Understanding of Phenotypes

정치량

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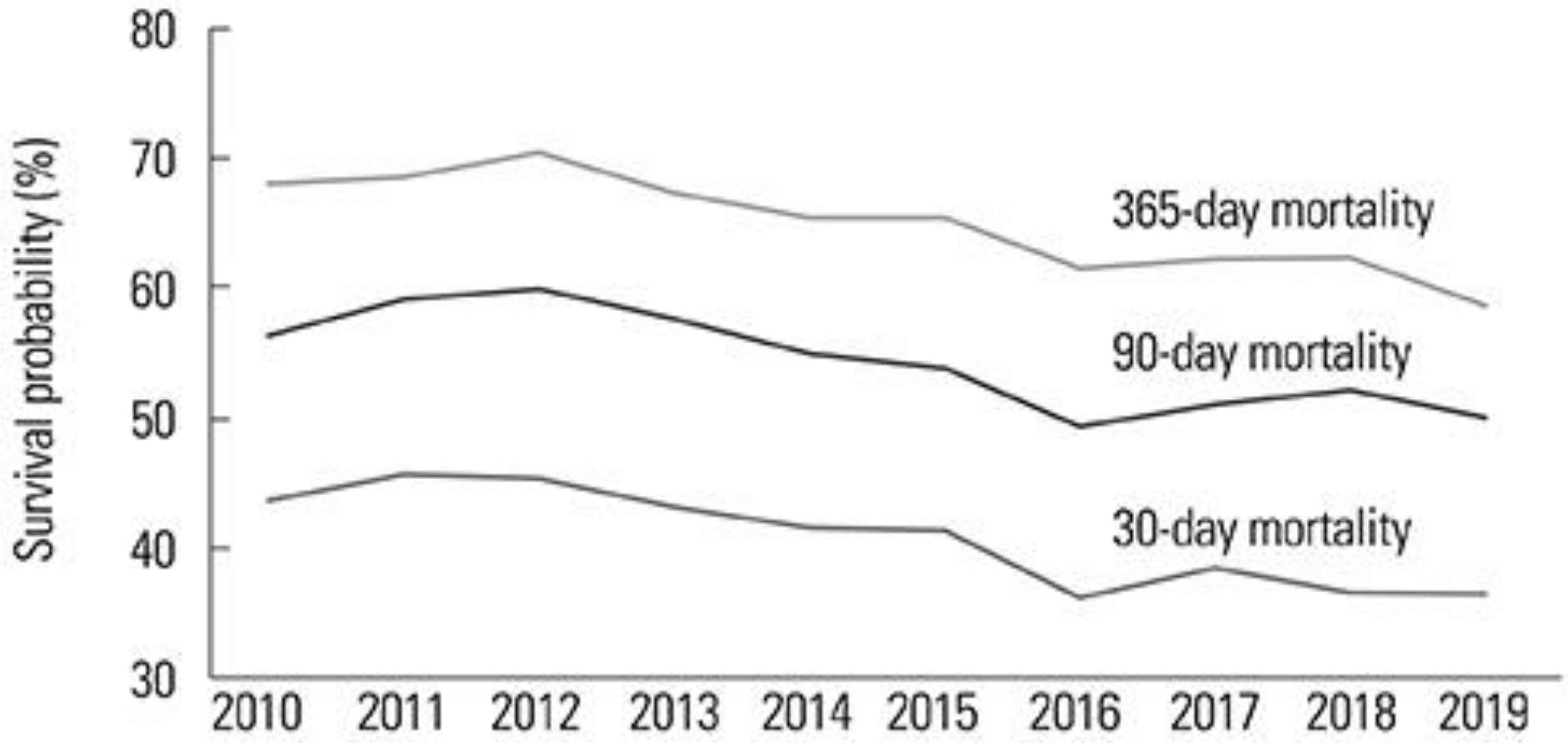
Trends in Mortality of ARDS in South Korea



Yonsei Med J. 2022 May;63(5):452-460.

Summary The respiratory-distress syndrome in 12 patients was manifested by acute onset of tachypnœa, hypoxæmia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy. The clinical and pathological features closely resembled those seen in infants with respiratory distress and to conditions in congestive atelectasis and postperfusion lung. The theoretical relationship of this syndrome to alveolar surface active agent is postulated. Positive end-expiratory pressure was most helpful in combating atelectasis and hypoxæmia. Corticosteroids appeared to have value in the treatment of patients with fat-embolism and possibly viral pneumonia.

Introduction

In the course of clinical and laboratory observations on 272 adult patients receiving respiratory support, a few patients did not respond to usual methods of therapy. They exhibited a clinical, physiological, and pathological course of events that was remarkably similar to the infantile respiratory distress syndrome (hyaline-membrane disease). Difficult cases of respiratory failure in conjunction with prolonged cardiopulmonary bypass (Baer and Osborn 1960), with congestive atelectasis (Berry and Sanislow 1963), with viral pneumonia (Petersdorf et al. 1959), and with fat-embolism (Ashbaugh and Petty 1966) have been recorded; and in these cases the pathophysiology of the illness closely resembled the infantile respiratory distress syndrome and findings in patients described here.

Lancet 1967; 2:319-23

Direct Lung Injury
Pneumonia
Aspiration of gastric contents
Pulmonary contusion
Near-drowning
Toxic inhalation injury

Indirect Lung Injury
Sepsis
Severe trauma
Multiple bone fractures
Flail chest
Head trauma
Burns
Multiple transfusions
Drug overdose
Pancreatitis
Postcardiopulmonary bypass

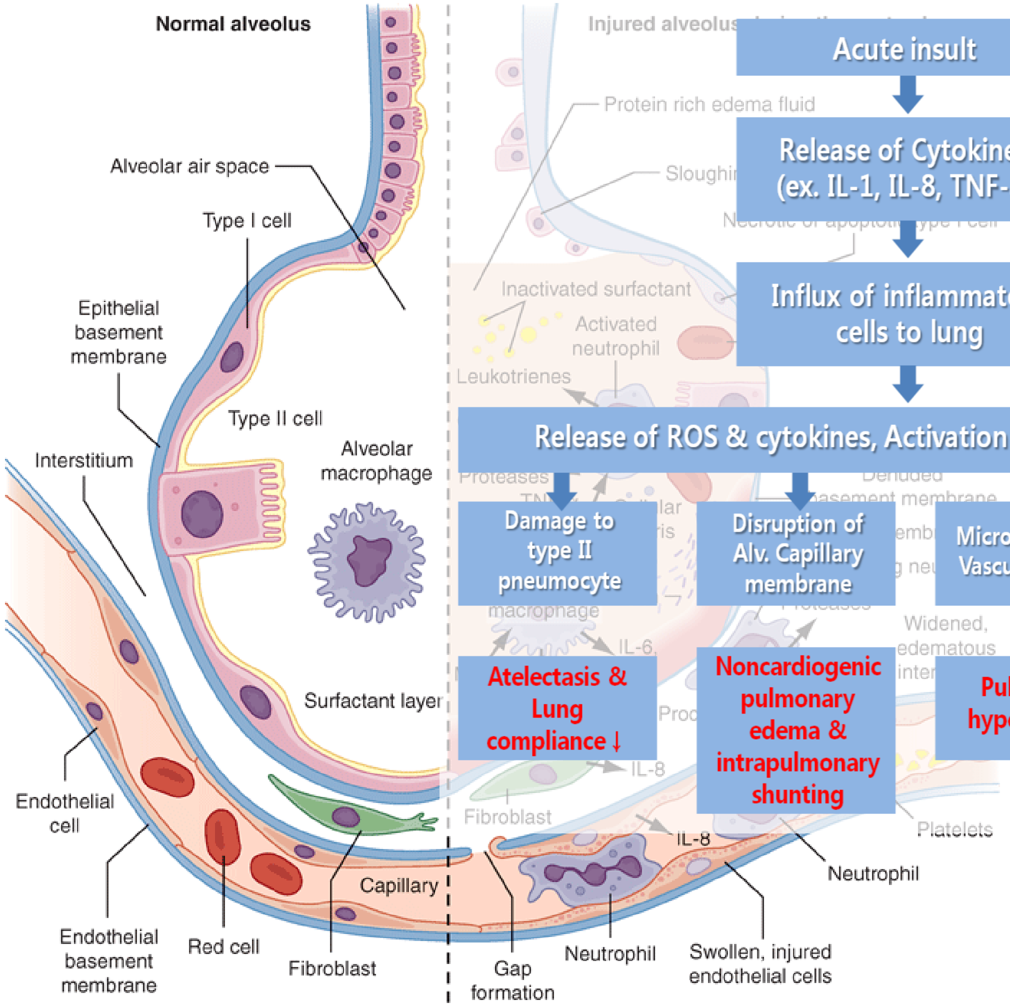
Acute insult

Release of Cytokines (ex. IL-1, IL-8, TNF-a)

Influx of inflammatory cells to lung

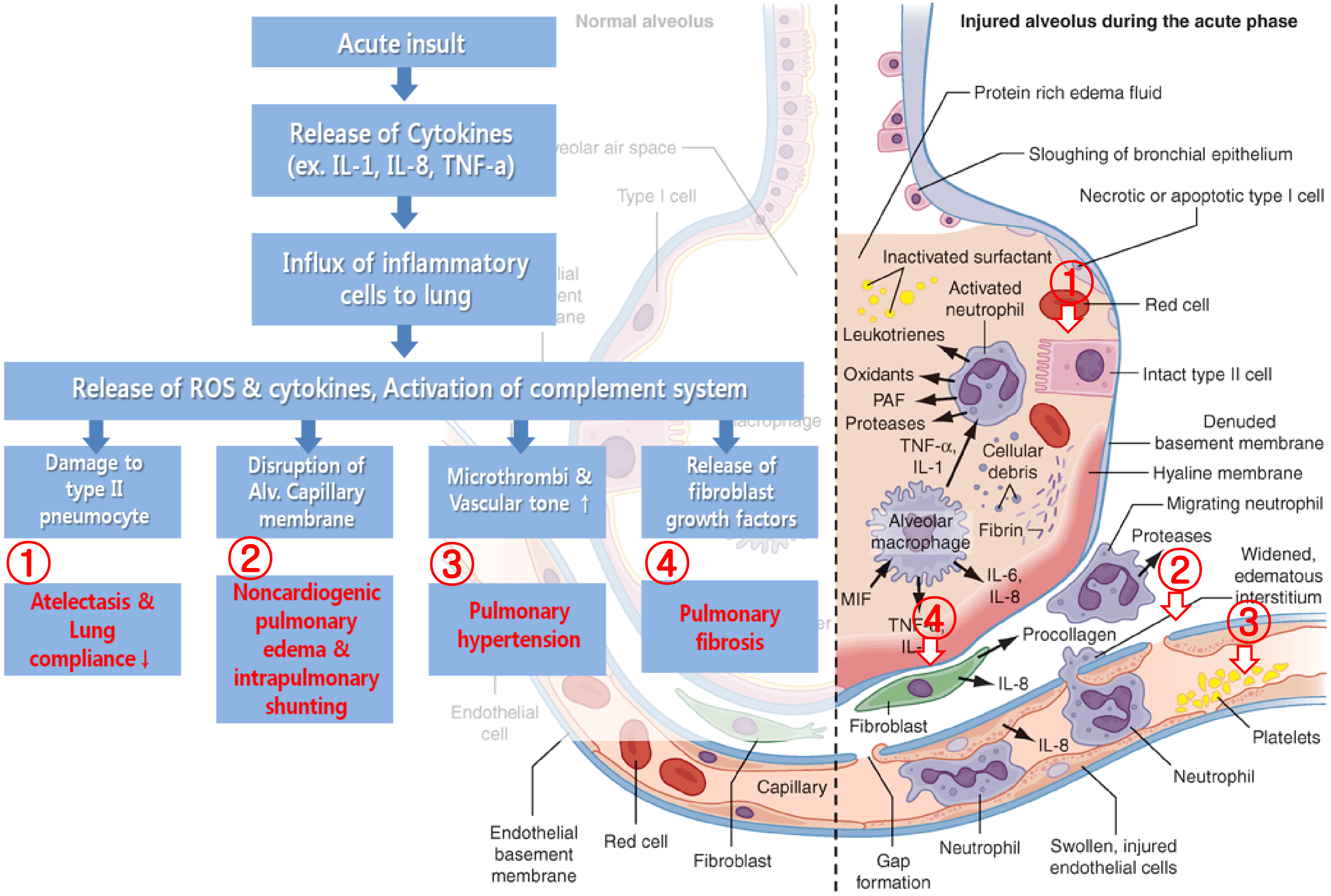
Release of ROS & cytokines, Activation of complement system

- Damage to type II pneumocyte → **Atelectasis & Lung compliance↓**
- Disruption of Alv. Capillary membrane → **Noncardiogenic pulmonary edema & intrapulmonary shunting**
- Microthrombi & Vascular tone ↑ → **Pulmonary hypertension**
- Release of fibroblast growth factors → **Pulmonary fibrosis**



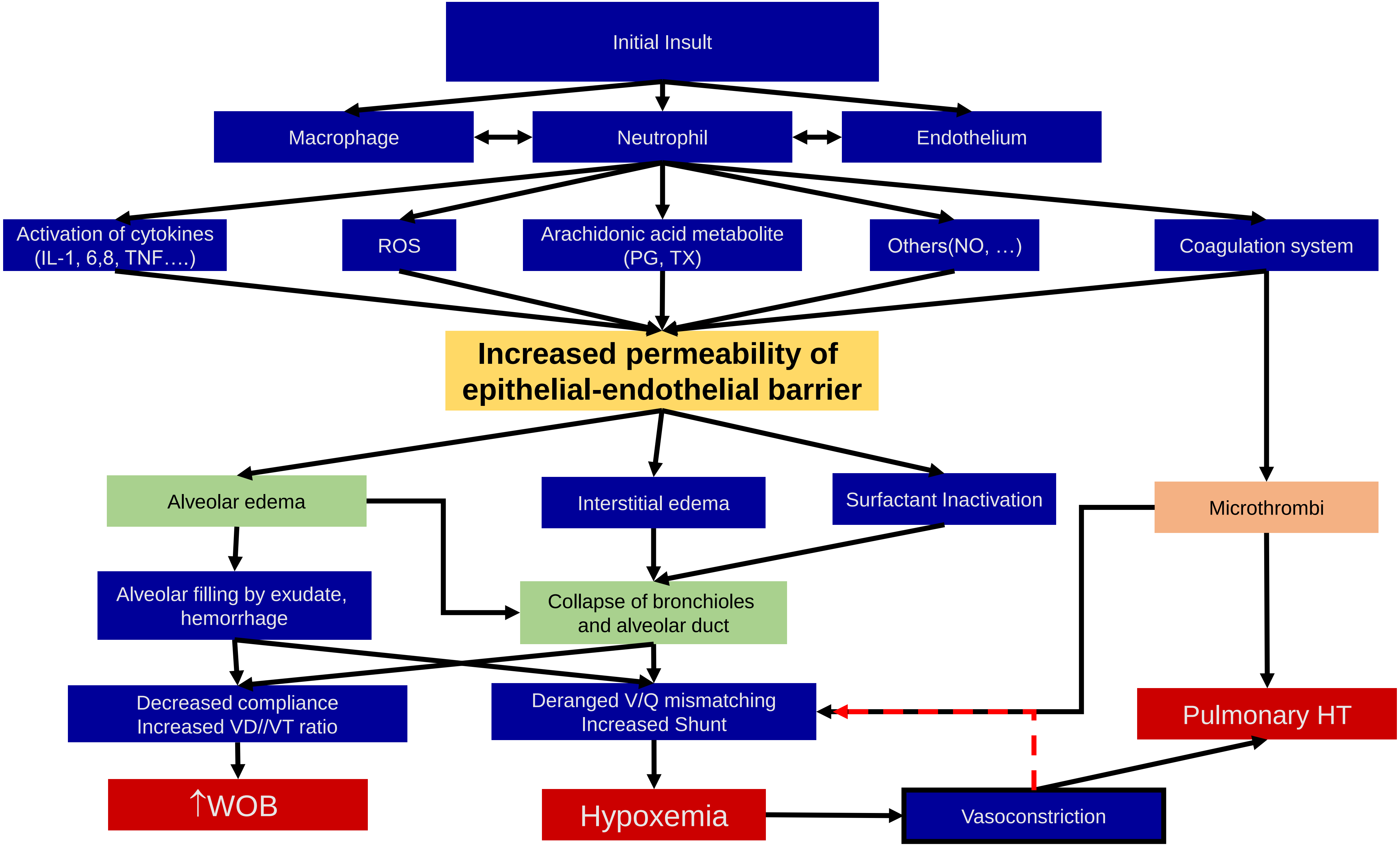
ARDS

(Acute Respiratory Distress Syndrome)



ARDS

(Acute Respiratory Distress Syndrome)


Initial Insult
Macrophage
Neutrophil
Endothelium
Activation of cytokines
(IL-1, 6,8, TNF….)
ROS
Arachidonic acid metabolite
(PG, TX)
Others(NO, …)
Coagulation system
Increased permeability of
epithelial-endothelial barrier
Alveolar edema
Interstitial edema
Surfactant Inactivation
Microthrombi
Alveolar filling by exudate,
hemorrhage
Collapse of bronchioles
and alveolar duct
Decreased compliance
Increased VD//VT ratio
Deranged V/Q mismatching
Increased Shunt
Pulmonary HT
↑WOB
Hypoxemia
Vasoconstriction

Physiologic	Clinical	Biologic
$PaO_2:FiO_2$	Trauma vs. medical	Genomic
Dead space fraction	Direct vs. indirect	Transcriptomic
Driving pressure	Focal vs. diffuse	Proteomic
	±Acute kidney injury	Metabolomic

Wilson and Calfee Critical Care (2020) 24:102

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

ARDS

[a] Chest radiograph or computed tomography scan.

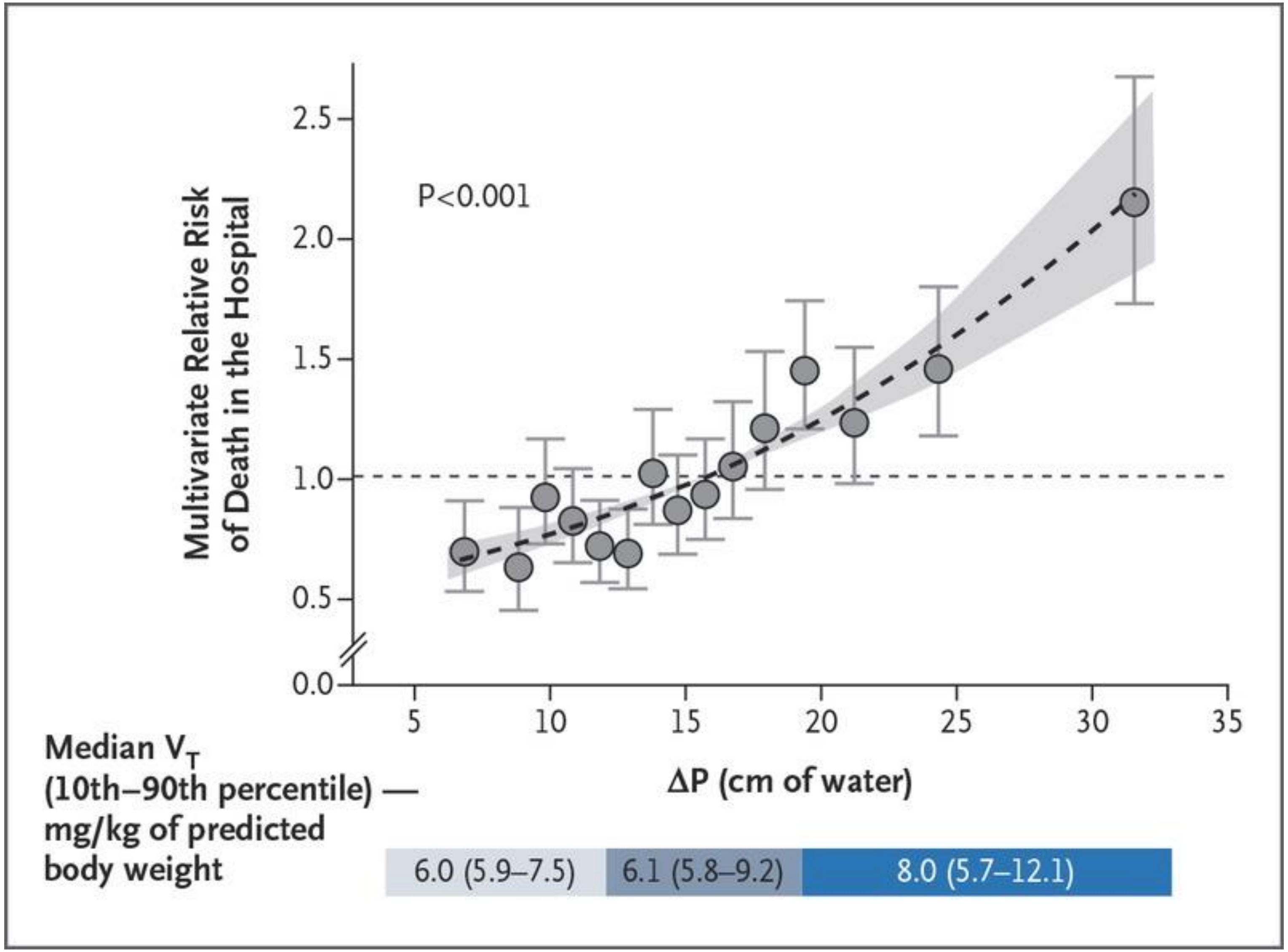
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Murray score
= average score of all 4 parameters

Parameter / Score	0	1	2	3	4
PaO2/FIO2 (On 100% Oxygen)	≥300mmHg ≥40kPa	225-299 30-40	175-224 23-30	100-174 13-23	<100 <13
CXR	normal	1 point per quadrant infiltrated			
PEEP	≤5	6-8	9-11	12-14	≥15
Compliance (ml/cmH2O)	≥80	60-79	40-59	20-39	≤19

Driving Pressure



Focal vs Non-focal

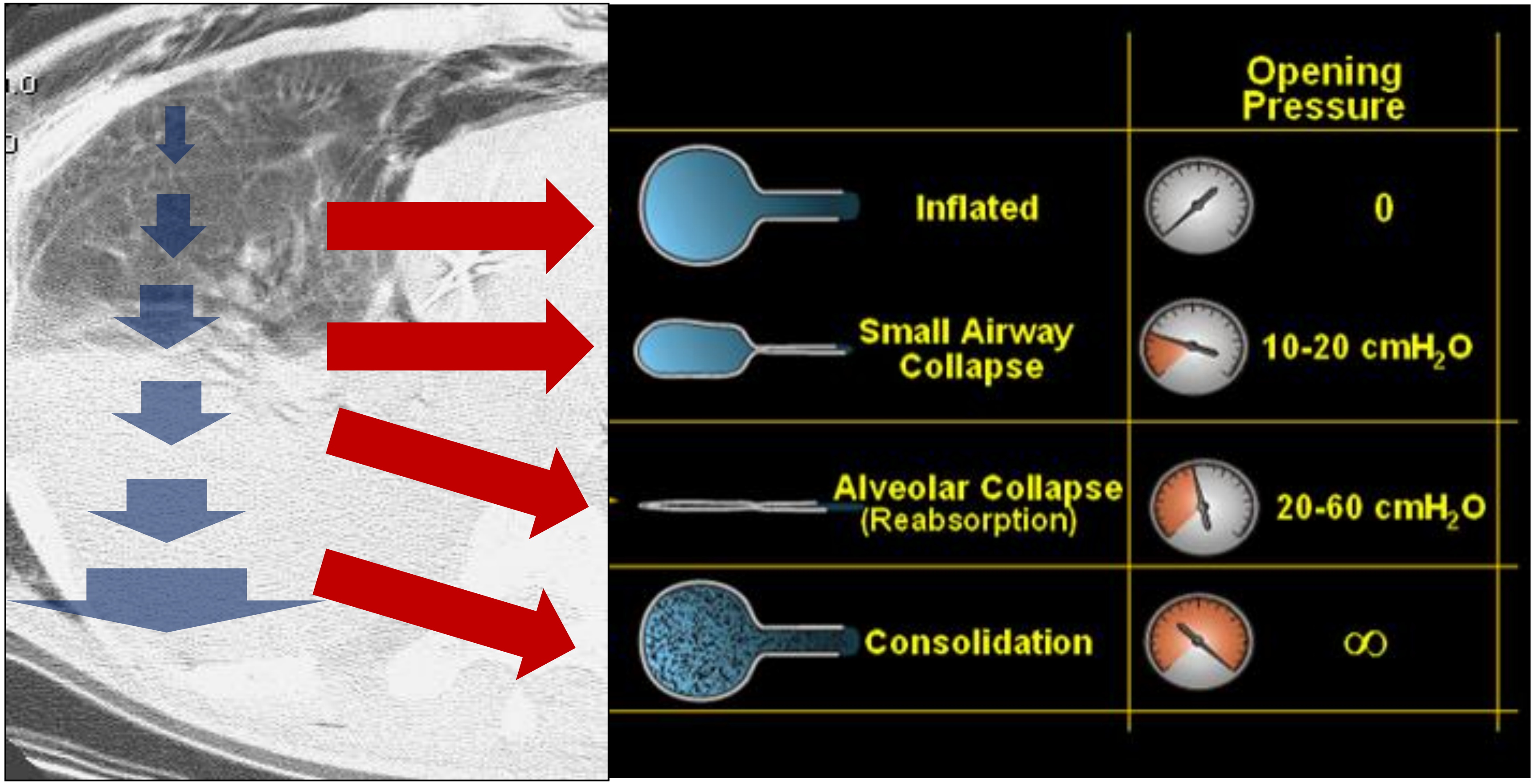
	Control group (n=204)	Personalised group (n=196)	
		Focal lung morphology	Non-focal lung morphology
Mode of ventilation	Volume control	Volume control	Volume control
Tidal volume	6 mL/kg IBW	8 mL/kg IBW	6 mL/kg IBW
PEEP	PEEP/FiO_2	5–9 cm H_2O	To reach Pplat of 30 cm H_2O
PEEP-PSV	Free	5–9 cm H_2O	≥10 cm H_2O
Recruitment manoeuvre	Rescue	Rescue	Mandatory
Prone position	Encouraged	Mandatory	Rescue

IBW=ideal body weight. PEEP=positive-end expiratory pressure. FiO_2=fraction of inspired oxygen. Pplat=end-inspiratory plateau pressure. PEEP-PSV=positive-end expiratory pressure used during pressure support ventilation.

Table 1: **Summary of ventilator settings according to lung morphology and randomisation group**

Lancet Respir Med. 2019;7:870–80.

Wide Variation in Lung Physiology in Early ARDS



Different Phenotypes of COVID-19 ARDS

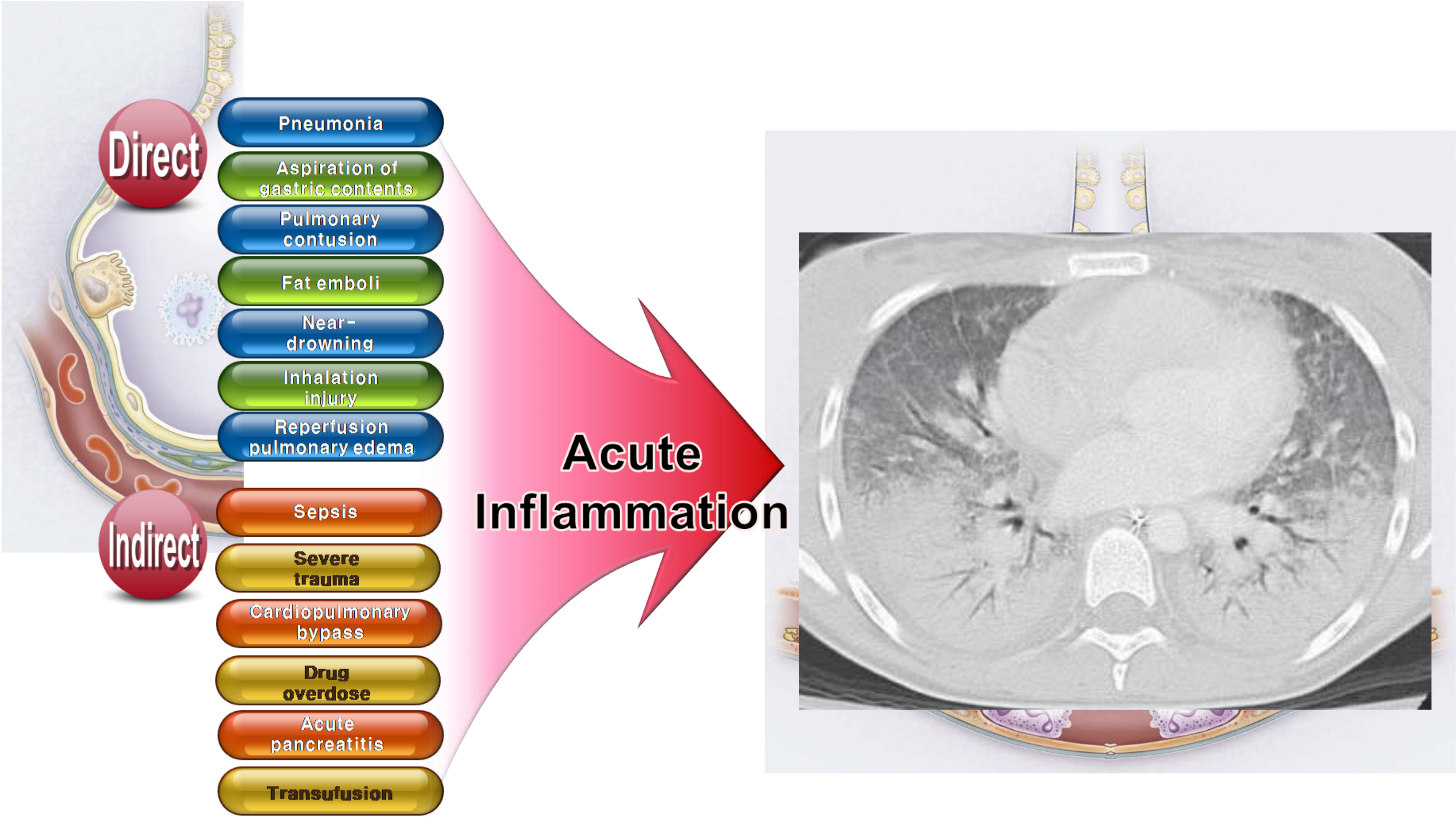
	Type L	Type H
Elastance	Low	High
Mechanism of hypoxia	Low V/Q	High shunt
Lung weight	Low	High
Lung recruitability	Low	High

Gattinoni et al. Intensive Care Med (2020) 46:1099–1102

Comparison of Early "Typical" ARDS vs Early COVID-19 ARDS

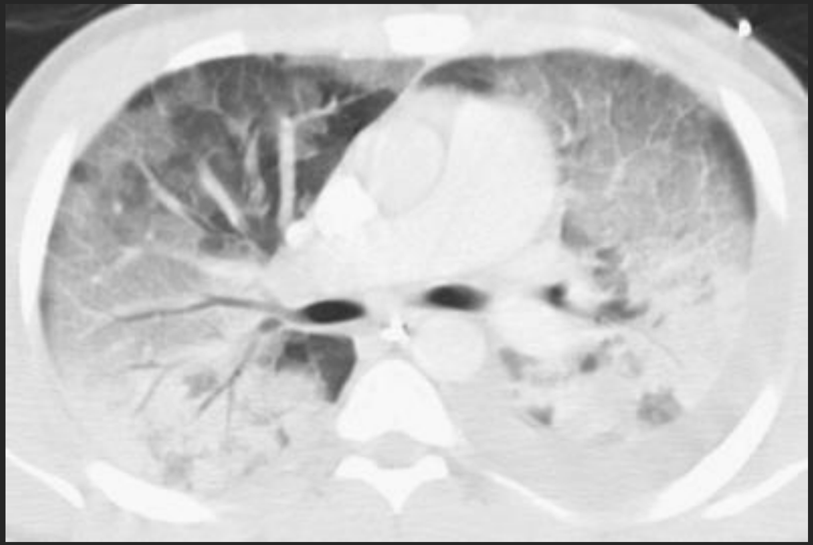
	"Typical" ARDS	COVID-19 ARDS
Vascular injury, microthrombosis	+	+++
Mechanism of hypoxia	Shunt due to increase in non-aerated tissue	Vasoplegia, increased V/Q mismatch due to microthrombi
Aerated lung volume	↓↓↓	↓
Recruitablility	Variable	Low?

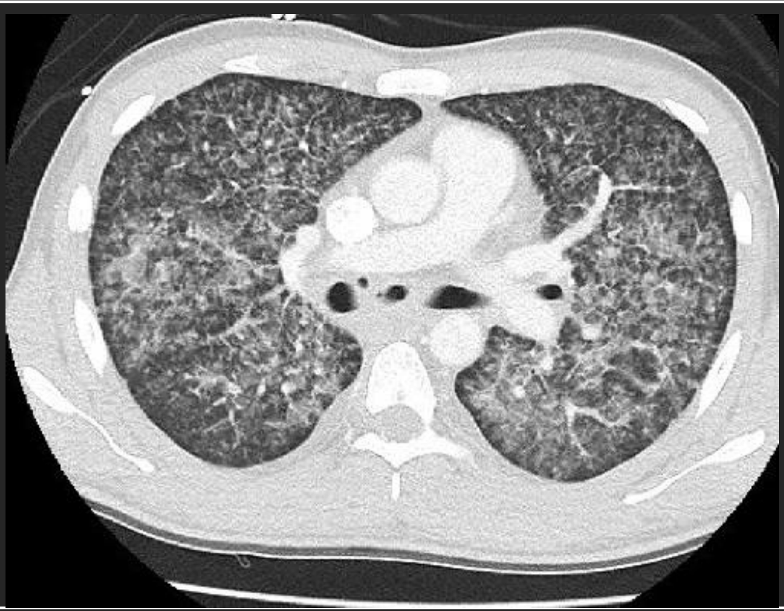
Pathophysiology of ARDS

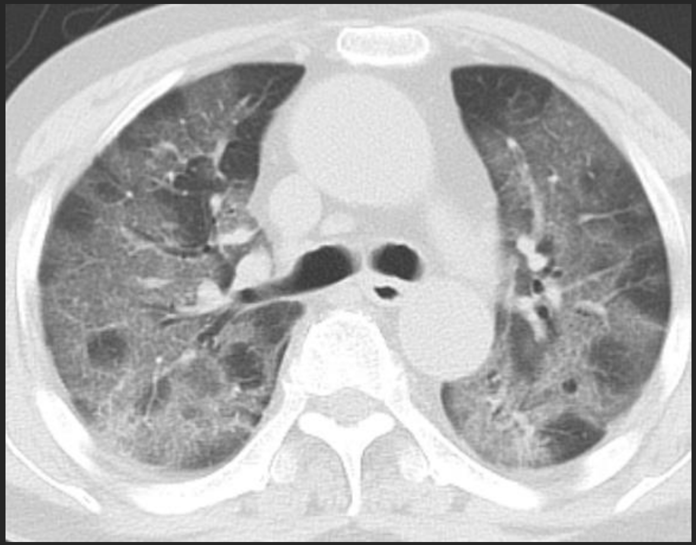


By courtesy of Kim, JH. Korea Uni.

Radiologic phenotype of ARDS



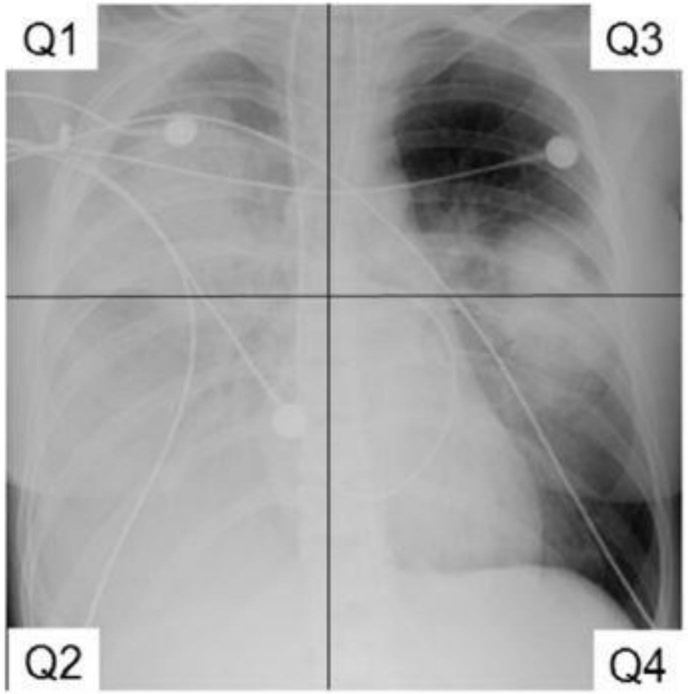




A The radiographic assessment of lung edema (RALE) score

Consolidation[a]	
Consolidation Score	Extent of alveolar opacities
0	None
1	<25%
2	25-50%
3	50-75%
4	>75%
Density[b]	
Density Score	Density of alveolar opacities
1	Hazy
2	Moderate
3	Dense
Final RALE Score[c]	
Right Lung	**Left Lung**
Upper Quadrant Cons x Den = Q1 score	Upper Quadrant Cons x Den = Q3 score
Lower Quadrant Cons x Den = Q2 score	Lower Quadrant Cons x Den = Q4 score
Total RALE = Q1+ Q2 + Q3 + Q4	

[a]Consolidation is scored for each quadrant
[b]Density is scored for each quadrant that has a consolidation score ≥ 1
[c]If Quadrant consolidation score is – then Quadrant score is 0



Calculation of the RALE Score for Left Radiograph					
Score	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
Consolidation	4	4	1	2	
Density	3	3	3	3	
Quadrant Score	4 x 3 = 12	4 x 3 = 12	1 x 3 = 3	2 x 3 = 6	**33**

B

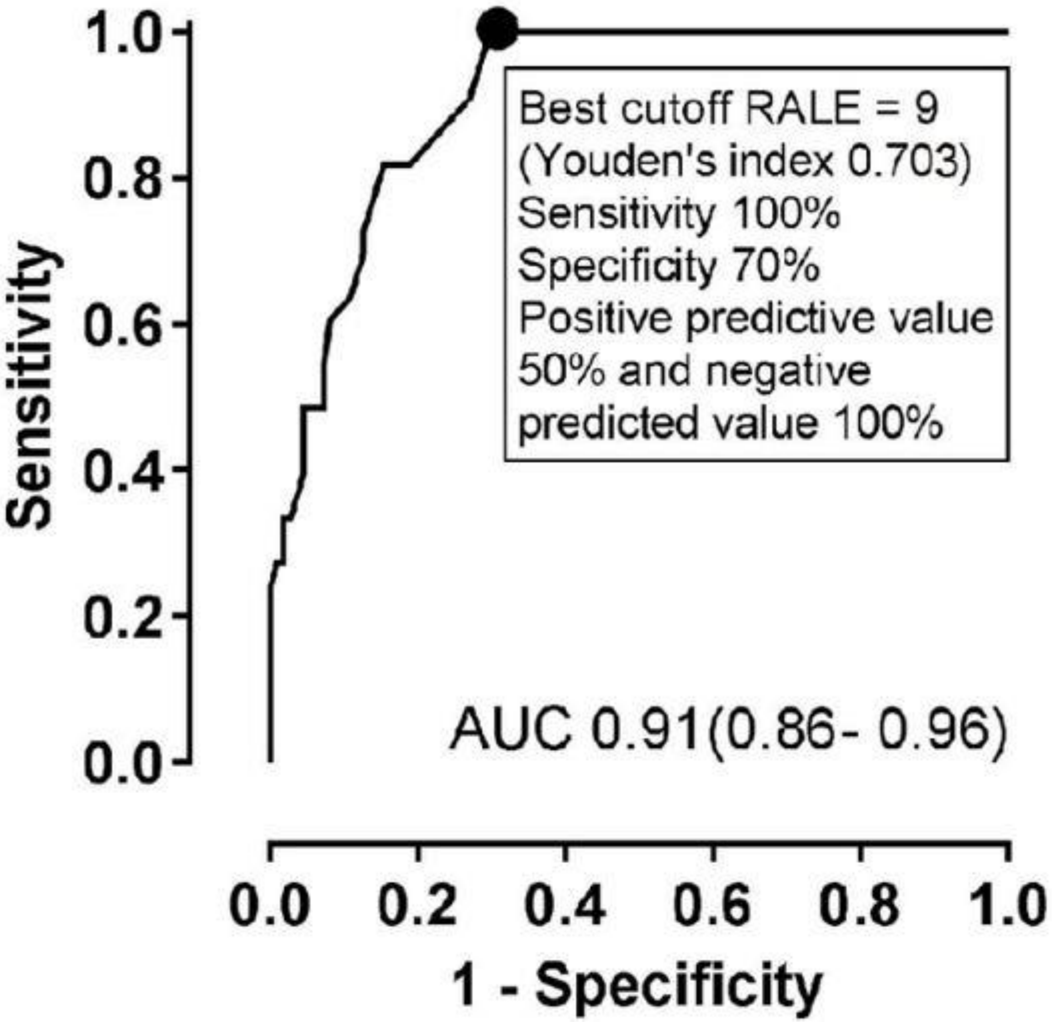


Figure1.

European Respiratory Journal 2019 54:

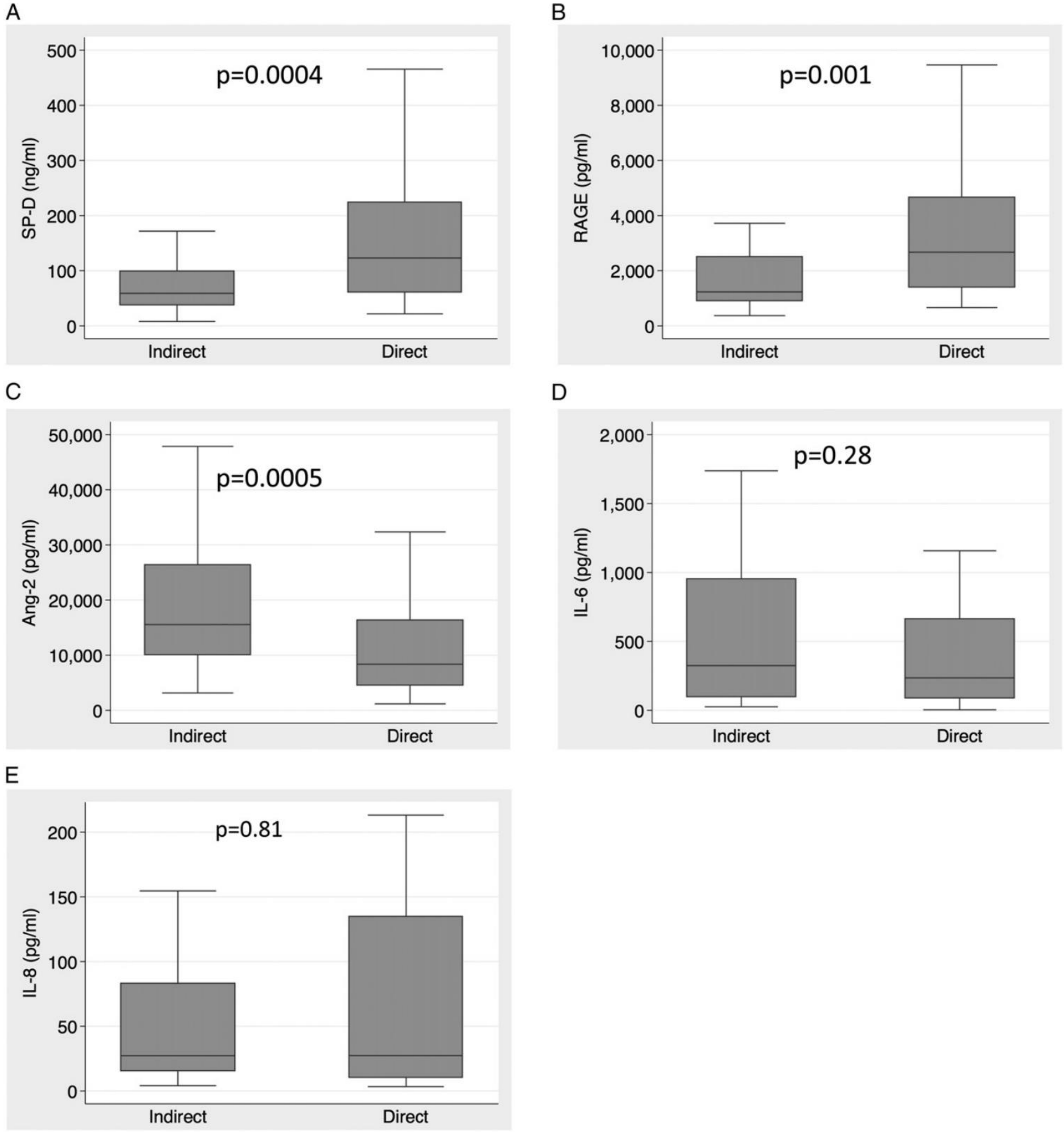
Distinct Molecular Phenotypes of Direct vs Indirect ARDS

- Epithelial markers
  - Surfactant protein D (SP-D), soluble receptor for advanced glycation end products (RAGE)

- Endothelial markers
  - angiopoietin-2 (Ang-2), von Willebrand Factor antigen (vWF)

- Inflammation markers
  - IL-6 and IL-8,

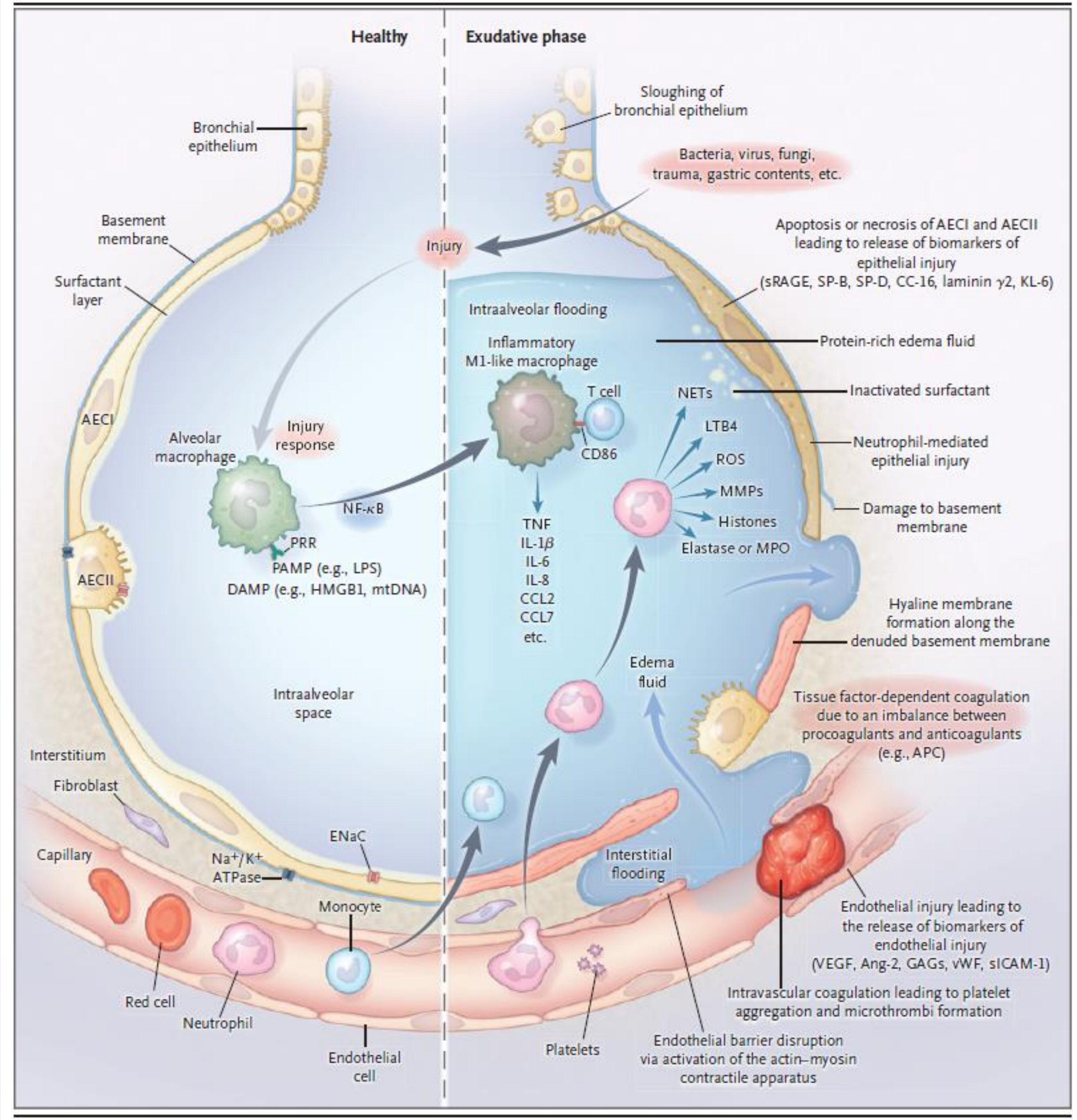
CHEST 2015; 147(6): 1539 - 1548



- Direct
  - Pneumonia, aspiration
  - Epithelial markers
- Indirect
  - Nonpulmonary sepsis
  - Endothelial

CHEST 2015; 147(6): 1539 - 1548

Biomarker, per 1-Log Increment	Death	*P* Value
Single center		
IL-8	1.65 (1.25-2.17)	<.001
IL-6	1.81 (1.34-2.45)	<.001
SP-D[a]	1.33 (0.82-2.14)	.25
RAGE	1.98 (1.18-3.33)	.01
Ang-2	2.54 (1.38-4.68)	.003
Multicenter		
IL-8	1.41 (1.27-1.57)	<.001
IL-6	1.24 (1.14-1.35)	<.001
SP-D	1.09 (0.95-1.24)	.23
RAGE	1.16 (1.003-1.34)	.045
Ang-2[b]	1.43 (1.19-1.73)	<.001
vWF	1.83 (1.46-2.30)	<.001



N Engl J Med 2017;377:562-72.

Plasma protein biomarkers of ARDS

- Systemic inflammation
  - (interleukin [IL]-6, IL-8, soluble tumor necrosis factor [TNF] receptor-1, IL-18),
- Epithelial injury
  - (angiopoietin-2, intercellular adhesion molecule-1),
- Endothelial injury
  - (soluble receptor for advanced glycation end products [sRAGE], surfactant protein-D)

Wilson and Calfee Critical Care (2020) 24:102

The hypo-inflammatory and hyper-inflammatory subphenotypes of ARDS

Table 3 Subphenotype-specific treatment response in the reanalyses of outcomes in four different clinical ARDS trials

Intervention/trial cohort analyzed		Hypoinflammatory subphenotype response		Hyperinflammatory subphenotype response	
	Outcome	Intervention	Control	Intervention	Control
High vs. low PEEP/ ALVEOLI* [27]	90-day mortality	24% high PEEP	16% low PEEP	42% high PEEP	51% low PEEP
Conservative vs. liberal fluid strategy/ FACCT* [29]	90-day mortality	18% conservative fluid strategy	26% liberal fluid strategy	50% conservative fluid strategy	40% liberal fluid strategy
Simvastatin/ HARP-2 [40]	28-day survival	No difference		Improved survival with simvastatin ($p = 0.008$)	
Rosuvastatin/SAILS [41]	90-day mortality	No difference		No difference	

Wilson and Calfee Critical Care (2020) 24:102

Latent class analysis: Hyper vs Hypo-

1022 patients: 473 in the ARMA cohort and 549 in the ALVEOLI cohort.

hyperinflammatory subphenotype

- higher plasma concentrations of inflammatory biomarkers,
- higher prevalence of vasopressor use,
- lower serum bicarbonate concentrations, and
- higher prevalence of sepsis

higher mortality and fewer ventilator-free days and organ failure-free days

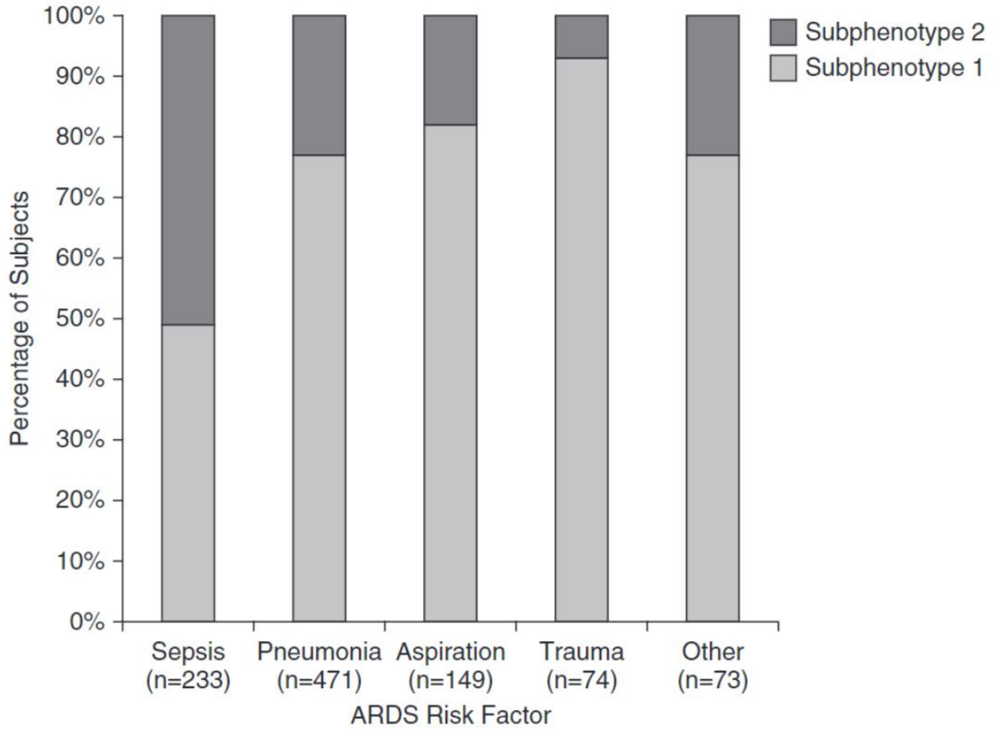
ALVEOLI cohort, the effects of ventilation strategy (high PEEP vs low PEEP)

- mortality, ventilator-free days and organ failure-free days
  (p=0·049 for mortality, p=0·018 for ventilator-free days, p=0·003 for organ-failure-free days).

Lancet Respir Med. 2014;2:611–20

FACCT re-analysis

IL-8, bicarbonate, and tumor necrosis factor receptor-1 accurately classified the subphenotype.



	Subphenotype 1 (*n* = 727)	Subphenotype 2 (*n* = 273)	*P* Value
60-d mortality, %	21	44	<0.0001
90-d mortality, %	22	45	<0.0001
Ventilator-free days, median	19	3	<0.0001

Am J Respir Crit Care Med. 2017;195:331 –8

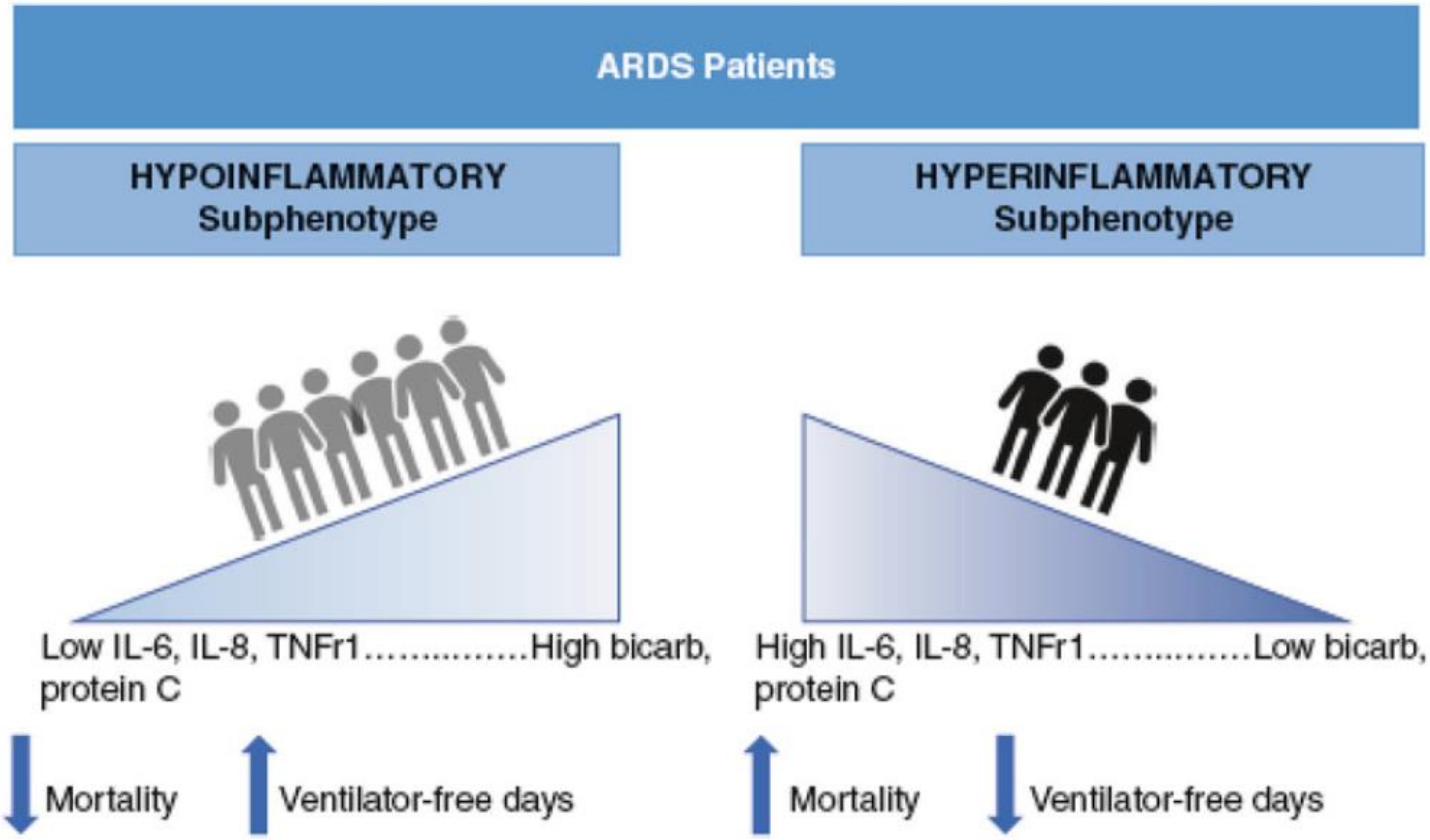
Interaction between ARDS Subphenotype and Fluid-Management Strategy

Fluid-management strategy	Subphenotype 1		Subphenotype 2		P Value
	Liberal (*n* = *355*)	Conservative (*n* = *372*)	Liberal (*n* = *142*)	Conservative (*n* = *131*)	
60-d mortality, %	24	17	39	49	0.0093
90-d mortality, %	26	18	40	50	0.0039
Ventilator-free days, median	17	21	5	0	0.35

	FACTT Derivation Cohort (*AUC*)	ARMA Validation Cohort (*AUC*)	ALVEOLI Validation Cohort (*AUC*)
Three-variable model (IL-8, bicarbonate, TNFr1)	0.95	0.94	0.91
Four-variable model (IL-8, bicarbonate, TNFr1, vasopressor use)	0.97	0.89	0.86
Five-variable model (IL-8, bicarbonate, TNFr1, vasopressor use, total minute ventilation)	0.97	0.90	0.88

Am J Respir Crit Care Med. 2017;195:331 –8

The hypo-inflammatory and hyper-inflammatory subphenotypes of ARDS

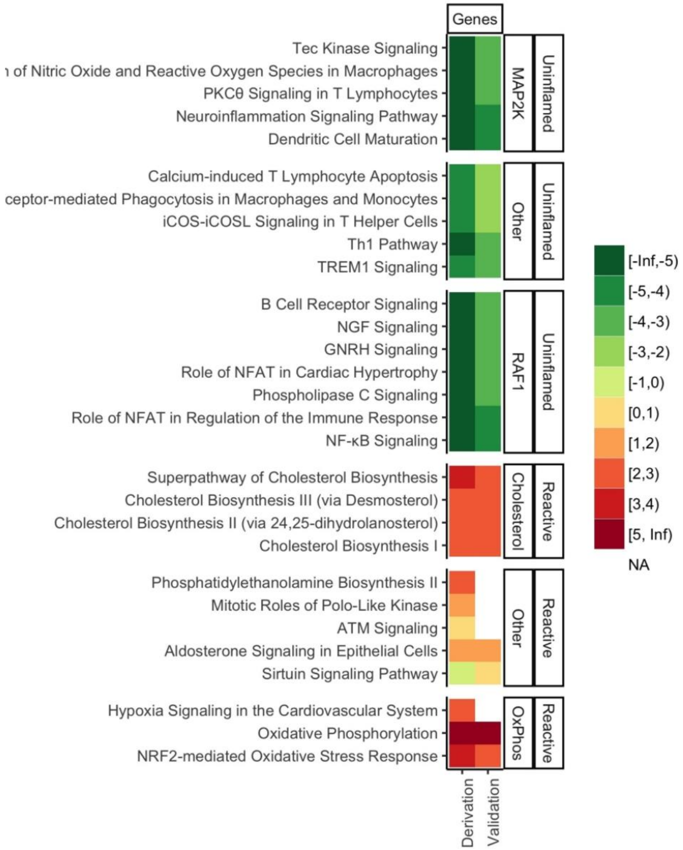


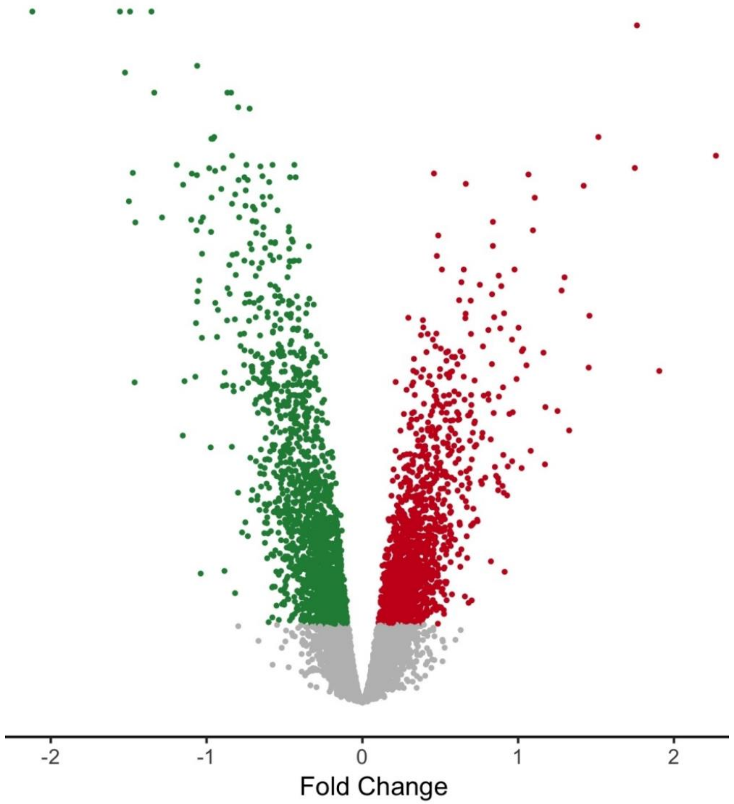
"Reactive" vs "Uninflamed" phenotype of ARDS

- "Molecular Diagnosis and Risk Stratification of Sepsis"
  - Plasma concentrations of IL-6, IFN–γ, ANG1/2 and PAI-1
- mRNA expression profiles 210 sepsis patients with ARDS.
  - 82(38%) "uninflamed" and 128 (62%) "reactive"

Am J Respir Crit Care Med. 2019;200:42 –50

Targeting the immune response in ARDS patients?





- “Reactive” phenotype
  - neutrophil activation
  - oxidative phosphorylation
- “Uninflamed” phenotype
  - MAP2K4
  - RAF1 dependent MAPK pathways.

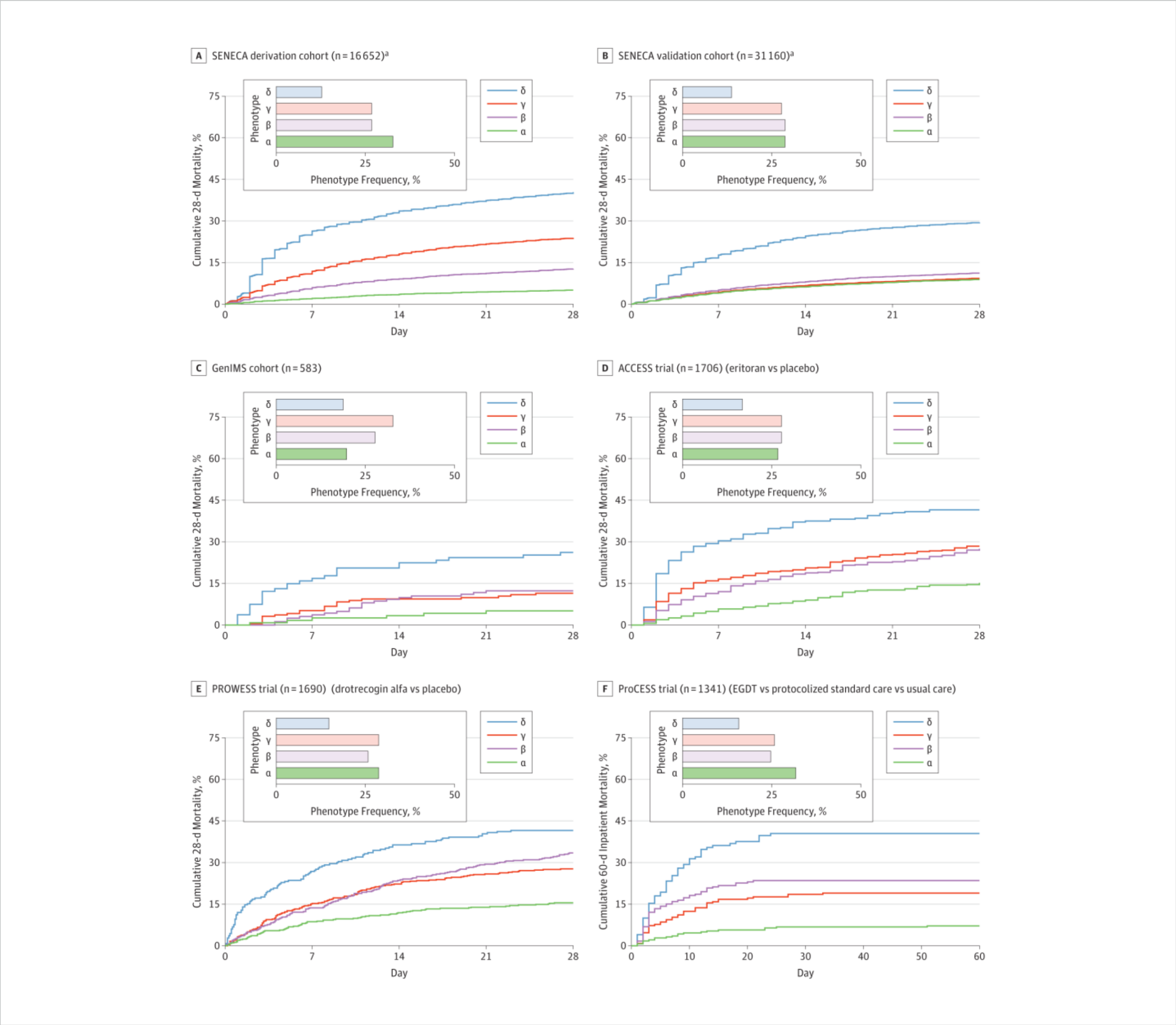
Am J Respir Crit Care Med. 2019;200:42 –50

Novel Clinical Phenotypes for Sepsis

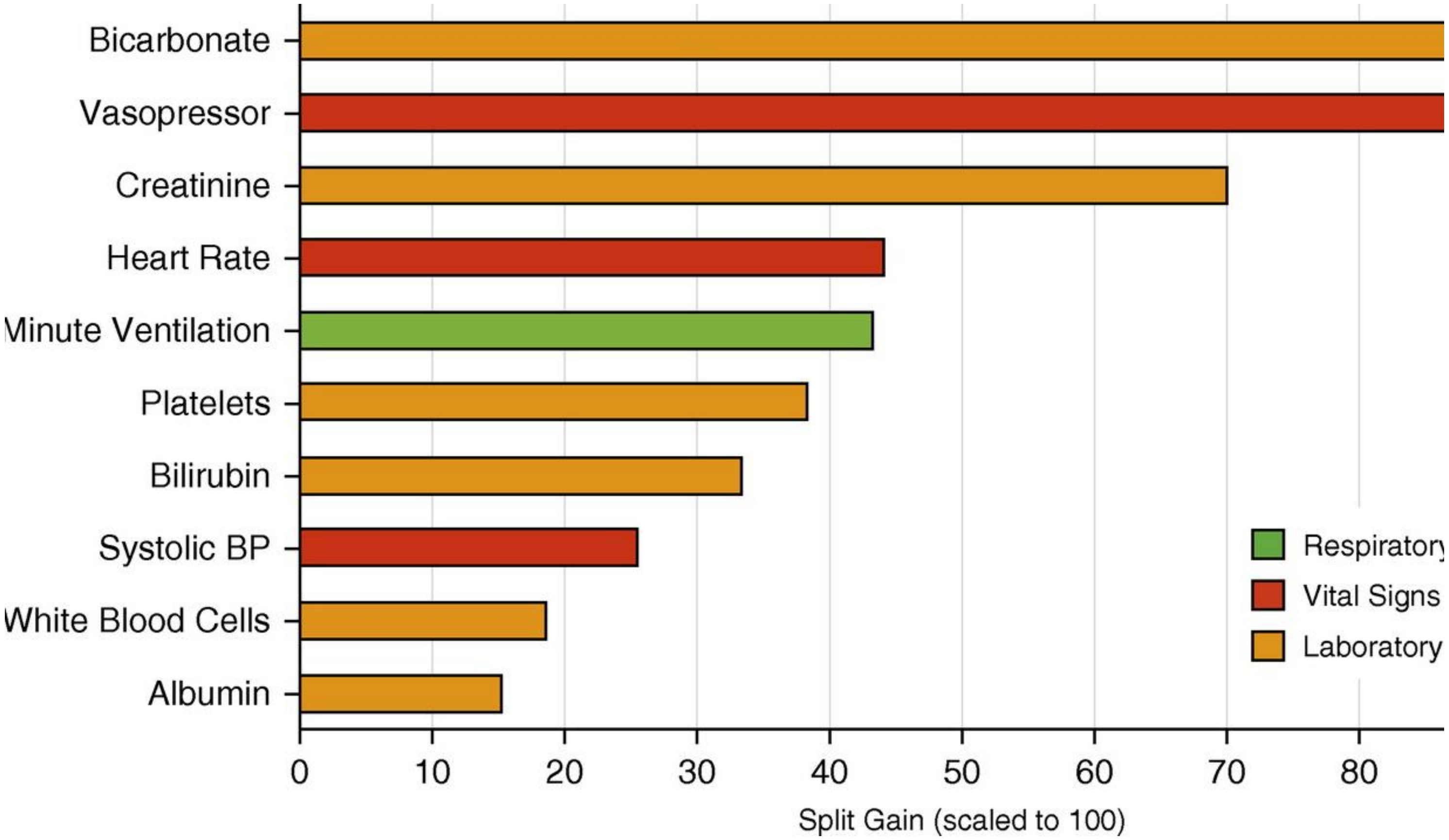
JAMA. 2019;321(20):2003-2017.

29 clinical variables

27 serum biomarkers

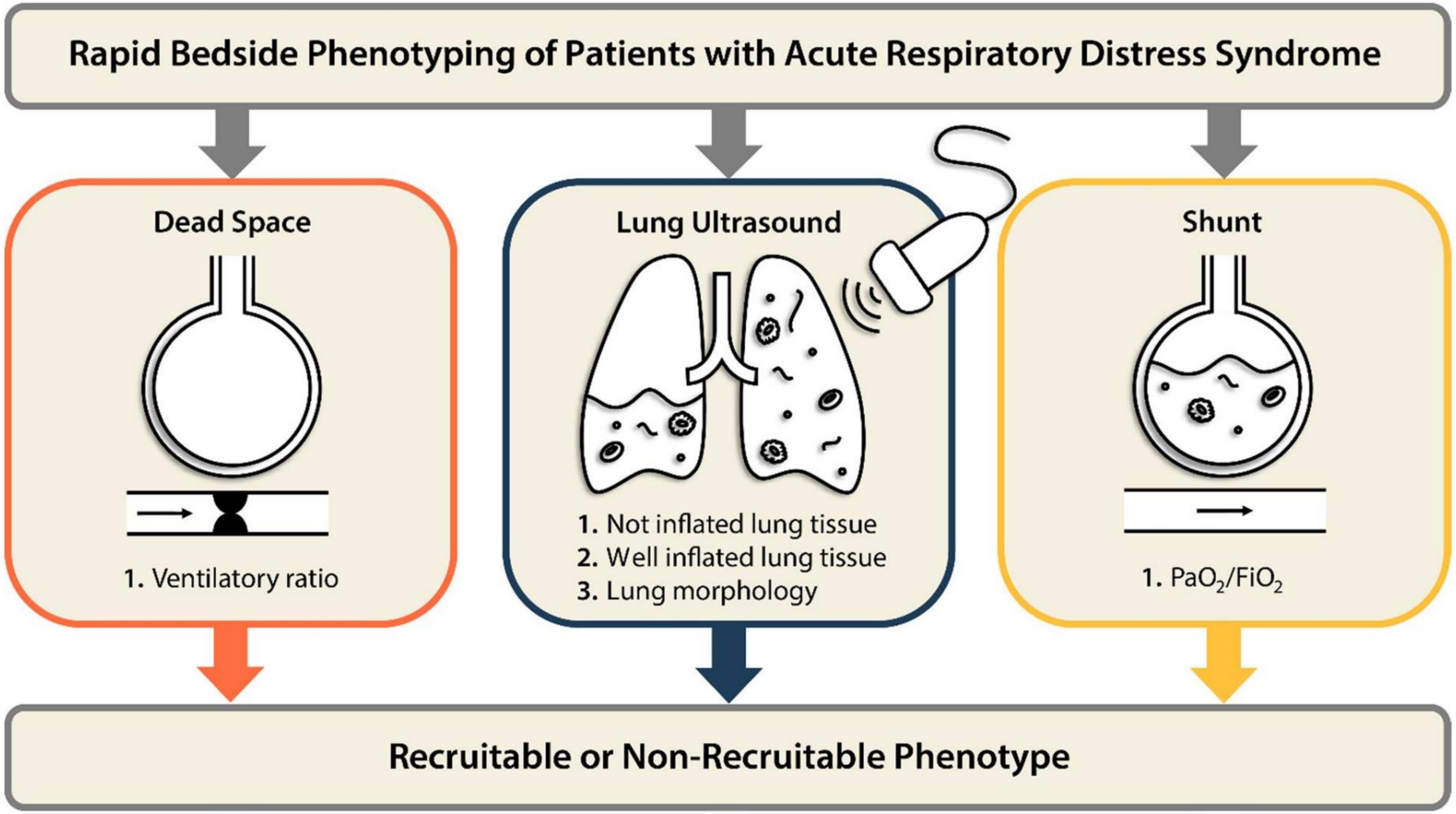


Machine Learning Classifier Models



- Training data set (ARMA [High vs. Low V_T], ALVEOLI [Assessment of Low V_T and Elevated End-Expiratory Pressure to Obviate Lung Injury], and FACTT [Fluids and Catheter Treatment Trial]; *n* = 2,022),
- Validation data set (SAILS [Statins for Acutely Injured Lungs from Sepsis]; *n* = 745).

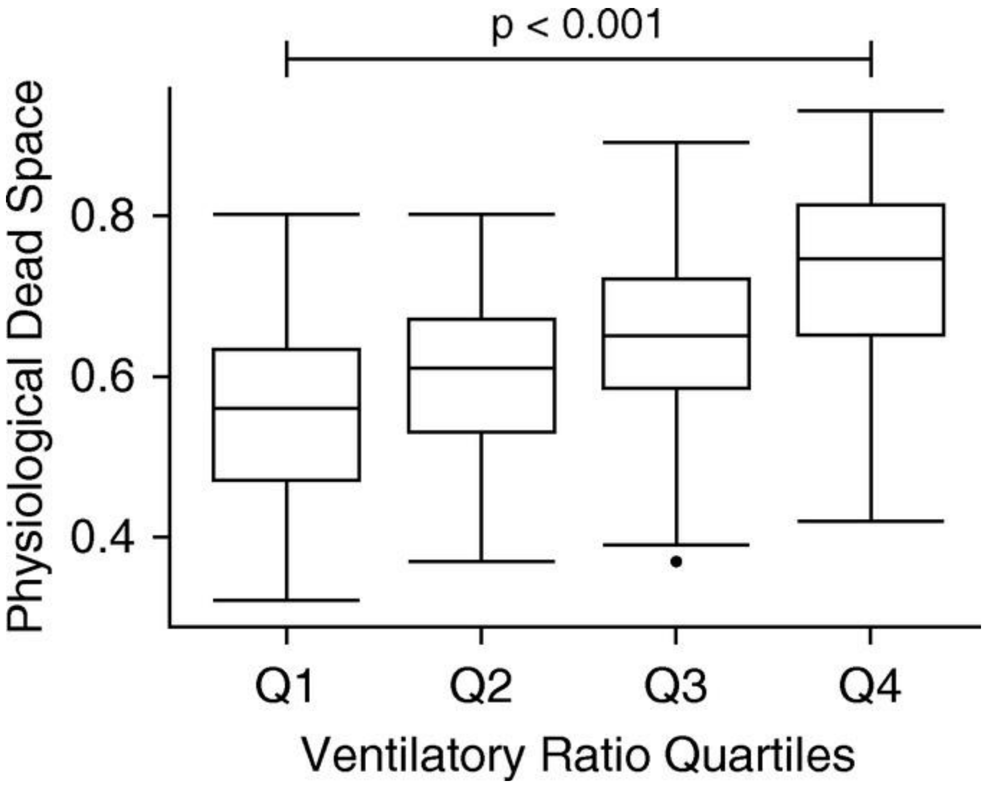
Bedside phenotype

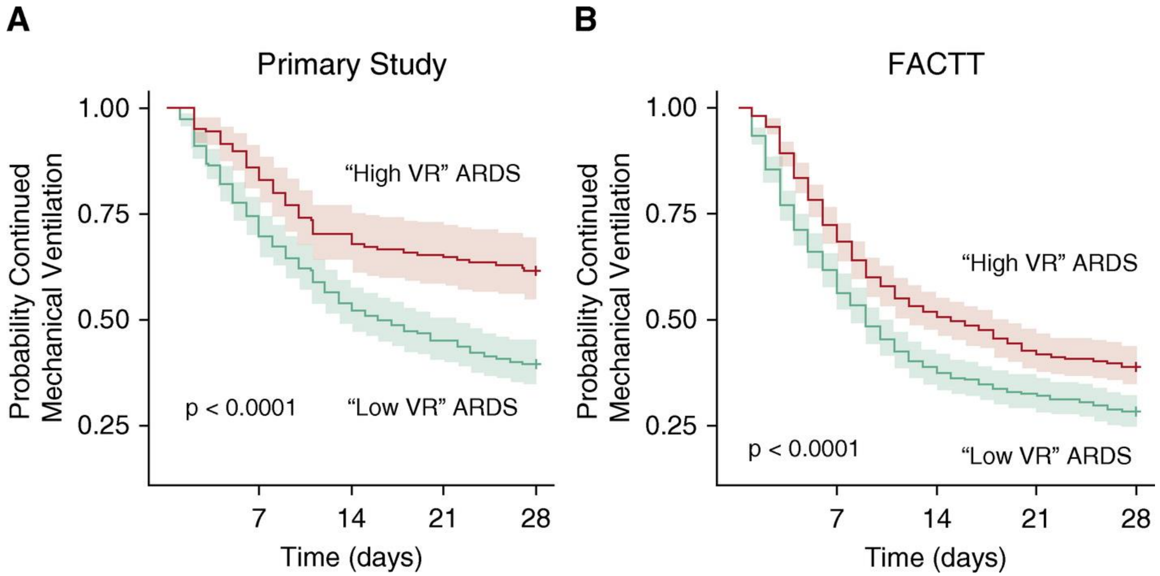


1. Ventilatory Ratio in ARDS

- Ventilatory ratio is defined as

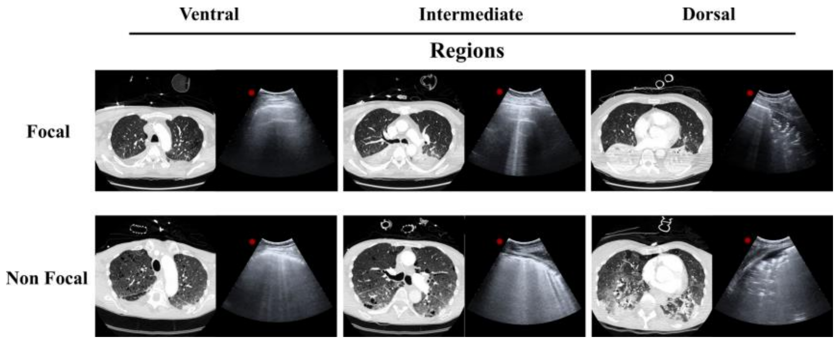
  [minute ventilation (ml/min) × Pa_{CO2} (mm Hg)]/(predicted body weight × 100 × 37.5)

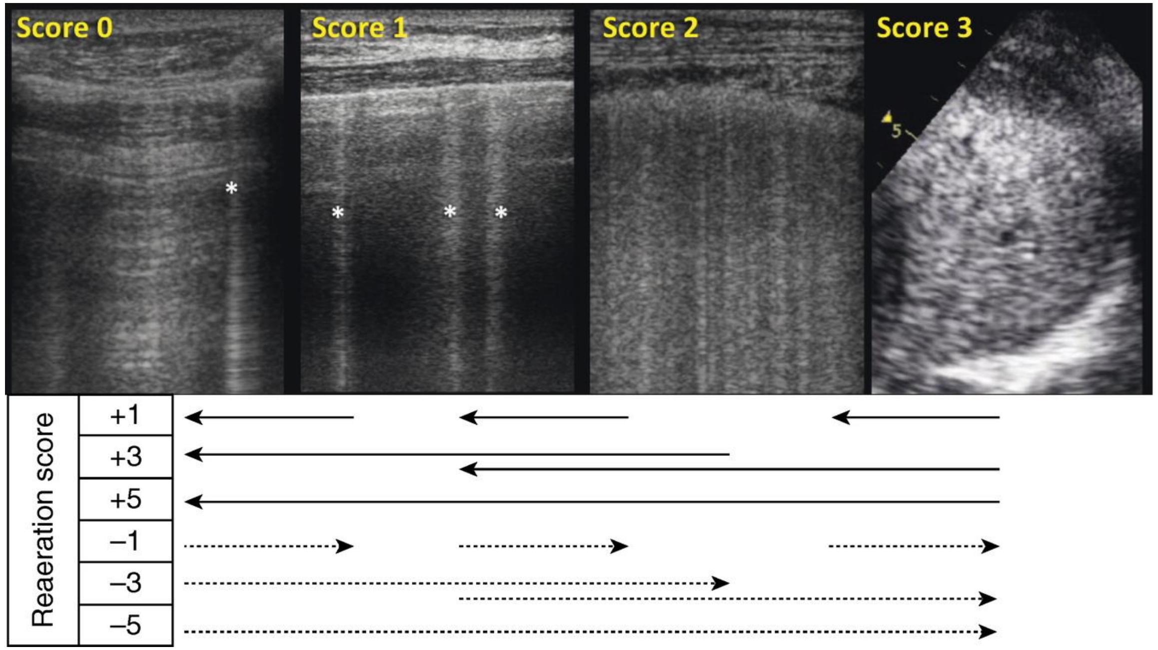


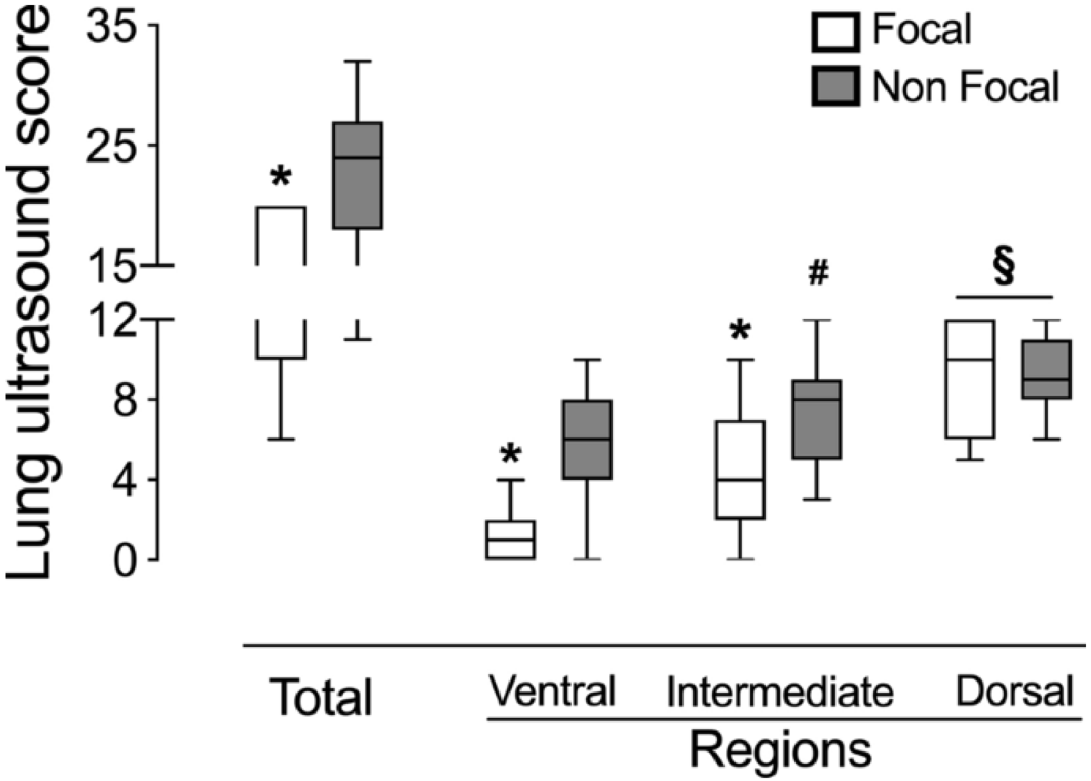


Am J Respir Crit Care Med . 2019 Feb 1;199(3):333-341.

2. Lung Ultrasound Score in ARDS







Am J Respir Crit Care Med . 2019 Feb 1;199(3):333-341.

3. Shunt in ARDS

$$FShunt = \left(1 + \frac{ctO_2(a) - ctO_2(v)}{ctO_2(A) - ctO_2(a)}\right)^{-1}$$

Veno-arterial oxygen content difference: $ctO_2(a) - ctO_2(v)$ ($ctO_2(a)$: O_2 content of arterial blood; $ctO_2(v)$: O_2 content of mixed venous blood)

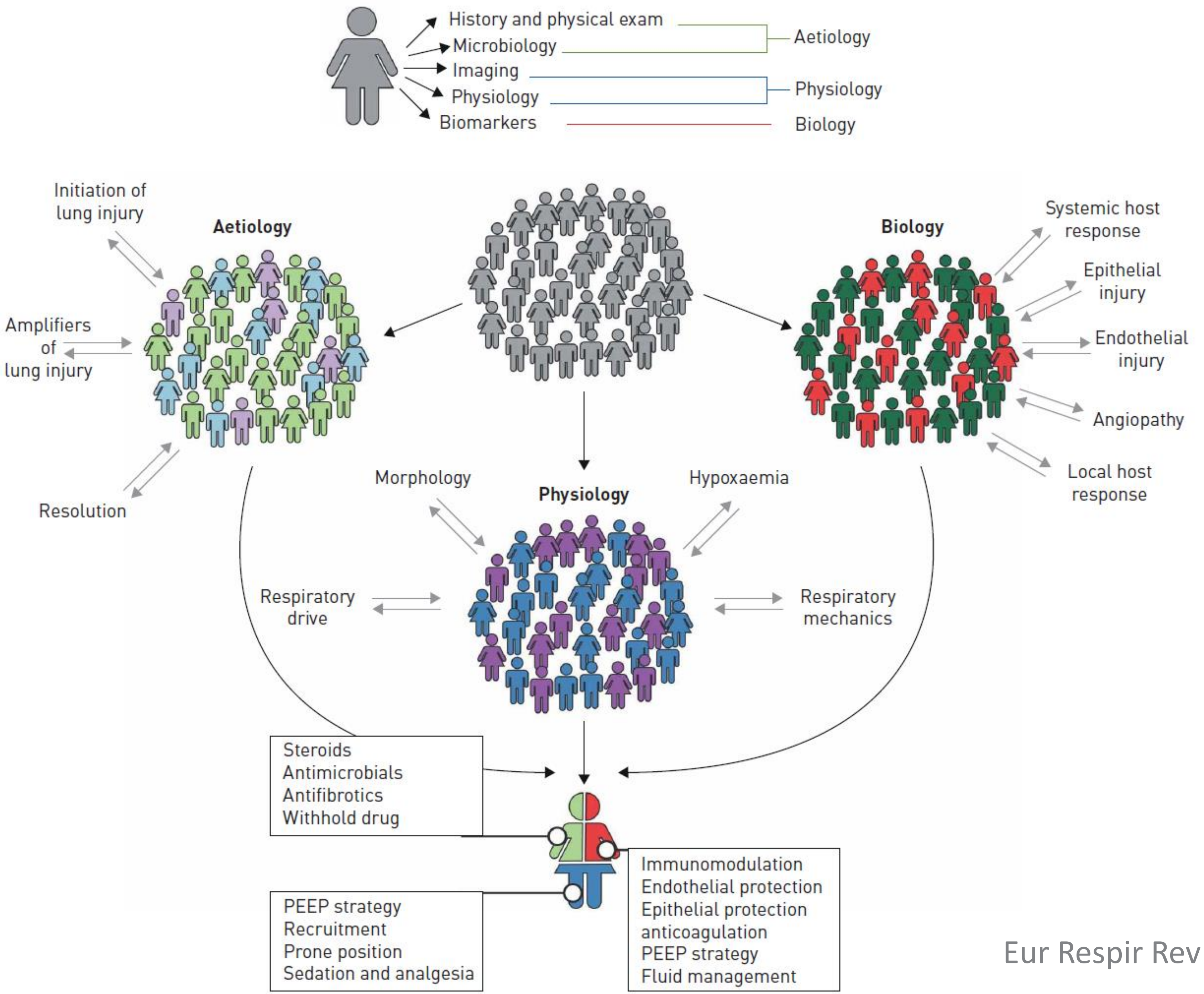
Alveolar-arterial oxygen content difference: $ctO_2(A) - ctO_2(a)$ ($ctO_2(A)$: O_2 content of alveolar air; $ctO_2(a)$: O_2 content of arterial blood)

Baseline values for typical ARDS patient

	Parameter	Normal range	ARDS patient
Four variables determine oxygenation:			
CO	Cardiac Ouput	5-6 L/min	5 L/min
HgB	Hemoglobin	12-15 g/dL	10 g/dL
	Shunt fraction	<0.05	25 %
VO2	Systemic oxygen uptake	200-270 ml/min	250 ml/min
Resulting systemic oxygenation:			
DO2	Systemic oxygen delivery	900-1,100 ml/min	587 ml/min
O2ER	Oxygen extraction rato	20-30%	43 %
O2 sat	Arterial oxygen saturation	>88%	88 %
MVO2	Mixed venous oxygen %	70-80%	50 %

Shunt %	F_IO_2 to restore normal P_{aO2}
10%	• 30%*
20%	• 57%* *all ~ 3x but doesn't continue
30%	• 97%*
40%	• normal P_{aO2} cannot be restored
50%	• increasing F_IO_2 has almost no effect on P_{aO2}

Domain	Subdomain	Trait	Test	Evidence	Interventions to be tested	Challenges
Aetiology	Causal pathogen	COVID-19	PCR for virus	[16]	Dexamethasone	
	ARDS-mimic	Diffuse acute interstitial lung diseases	History Imaging Immunological analysis	[75–77]	Immunosuppression	Relatively rare and requires systematic investigation to identify
		Diffuse pulmonary infections	History Serology Imaging Culture Metabolic products Metagenomics	[78]	Antimicrobials	
		Drug-induced diffuse lung disease	History	www.pneumotox.com	Withhold drug	
	Amplifiers of lung injury	Fluid overload	History Clinical examination Ultrasound Extravascular lung water	[79]	Diuretics Vasopressors	Diagnosis of fluid overload can be challenging
		Ventilator-induced lung injury	Tidal volume Driving pressure Mechanical power	[80]	Lower tidal volumes	No direct test for the actual development of VILI
	Nonresolving lung injury	Fibroproliferation	Markers of fibroproliferation in bronchoalveolar lavage fluid	[27]	Corticosteroids Antifibrotics	Biomarker test not routinely available
		Secondary infection	Imaging Culture Metagenomics	[81]	Antimicrobials	Identify ventilator-associated pneumonia in patient with ARDS
Physiology	Shunt	P_{aO_2}/F_{IO_2}	Blood gas	[43, 44]	Prone positioning Adjust PEEP Lung recruitment	Various thresholds proposed in different studies Influence of PEEP on P_{aO_2}/F_{IO_2}
	Ventilation	Dead space ventilation	Dead space calculation Ventilatory ratio	[82]	Adjust PEEP	Volumetric capnography not widely available
	Drive	High respiratory drive on NIV	Oesophageal pressure	[34]	Analgesia and sedation	Balance between high drive and too low drive
	Mechanics	High mechanical power	Formula based	[49]	Adjust PEEP, tidal volume and/or respiratory rate	Various thresholds proposed and unclear how to adjust settings based on value
		Driving pressure	Ventilator settings Oesophageal pressure	[83]	Adjust PEEP	Various thresholds proposed in different studies
Morphology	Imaging	Focal	Imaging	[53, 84, 85]	Prone positioning Low PEEP	Misclassification of morphology common and associated with worse outcome
		Nonfocal	Imaging	[53, 84, 85]	Lung recruitment High PEEP	
Biology	Systemic host response	Hyperinflammatory (or Reactive)	IL-8, bicarbonate and protein C IL-6, bicarbonate and TNFRI	[31, 60, 62, 63, 86]	High PEEP Restrictive fluid Simvastatin Immunomodulation	No routine test available Frequently unknown if cause or effect of lung injury
	Epithelial injury	Damaged epithelium	Biomarkers *e.g.* sRAGE	[87]	Epithelial protection	
	Endothelial injury	Vascular permeability and endothelial injury	Biomarkers *e.g.* angiopoietin 1 and 2	[88]	Endothelial protection Immunomodulation	
	Angiopathy	Microthrombosis	Biomarkers *e.g.* D-dimers, PAI-1 Perfusion imaging	[89, 90]	Anticoagulation Immunomodulation	
	Local host response	Pulmonary hyper-inflammation	Biomarkers in bronchoalveolar lavage fluid	[91]	Immunomodulation	



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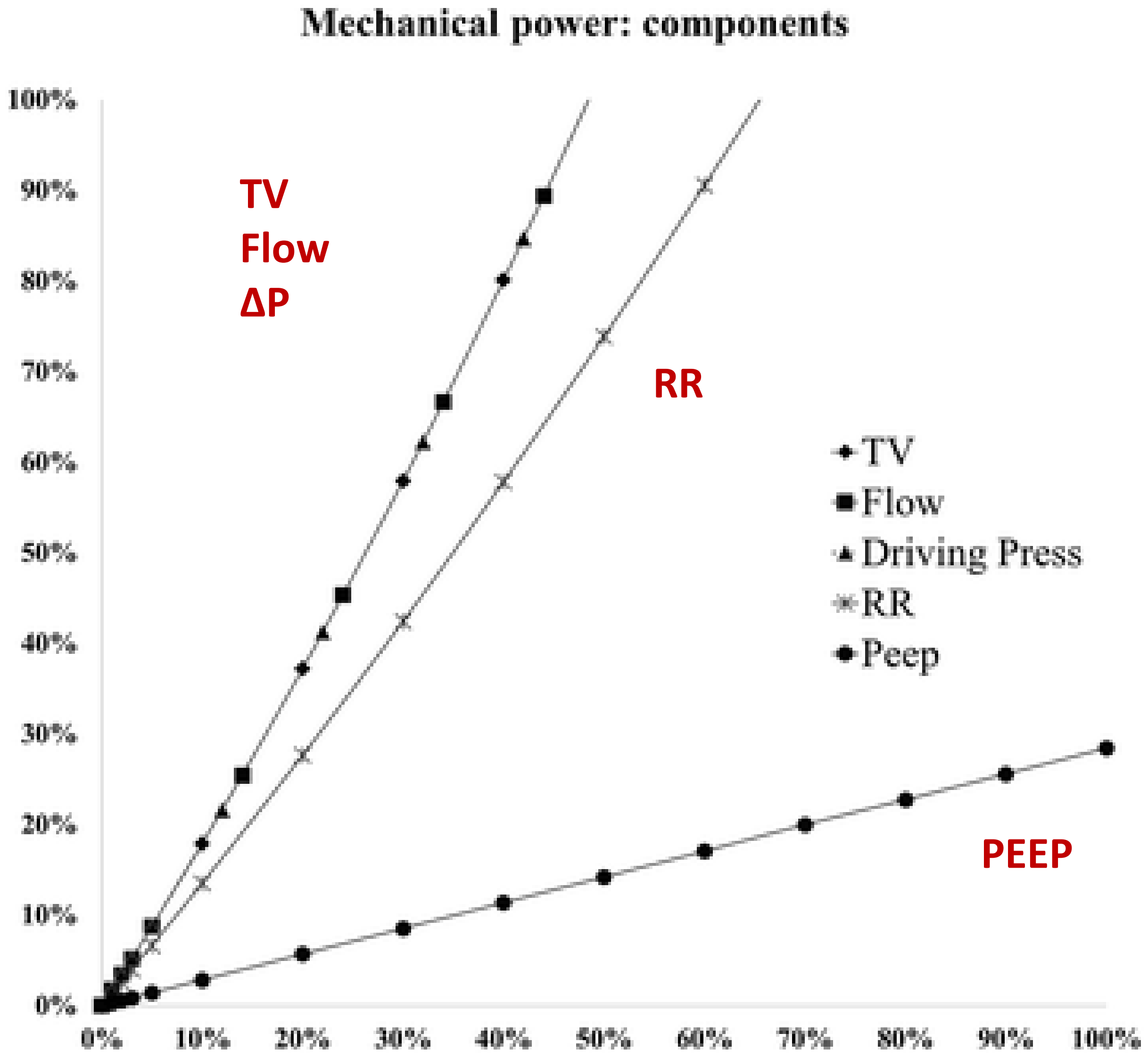
Disease vs Syndrome

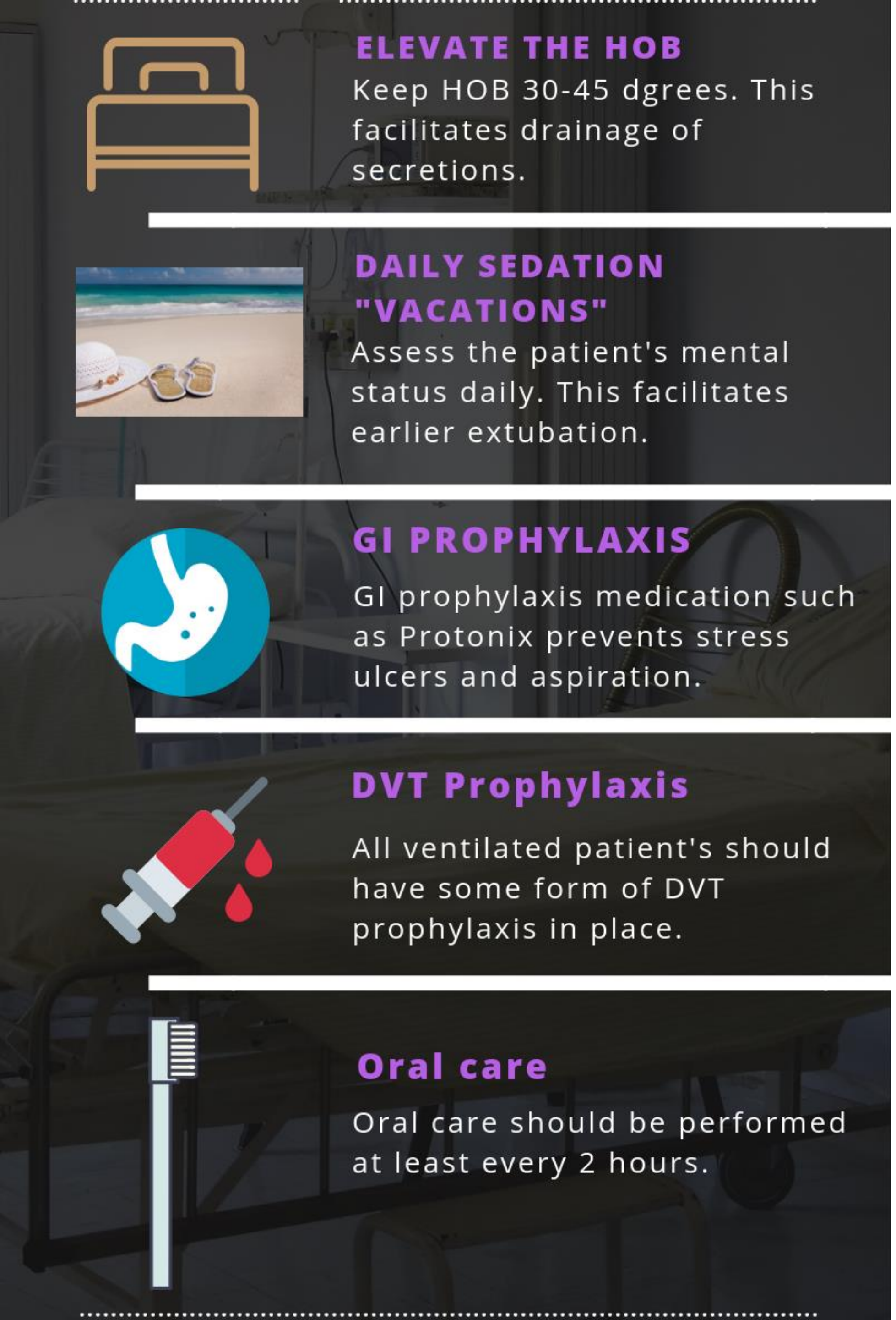
- Disease = a morbid process having characteristic symptoms; pathology, etiology, and prognosis may be known

- Syndrome = a set of symptoms occurring together; different etiologies but similar presentation

Protective Ventilator Care

$$MP = 0.098 \cdot RR \cdot V_t \cdot \left[PEEP + \Delta P_{insp}\right]$$

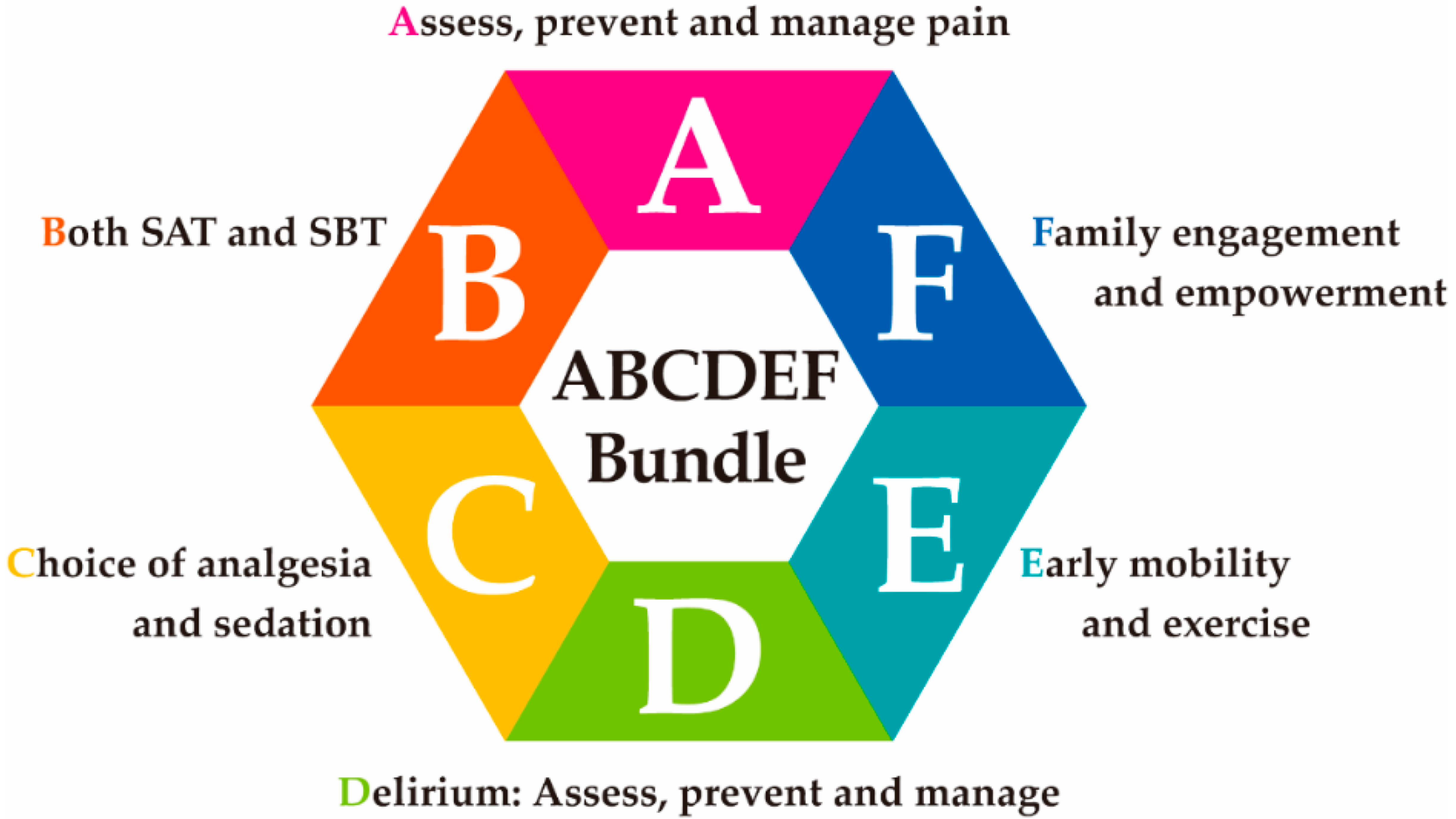




Back to the Basic (Best Supportive Care)

- Ventilator bundle
- Prevent Hospital acquired infection
- Nutrition support

- Routine practice is NOT ROUTINE in COVID-19 pts.


Assess, prevent and manage pain
A
Both SAT and SBT
B
F
Family engagement
and empowerment
ABCDEF
Bundle
C
E
Choice of analgesia
and sedation
Early mobility
and exercise
D
Delirium: Assess, prevent and manage

Thank you for your Attention!!