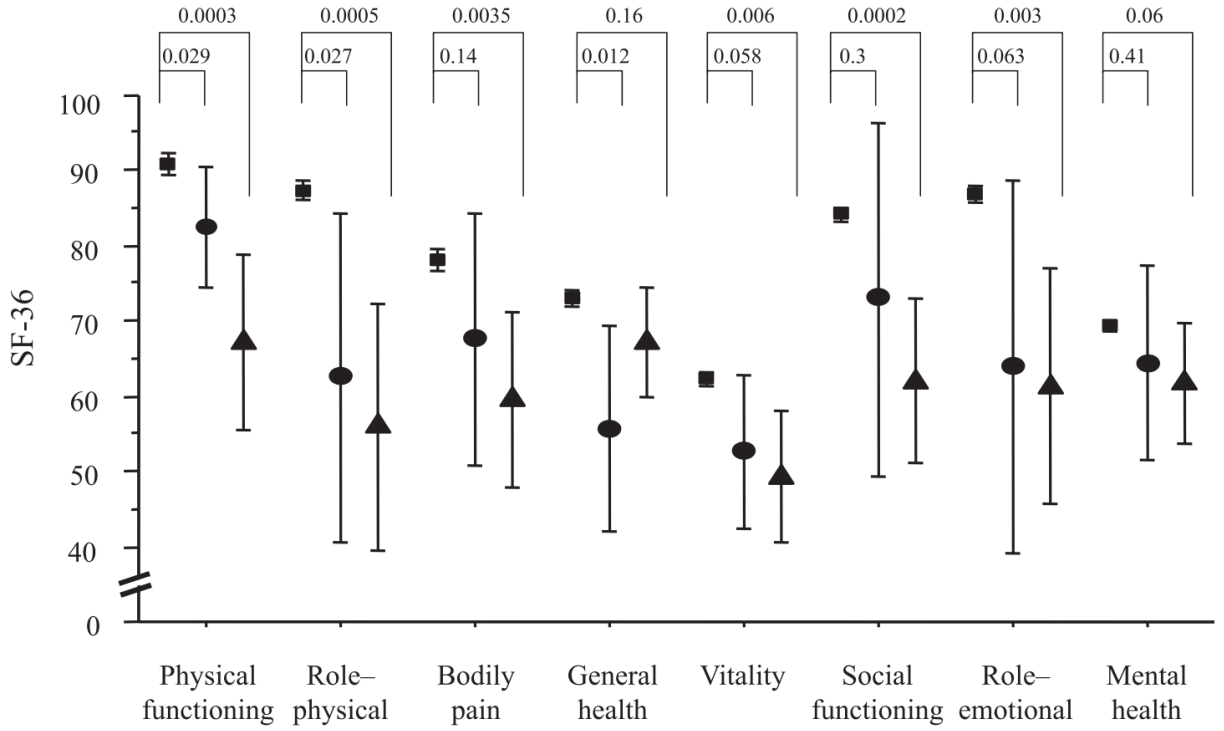


FIGURE 2. Comparison of the SF-36 scores of patients with ARDS who required ECLA (●) with those who did not (▲) vs the normative values of an age- and sex-matched French general population group (■). The T-bars indicate 95% CIs. *P* values are given for comparisons between ECLA and normative values and between no-ECLA and normative values. SF-36 = 36-Item Short-Form Health Survey. See Figure 1 legend for expansion of other abbreviation.

Chest 2012;142:583-92

Influenza A(H1N1) pandemic

Extracorporeal Membrane Oxygenation for Pandemic Influenza A(H1N1)–induced Acute Respiratory Distress Syndrome
A Cohort Study and Propensity-matched Analysis

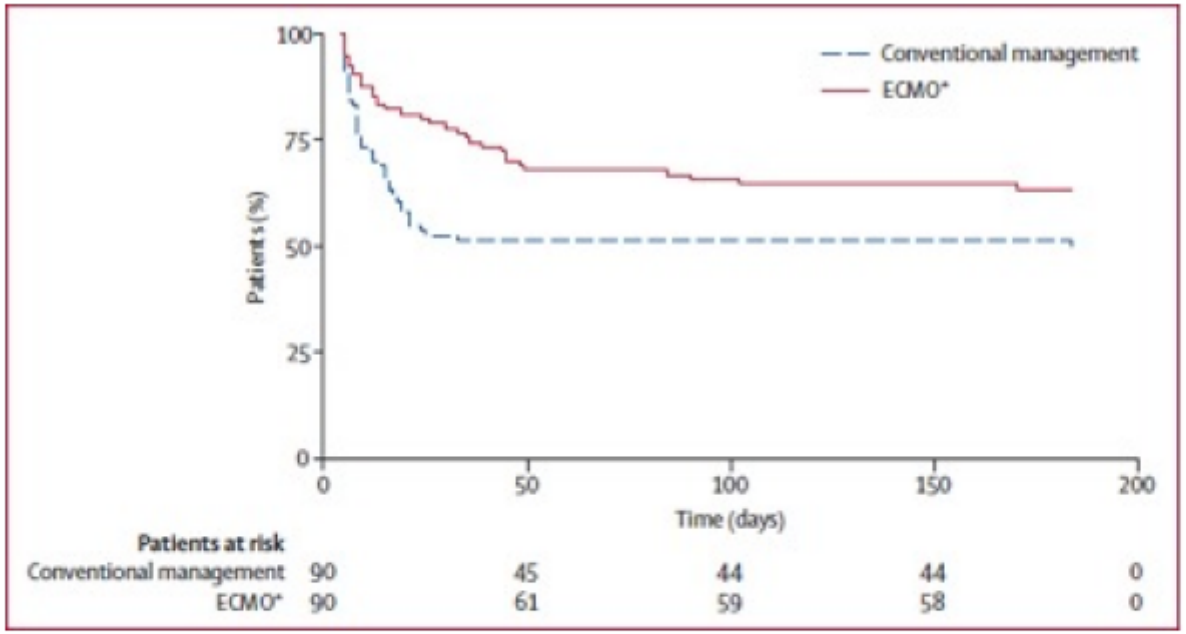
The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks

Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1)

Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome

National observational cohorts from France, Italy, UK, Australia and New Zealand
: reported low mortality (21-36%) in ARDS pts treated with ECMO

CESAR trial

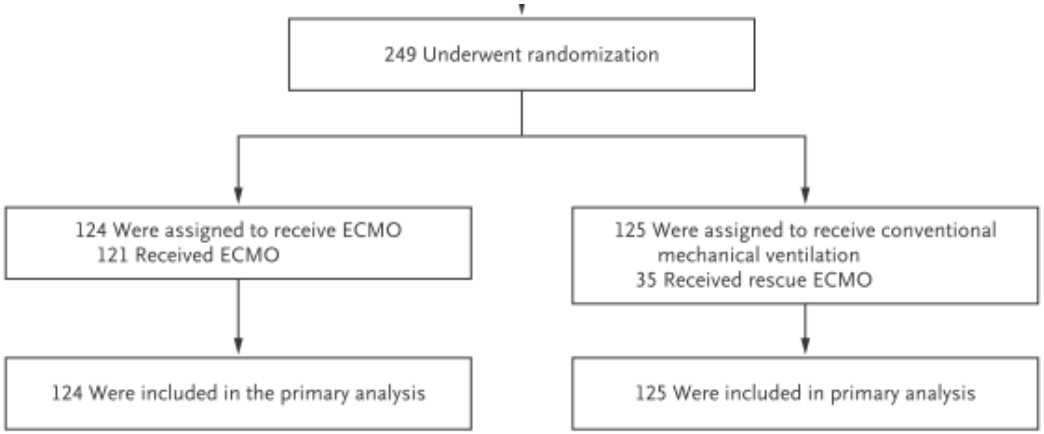


- Fewer patients in the ECMO arm than in the CM arm had died or were severely disabled 6 months
- 33/90 (36.7%) vs 46/87(52.9%)
- relative risk (RR) = 0.69 [95%(CI) 0.50 to 0.97]; $p = 0.030$].

Lancet 2009;374:1351-63

EOLIA trial

- International multicenter randomized trial testing the efficacy of early VV-ECMO in pts with severe ARDS with conventional MV



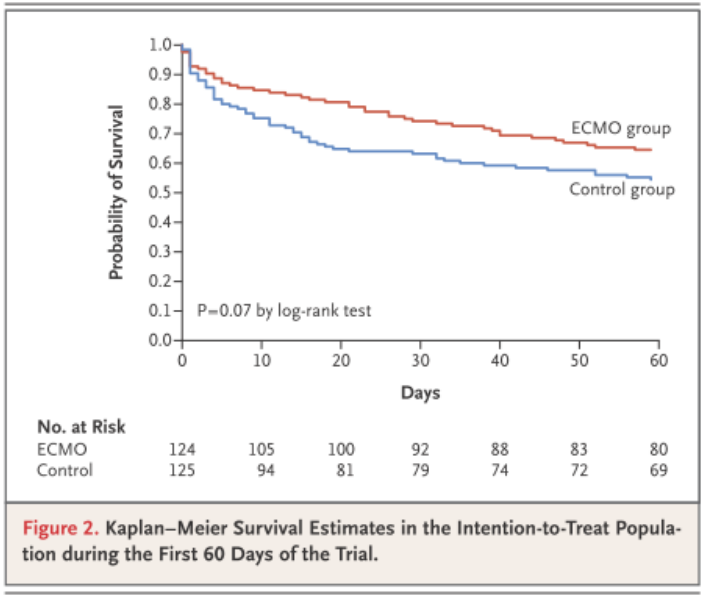


Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

28% rate of crossover to ECMO among pts with refractory hypoxemia in control group (43% of them survived) may have diluted potential effect of ECMO …

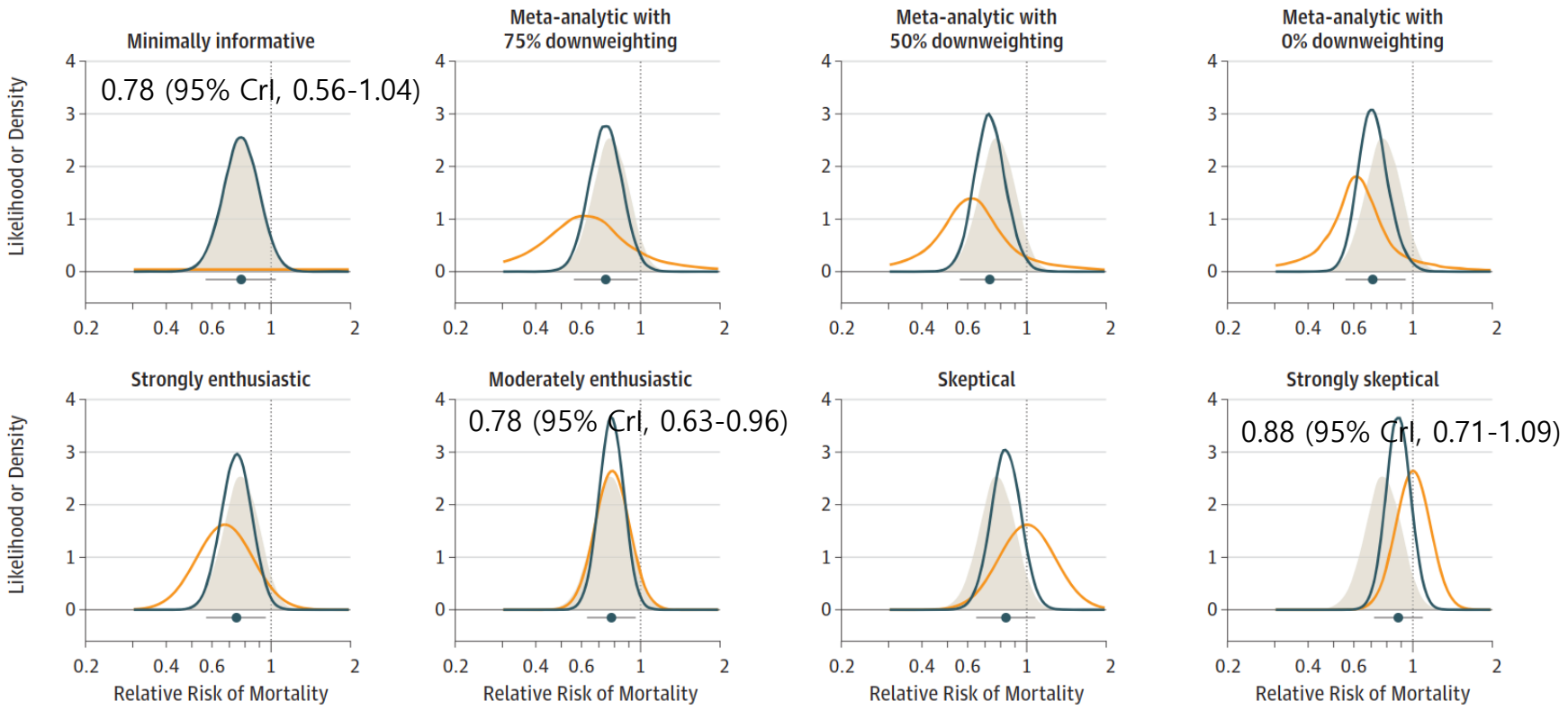
N Engl J Med 2018;378:1965-75

EOLIA trial

- **90% of control group** and 66% of ECMO group received a trial of **prone positioning**
- ECMO group: significant reduction of cardiac failure, renal failure, need for dialysis
- Vt and ΔP: reduced from 6.0 mL/kg → 3.4 mL/kg and 17.8 cmH_2O → 13.2 cmH_2O after 24 h
- Greatest absolute mortality reduction: in group with severe respiratory acidosis with maximum Pplat of 32 cmH_2O

N Engl J Med 2018;378:1965-75

Post hoc Bayesian analysis of EOLIA



High likelihood of survival benefit using ECMO, even when skeptical prior distribution was used

JAMA 2018;320:2251-9

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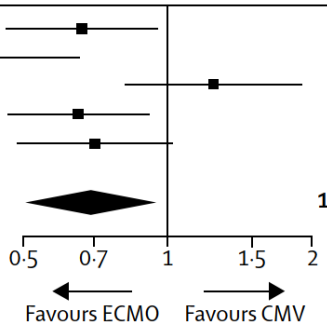
Meta-analysis

30-d mortality

	ECMO		CMV		Weight (%)	Risk ratio (95% CI)
	Events	Total	Events	Total		
Peek et al (2009)[3]	29	90	44	90	21·8%	0·66 (0·46–0·95)
Noah et al (2011)[5]	11	75	31	75	14·4%	0·35 (0·19–0·65)
Pham et al (2013)[6]	26	52	21	52	19·7%	1·24 (0·81–1·90)
Tsai et al (2015)[18]	22	45	34	45	22·7%	0·65 (0·46–0·91)
Combes et al (2018)[10]	32	124	46	125	21·4%	0·70 (0·48–1·02)
Combined	**120**	**386**	**176**	**387**	**100·0%**	**0·69 (0·50–0·95)**

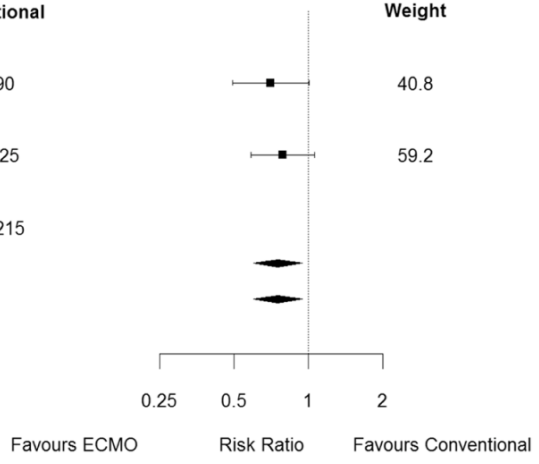
Heterogeneity: τ^2=0·08; χ^2=11·92, df=4, (p=0·02); I^2=66%
Test for overall effect: Z=2·31 (p=0·02)



90-d mortality

Study	ECMO	Conventional	Weight	Risk Ratio [95% CI]
CESAR	31 / 90	44 / 90	40.8	0.70 [0.49, 1.00]
EOLIA	46 / 124	59 / 125	59.2	0.79 [0.59, 1.06]
Total	77 / 214	103 / 215		
RE one-step model				0.75 [0.60, 0.94]
RE two-steps model				0.75 [0.60, 0.94]

Q = 0.22, df = 1, p = 0.64; I^2 = 0.0%, τ^2 = 0.00



Lancet Respir Med 2019;7:163-72
Intensive Care Med 2020;46:2048-57

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국내 ARDS CPG 개정

임상질문

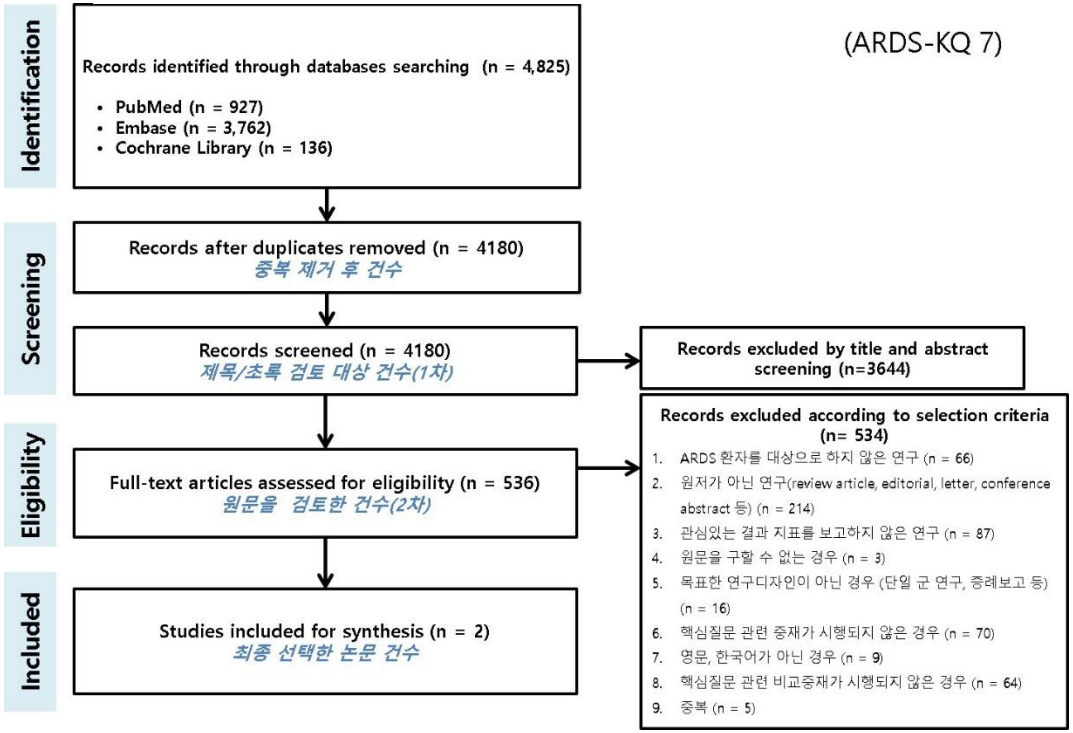
성인 급성호흡곤란증후군 환자에서 체외막산소공급(extracorporeal membrane oxygenation, ECMO)이 기계환기에 비해 사망률을 낮추는가?

PICO 요소

Population: 성인 급성호흡곤란증후군 환자
Intervention: 체외막산소공급
Comparators: 기계환기
Outcomes:
- 핵심적 결과지표: 60-day mortality, 90-day mortality

Study design: 무작위배정비교임상시험

(ARDS-KQ 7)

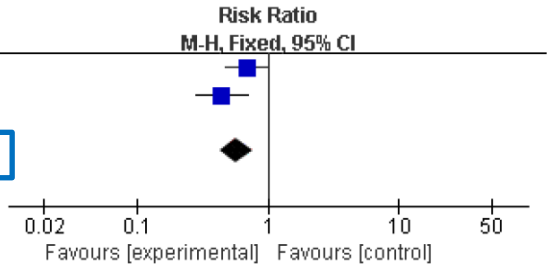


국내 ARDS CPG 개정

Forest plot of comparison: 1 ECMO vs MV, outcome: 1.1 30-day mortality.

Study or Subgroup	ECMO Events	ECMO Total	MV Events	MV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Combes 2018	32	124	46	125	51.6%	0.70 [0.48, 1.02]
Peek 2009	19	90	43	90	48.4%	0.44 [0.28, 0.70]
Total (95% CI)		**214**		**215**	**100.0%**	**0.58 [0.43, 0.77]**
Total events	51		89			

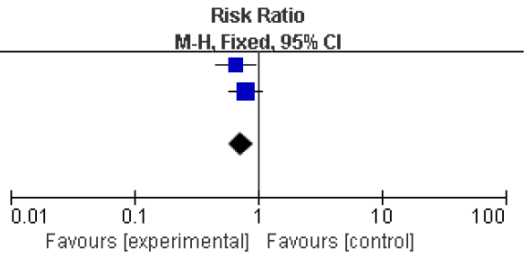
Heterogeneity: Chi² = 2.36, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 3.76 (P = 0.0002)



Forest plot of comparison: 1 ECMO vs MV, outcome: 1.2 60-day mortality.

Study or Subgroup	ECMO Events	ECMO Total	MV Events	MV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Peek 2009	29	90	44	90	44.1%	0.66 [0.46, 0.95]	2009
Combes 2018	44	124	56	125	55.9%	0.79 [0.58, 1.08]	2018
Total (95% CI)		**214**		**215**	**100.0%**	**0.73 [0.58, 0.93]**	
Total events	73		100				

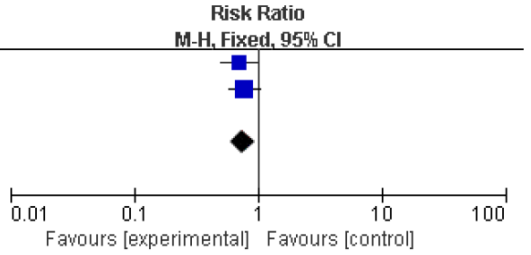
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)



Forest plot of comparison: 1 ECMO vs MV, outcome: 1.3 90-day mortality.

Study or Subgroup	ECMO Events	ECMO Total	MV Events	MV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Peek 2009	31	90	44	90	42.8%	0.70 [0.49, 1.00]	2009
Combes 2018	46	124	59	125	57.2%	0.79 [0.59, 1.06]	2018
Total (95% CI)		**214**		**215**	**100.0%**	**0.75 [0.60, 0.94]**	
Total events	77		103				

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)



국내 ARDS CPG 개정

권고문

중등도도 이상의 급성호흡곤란증후군 환자에서 체외막산소공급을 권고할 수 있다. (권고등급: A, 근거수준: moderate) (2016 ARDS 임상진료지침 2C)

-흡입산소분율(FiO2)에 대한 동맥혈산소분압(PaO2)의 비율 (P/F ratio)이 3시간 이상 50 mmHg 이하인 경우이거나 또는 6시간 이상 80 mmHg 이하인 경우 ECMO 적용을 권고한다.
-6시간 이상 동맥혈 pH of <7.25면서 동맥혈 이산화탄소분압 ≥60 mmHg 인 경우 ECMO 적용을 권고한다.

■ 권고 고려사항

1) 근거수준

포함된 2개의 RCT의 이질성은 낮았다. 비례위험도의 신뢰구간이 1을 넘지 않고 구간도 좁아서 신뢰구간의 정밀성에 문제는 없으나 event 수가 적고 전제 n 수가 적어서 비정밀성 항목에서 1단계 등급을 낮추었다. 그러므로 본 임상질문에 대한 종합 근거수준을 '중등도'로 평가하였다.

2) 이득과 위해

중등증의 호흡부전 환자에서 ECMO 사용의 60일 사망률에 대한 효과는 유의한 사망률 감소 효과를 보여주었다. 비록 한 논문에서 제시된 것이긴 하지만, Bleeding events leading to transfusion와 Severe thrombocytopenia 가 ECMO 군에서 증가하는 것은 ECMO 사용에 주의해야할 문제점이다.

EOLIA study에서 MV 군에서 delayed ECMO transfer 군에서 사망률이 유의하게 증가하는 것을 보여주고 있다. 이는 ECMO 사용의 중요한 시간적인 delay 를 하지 말것을 제시하는 것이다.

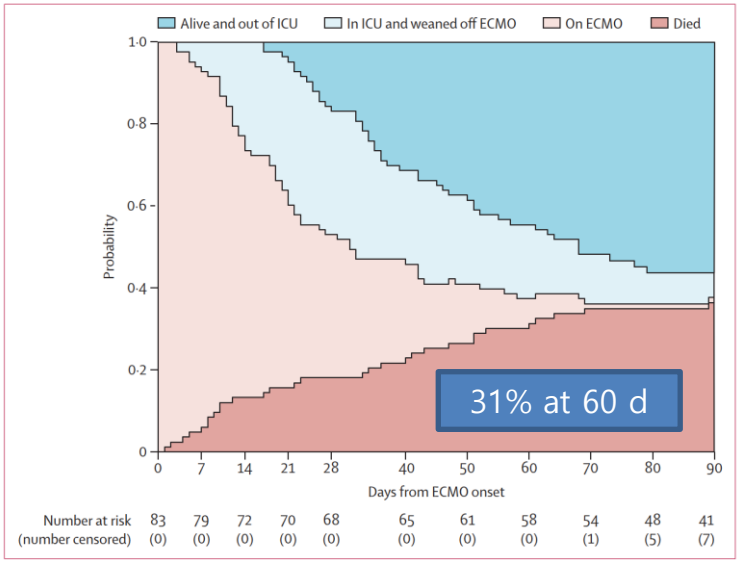
ECMO in COVID-19 ARDS

Early reports (Wuhan, China) suggested poor prognosis for pts with COVID-19 ARDS treated with ECMO, with mortality exceeding 80%

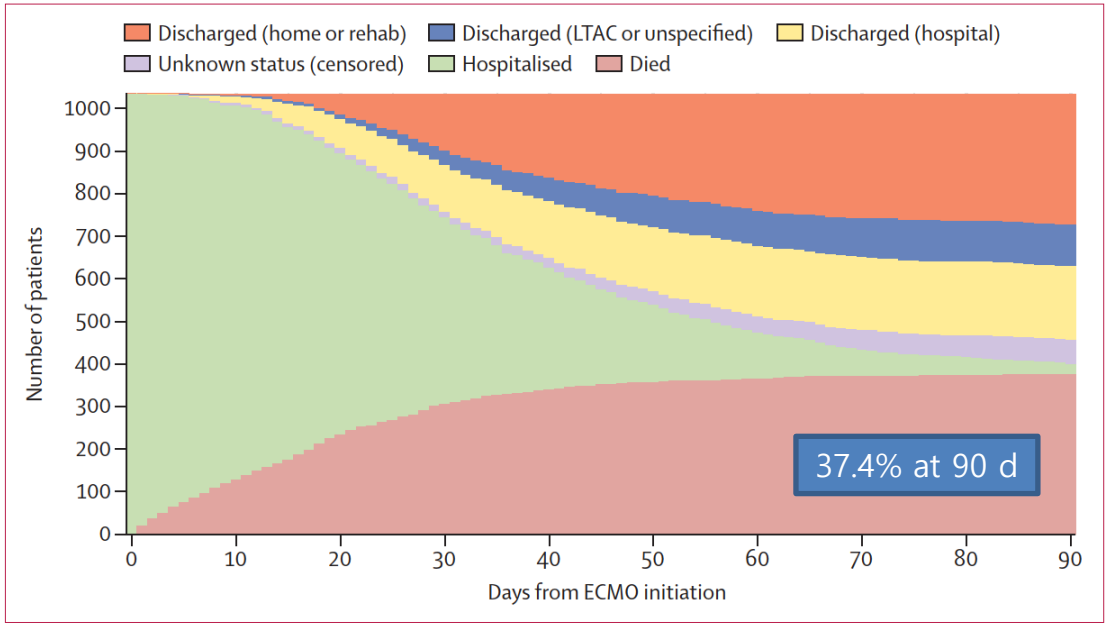
	Huang C et al.[3]	Nanshan Chen et al. [4]	Wang D et al.[5]	Yang X et al. [6]	Guan WJ et al.[7]	Zhou F et al. [8]
Study type	Cross-sectional	Retrospective, observational	Case series	Retrospective, observational	Cross-sectional	Retrospective, cohort study
n	41	99	138	710	1099	191
ICU admission, proportion,% (95% CI)	31.7 (18.08–48.08)	17.17 (10.33–26.06)	26.08 (18.98–34.24)	7.32 (5.51–9.49)	5.0 (3.79–6.46)	26,17 (20.09–33.01)
ARDS, proportion,% (95% CI)	29.26 (16.13–45.53)	17.17 (10.33–26.06)	19.56 (13.3–27.17)	4.93 (3.45–6.78)	3.36 (2.38–4.6)	30.89 (24.1–37.96)
Risk of death during ECMO support, relative risk (95% CI)	Data were unavailable to calculate	0.46 (0.09–2.39)	Data were unavailable to calculate)	0.89 (0.61–1.29)	2.88 (1.65–5.01)	0.96 (0.66–1.41)
Overall mortality rate, proportion,% (95% CI)	14.63 (5.56–29.17)	11.11 (5.67–19.01)	4.34(1.61–9.22)	4.50 (3.10–6.30)	1.36 (0.76–2.24)	28,27 (22.0–35.22)

Heart Lung 2020;49:348-9

ECMO in COVID-19 ARDS



Single-center (France, n = 83)



ELSO registry (36 countries, n = 1,035)

Lancet Respir Med 2020;8:1121-31
Lancet 2020;396:1071-8

Mortality increasing over time

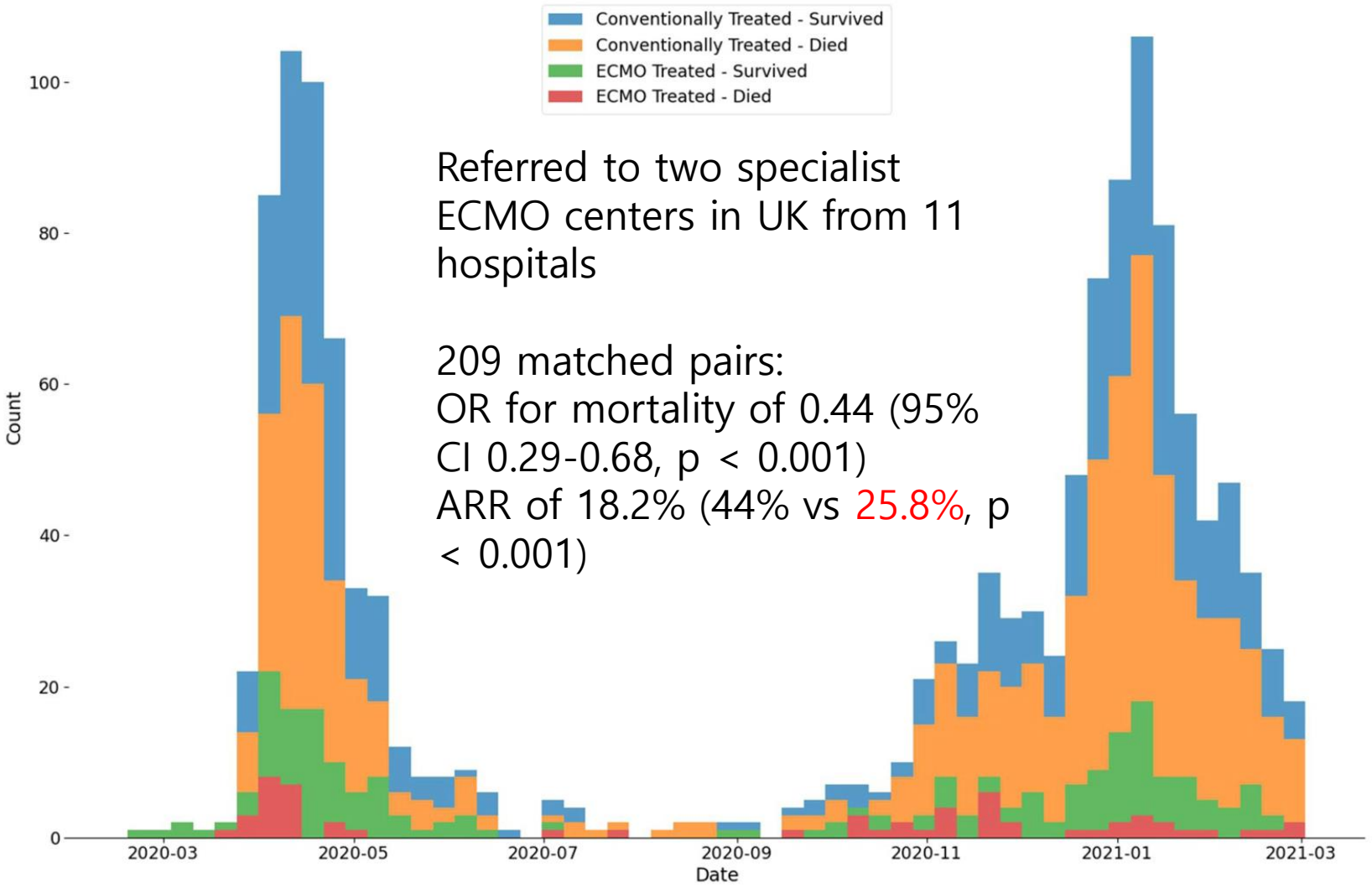
Study and setting	Cohorts by date of ECMO initiation	N	Outcome (earlier vs later cohorts)	Notable differences (earlier vs later cohorts)
Barbaro (20)*, International	Jan 1 2020 – May 1 2020 (A1) May 2 2020 – Dec 31 2020 (A2) May 2 2020 – Dec 31 2020 (B)	1182 2824 806	In-hospital mortality at day 90 A1 36.9% vs A2 51.9% vs B 58.9% A1 vs A2: HR 0.82 [0.70–0.96] B vs A2: HR 1.42 [1.17–1.73]	Duration of ECMO (A1 vs A2): 14.1 vs 20.0 days Pre-intubation noninvasive respiratory support: A1 58% A2 76% B 70% Pre-ECMO IMV duration: A1 4.0 (1.7-6.3) days A2 3.1 (0.9-6.3) days B 2.7 (0.8-5.9) days Steroids: A1 43% A2 78% B 72%
Broman (21), Europe	Mar 12 2020 – Sept 14 2020 Sept 15 2020 – Mar 8 2021	1442 1723	In-hospital mortality† 47% vs 56%, p<0.0001	
Riera (22), Spain and Portugal	Mar 1 2020 – Jun 30 2020 July 1 2020 – Dec 1 2020	151 168	In-hospital mortality 41.1% vs 60.1%, p=0.001	Age: 51.2 ± 10.5 vs 54.6 ± 9.9 Age >65: 5.3% vs 13.1% ICU admission to ECMO: 6 vs 8 days % of cases at high-volume‡ centers: 35.8% vs 25.0% Steroids: 69.5% vs 93.4%
Schmidt (23), France	Mar 8 2020 – Jun 30 2020 July 1 2020 – Jan 28 2021	88 71	90-day mortality 36% (27-47%) vs 48% (37-60%) HR 2.27, 95% CI 1.02-5.07	Dexamethasone: 18% vs 82% HFNC: 19% vs 82% NIV: 7% vs 37%

Am J Respir Crit Care Med 2022 Feb 25

Possible explanations

- ↑ Noninvasive respiratory support prior to intubation → leading to more P-SILI pre-ECMO?
- Selection bias for more Tx refractory disease?
- COVID-19 targeted Tx → superimposed bacterial infections?
- Emergence of SARS-CoV-2 variants?
- Use of ECMO in less experienced centers in later pandemic?
- More liberal application of ECMO in later pandemic?

ECMO in COVID-19 ARDS



Referred to two specialist ECMO centers in UK from 11 hospitals

209 matched pairs:
OR for mortality of 0.44 (95% CI 0.29-0.68, $p < 0.001$)
ARR of 18.2% (44% vs 25.8%, $p < 0.001$)

Intensive Care Med 2022;48:467-78

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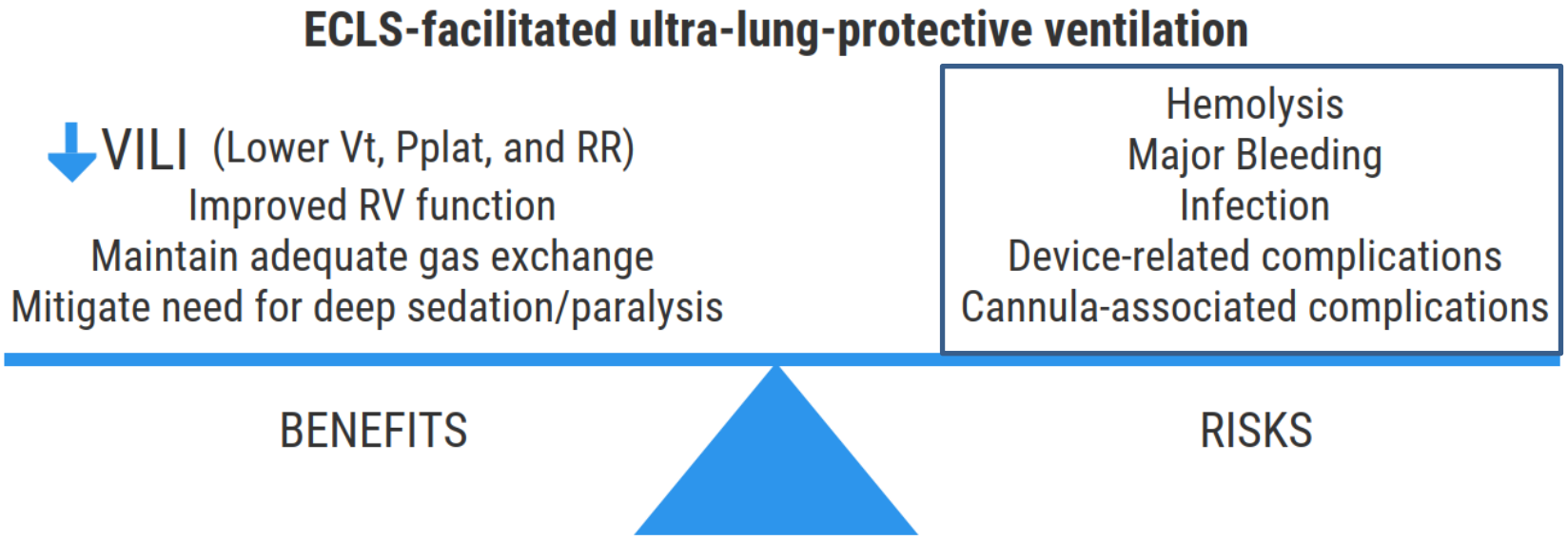
Risks


ECLS-facilitated ultra-lung-protective ventilation
VILI (Lower Vt, Pplat, and RR)
Improved RV function
Maintain adequate gas exchange
Mitigate need for deep sedation/paralysis
Hemolysis
Major Bleeding
Infection
Device-related complications
Cannula-associated complications
BENEFITS
RISKS

Indications

- Pts who are younger, with reversible etiology, few co-morbidities
- Employed in experienced centers
- Only 1 or 2 organ failures
- Highest baseline alveolar dead space fraction and highest respiratory system elastane (or lowest compliance) → most likely to benefit from ECLS-facilitated ultra-lung-protective ventilation (Goligher et al.)

Intensive Care Med 2019;45:1219-30

Predictive survival models

RESP score

Parameter	Score
Age, yr	
18 to 49	0
50 to 59	−2
⩾60	−3
Immunocompromised status*	−2
Mechanical ventilation prior to initiation of ECMO	
<48 h	3
48 h to 7 d	1
>7 d	0
Acute respiratory diagnosis group (select only one)	
Viral pneumonia	3
Bacterial pneumonia	3
Asthma	11
Trauma and burn	3
Aspiration pneumonitis	5
Other acute respiratory diagnoses	1
Nonrespiratory and chronic respiratory diagnoses	0
Central nervous system dysfunction†	−7
Acute associated (nonpulmonary) infection‡	−3
Neuromuscular blockade agents before ECMO	1
Nitric oxide use before ECMO	−1
Bicarbonate infusion before ECMO	−2
Cardiac arrest before ECMO	−2
Pa_{CO_2}, mm Hg	
<75	0
⩾75	−1
Peak inspiratory pressure, cm H_2O	
<42	0
⩾42	−1
Total score	−22 to 15

Hospital Survival by Risk Class		
Total RESP Score	**Risk Class**	**Survival**
⩾6	I	92%
3 to 5	II	76%
−1 to 2	III	57%
−5 to −2	IV	33%
⩽−6	V	18%

PRESERVE score

Parameter	Score
Age (years)	
<45	0
45–55	2
>55	3
Body mass index >30	−2
Immunocompromised	2
SOFA >12[a]	1
MV >6 days	1
No prone positioning before ECMO	1
PEEP < 10 cm H_2O	2
Plateau pressure >30 cm H_2O	2
Total score[c]	0–14

Am J Respir Crit Care Med 2014;189:1374-82
Intensive Care Med 2013;39:1704-13

Conclusions

- Traditional lung-protective ventilation may not be enough in patients with ARDS
- Achieving ultra-lung-protective ventilation with conventional MV is neither feasible nor safe
- ECMO can markedly enhance reductions in Vts, airway pressures, and RR
- Current evidences suggest efficacy of ECMO in severe ARDS due to various etiologies, including COVID-19

Thank you for your attention