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ARDS PHENOTYPES AND PERSONALIZED MEDICINE

K. Gohari Moghadam 1401/04/16

- To one-size-fits-all management of ARDS patients
- OR
- To tailored therapies based on personalized medicine ?
- That is the question:

All patients with ARDS are not the same ,

ARDS is a heterogeneous syndrome with different types of etiology , different inflammatory and therapeutic responses .

Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials



Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network

Summary

Background Subphenotypes have been identified within heterogeneous diseases such as asthma and breast cancer, with important therapeutic implications. We assessed whether subphenotypes exist within acute respiratory distress syndrome (ARDS), another heterogeneous disorder.

Methods We used data from two ARDS randomised controlled trials (ARMA trial and ALVEOLI trial), sponsored by the National Heart, Lung, and Blood Institute. We applied latent class modelling to identify subphenotypes using clinical and biological data. We modelled data from both studies independently. We then tested the association of subphenotypes with clinical outcomes in both cohorts and with the response to positive end-expiratory pressure (PEEP) in the ALVEOLI cohort.

Findings We analysed data for 1022 patients: 473 in the ARMA cohort and 549 in the ALVEOLI cohort. Independent latent class models indicated that a two-class (ie, two subphenotype) model was the best fit for both cohorts. In both cohorts, we identified a hyperinflammatory subphenotype (phenotype 2) that was characterised by higher plasma concentrations of inflammatory biomarkers, a higher prevalence of vasopressor use, lower serum bicarbonate concentrations, and a higher prevalence of sepsis than phenotype 1. Participants in phenotype 2 had higher mortality and fewer ventilator-free days and organ failure-free days in both cohorts than did those in phenotype 1 ($p < 0.007$ for all). In the ALVEOLI cohort, the effects of ventilation strategy (high PEEP vs low PEEP) on mortality, ventilator-free days and organ failure-free days differed by phenotype ($p = 0.049$ for mortality, $p = 0.018$ for ventilator-free days, $p = 0.003$ for organ-failure-free days).

Interpretation We have identified two subphenotypes within ARDS, one of which is categorised by more severe inflammation, shock, and metabolic acidosis and by worse clinical outcomes. Response to treatment in a randomised trial of PEEP strategies differed on the basis of subphenotype. Identification of ARDS subphenotypes might be useful

Lancet Respir Med 2014

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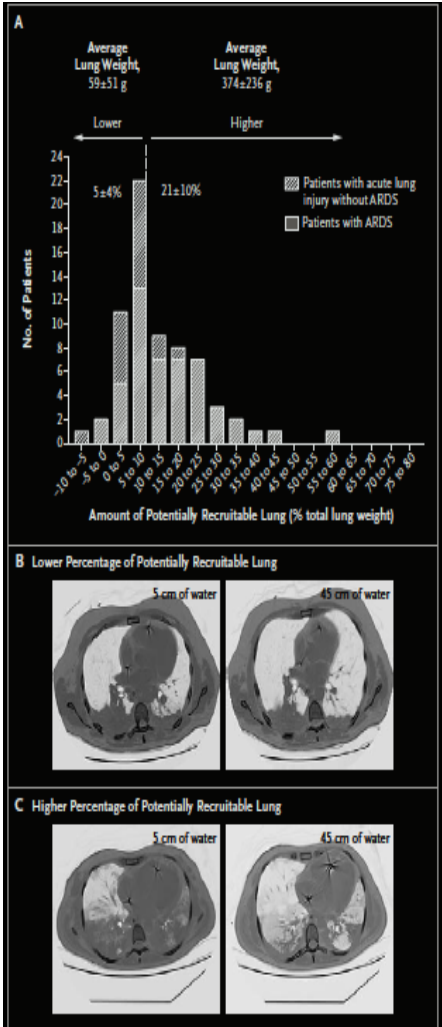
[http://dx.doi.org/10.1016/S2213-2600\(14\)70097-9](http://dx.doi.org/10.1016/S2213-2600(14)70097-9)

See Online/Comment

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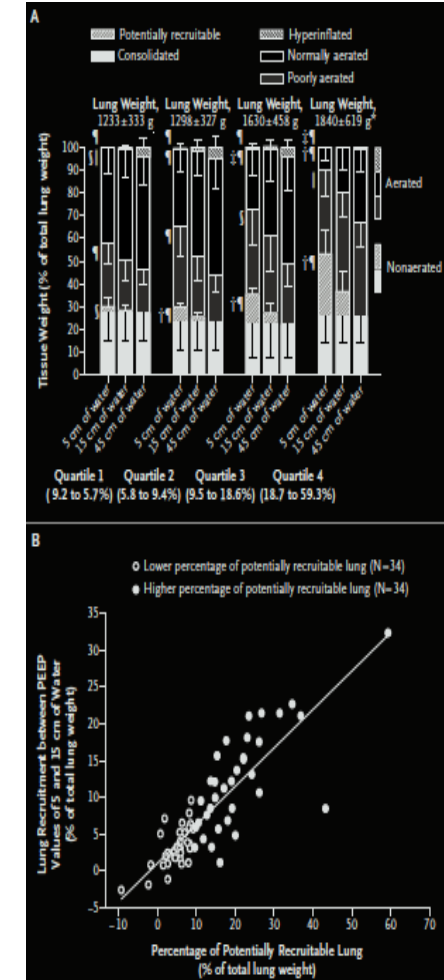


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 27, 2006 VOL. 354 NO. 17

Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D., F.R.C.P., Pietro Caironi, M.D., Massimo Cressoni, M.D., Davide Chiumello, M.D., V. Marco Ranieri, M.D., Michael Quintel, M.D., Ph.D., Sebastiano Russo, M.D., Nicolò Patroniti, M.D., Rodrigo Cornejo, M.D., and Guillermo Bugedo, M.D.



- Assessment of response to recruit maneuver by CT revealed wide range from 5% to 50% of lung volume.
- NEJM Vol 354 No 17 2006

- So it is important to find different phenotypes of ARDS in order to manage each type by the most relevant and effective strategies .
- For example in cancer and asthma , tailored therapy based on phenotypes is suggested and ongoing .
- For heterogeneous diseases subtyping is made by two methods :
 - Prognosis Enrichment
 - Predictive Enrichment

PROGNOSIS ENRICHMENT

Physiologic :(Berlin criteria, ventilatory ratio V_d/V_t ,driving pressure)

Clinical & Radiographical: (trauma vs non trauma, AKI , focal vs non focal)

Biological :(IL6,IL8 , IL18,protein C, sRAGE, TNF, low pH,

Parsimonous model: (Hypo vs Hyperinflammatory)

This type of classification is focused mainly on mortality rate and VFD (Ventilator Free Days).

PREDICTIVE ENRICHMENT

- Physiologic: Direct vs Indirect ARDS(epithelial vs endothelial)
 - Biological
-
- This type of classification is focused mainly on choosing more relevant and efficacious treatment strategies .

Personalized Mechanical Ventilation in ARDS

1



RATIONALE

Regulate ventilatory parameters based on close monitoring of targeted physiologic variables, intervention responses and individual integrated goals.

2



TIDAL VOLUME

Low V_T (4-6 ml/Kg PBW) is a standard of care. Personalized targeting requires evaluation of EELV and IC, AI and closed-loop systems may provide better monitoring.

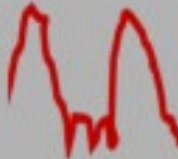
3



DRIVING AND PLATEAU PRESSURE

Low ΔP (< 13 cmH₂O) is a target in most patients. ΔP could help individualize V_T and PEEP levels. P_{PLAT} should be kept below 27 cmH₂O.

4



TRANSPULMONARY PRESSURE

P_L estimated on esophageal pressure can be used to titrate ventilation, but requires correct physiological interpretation.

5



MECHANICAL POWER

Mechanical power is a summary variable including recognized determinants of VILI.

6



ALVEOLAR RECRUITMENT

The identification of recruitable patients and estimation of recruitment are essential to individualize recruitment strategies.

7



GAS-EXCHANGE

Gas-exchange including oxygenation is commonly targeted to set ventilation. However, dead space, ventilatory ratio and oxygen transport should be considered.

8



LUNG IMAGING

Computed tomography remains the gold standard. Lung ultrasound and electrical impedance tomography are promising bedside tools.

9



PHENOTYPES

Patient stratification according to biological phenotypes is promising, but translation into clinical practice requires further research.

10



LIMITS OF PHYSIOLOGICAL GAIN

When applying physiological manipulations, clinicians should consider the uncertainty surrounding their effect on patient-centered outcomes

- Some ARDS patients respond better to some maneuvers ,for example non focal forms respond much more to recruitment and conservative fluid intake than focal and the reverse is true for prone positioning ,lower PEEP , higher V_t and liberal fluid intake in the focal group.
- Another example is effectiveness of statins in hyperinflammatory type.

Criteria for ARDS classification	Sub-phenotype	Tidal volume	PEEP
Recruitability	Higher	5–6 mL/kg PBW and DP <14 cmH ₂ O	Higher by assessing recruitment and over-distension by bedside method (EIT, EELV measure, mechanics)
	Lower	6–8 mL/kg PBW and DP <14 cmH ₂ O	Lower PEEP/FiO ₂ table
Oxygenation	P/F ≤150	5–6 mL/kg PBW and DP <14 cmH ₂ O	Higher by increasing P _{plat} to 28–30 cmH ₂ O or elastance-derived P _L to 20–22 cmH ₂ O
	P/F >150	6–8 mL/kg PBW and DP <14 cmH ₂ O	Lower PEEP/FiO ₂ table
Lung morphology	Non-focal	5–6 mL/kg PBW and DP <14 cmH ₂ O	Higher by assessing recruitment and over-distension by bedside method (EIT, EELV measure, mechanics)
	Focal	6–8 mL/kg PBW and DP <14 cmH ₂ O	Lower PEEP/FiO ₂ table
Inflammation	Hyper-inflammatory	6 mL/kg PBW and DP <14 cmH ₂ O	Higher PEEP/FiO ₂ table
	Hypo-inflammatory	6 mL/kg PBW and DP <14 cmH ₂ O	Lower PEEP/FiO ₂ table

ARDS, acute respiratory distress syndrome; PEEP, positive end expiratory pressure; PBW, predicted body weight; DP, driving pressure; EIT, electrical impedance tomography; EELV, end-expiratory lung volume; P/F, PaO₂/FiO₂ ratio; P_{plat}, inspiratory plateau pressure; P_L, transpulmonary pressure.

RECRUITABLE & NON RECRUITABLE PHENOTYPES

- Depending on degree of alveolar endothelial injury , the response to high PEEP 35 cmH₂O is observed by 5% to 50% increased lung volume as assessed by Gattioni et al .
- It seems anatomic recruitment as assessed by CT imaging is some what correlates with functional and physiologic response by increased lung compliance and decreased dead space , if high PEEP does not lead to decreased perfusion of ventilated alveoli.

FOCAL & NON FOCAL PHENOTYPES

- Greater response to higher PEEP , recruitment and lower V_t in nonfocal, whereas prone positioning and higher V_t and lower PEEP is much more effective in focal type.
- The main limitation is misclassification .

Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial



Lancet Respir Med 2019

Published Online

August 6, 2019

*Jean-Michel Constantin, Matthieu Jabaudon, Jean-Yves Lefrant, Samir Jaber, Jean-Pierre Quenot, Olivier Langeron, Martine Ferrandière, Fabien Grelon, Philippe Seguin, Carole Ichai, Benoit Veber, Bertrand Souweine, Thomas Uberti, Sigismond Lasocki, François Legay, Marc Leone, Nathanael Eisenmann, Claire Dahyot-Fizelier, Hervé Dupont, Karim Asehnoune, Achille Sossou, Gérald Chanques, Laurent Muller, Jean-Etienne Bazin, Antoine Monsel, Lucile Borao, Jean-Marc Garcier, Jean-Jacques Rouby, Bruno Pereira, Emmanuel Futier, for the AZUREA Network**

Summary

Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial

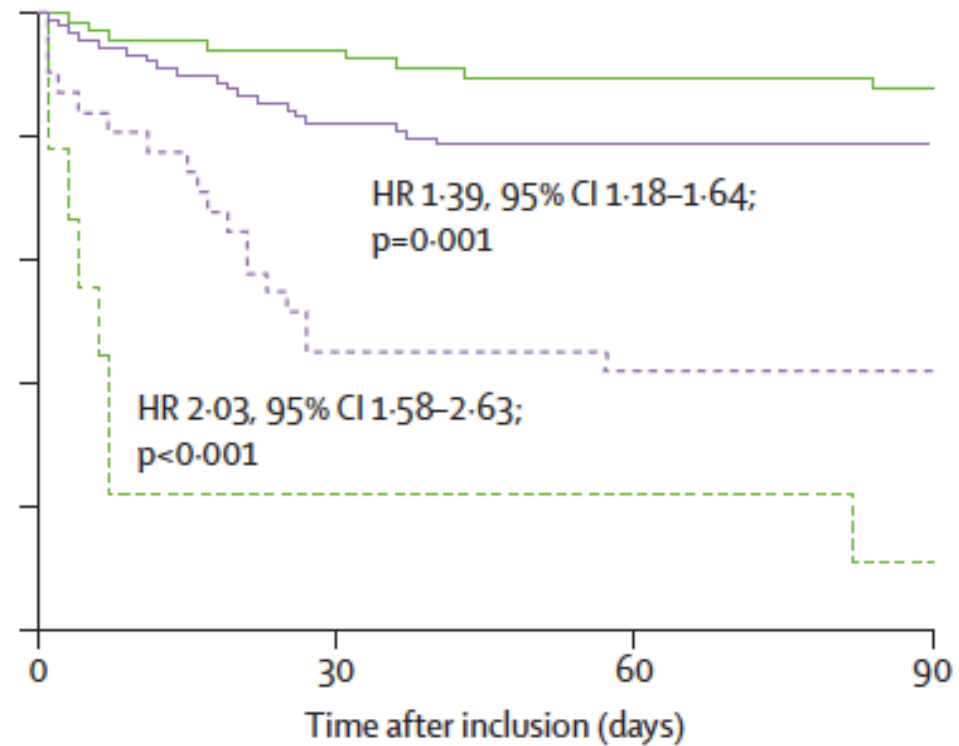
Jean-Michel Constantin, Matthieu Jabaudon, Jean-Yves Lefrant, Samir Jaber, Jean-Pierre Quenot, Olivier Langeron, Martine Ferrandière, Fabien Grelon, Philippe Seguin, Carole Ichai, Benoît Veber, Bertrand Souweine, Thomas Uberti, Sigismond Lasocki, François Legay, Marc Leone, Nathanael Eisenmann, Claire Dahyot-Fizelier, Hervé Dupont, Karim Asehnoune, Achille Sossou, Gérald Chanques, Laurent Muller, Jean-Etienne Bazin, Antoine Monsel, Lucile Borao, Jean-Marc Garcier, Jean-Jacques Rouby, Bruno Pereira, Emmanuel Futier, for the AZUREA Network*

Summary



D Personalised group (n=196)

- Focal correctly classified
- - - Focal misclassified or misaligned
- Non-focal correctly classified
- - - Non-focal misclassified or misaligned



INFLAMMATORY (TYPE2) & NON INFLAMMATORY (TYPE1)-

- The severity of ARDS by $\text{PaO}_2/\text{FiO}_2$, leukocytosis , liver and kidney failure in two groups does not differ.
- Lactic acidosis , shock, increased levels of IL6 , IL8 , IL18 , shock , vasopressor dependency and sepsis is much more prominent in type 2.

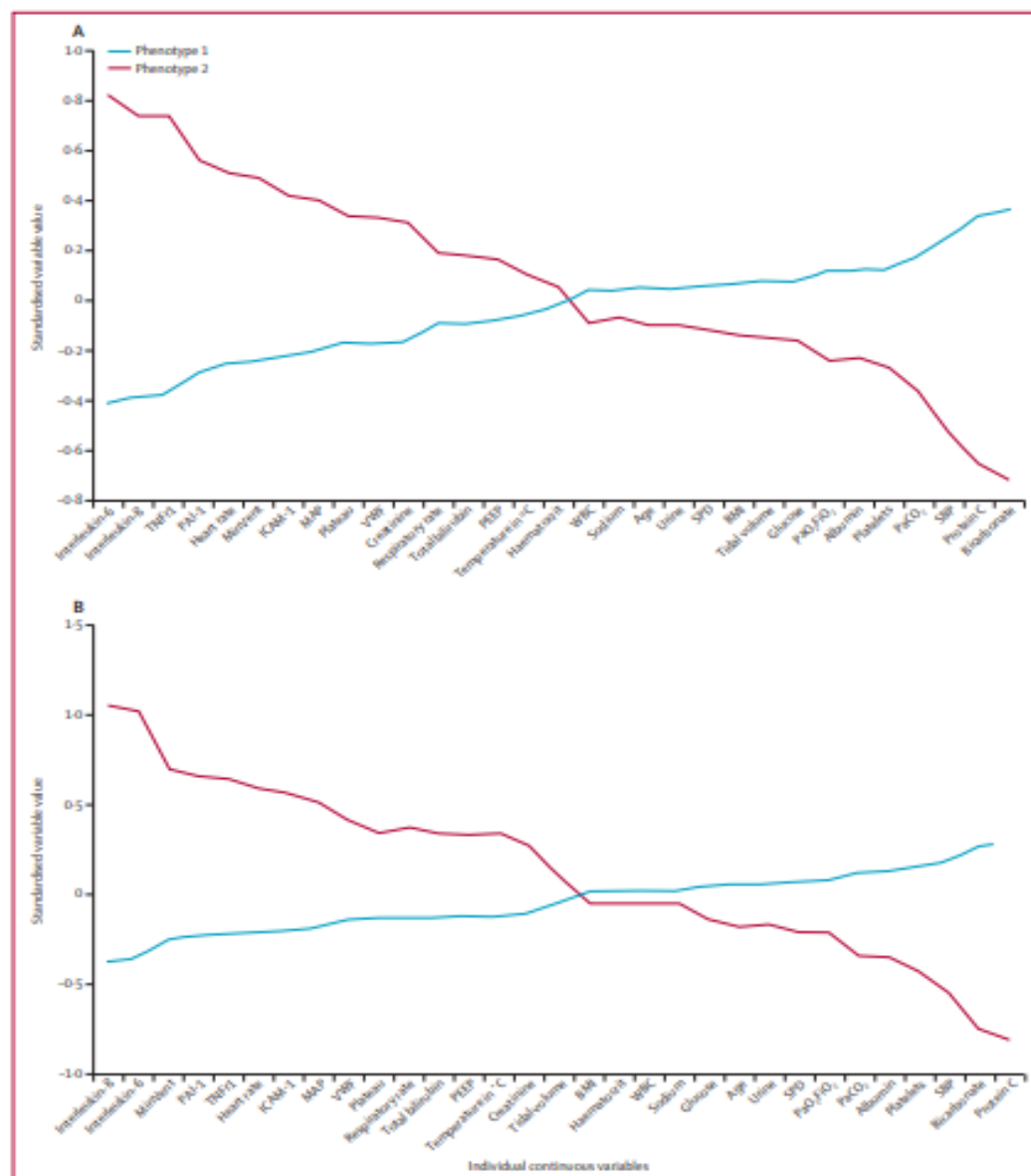
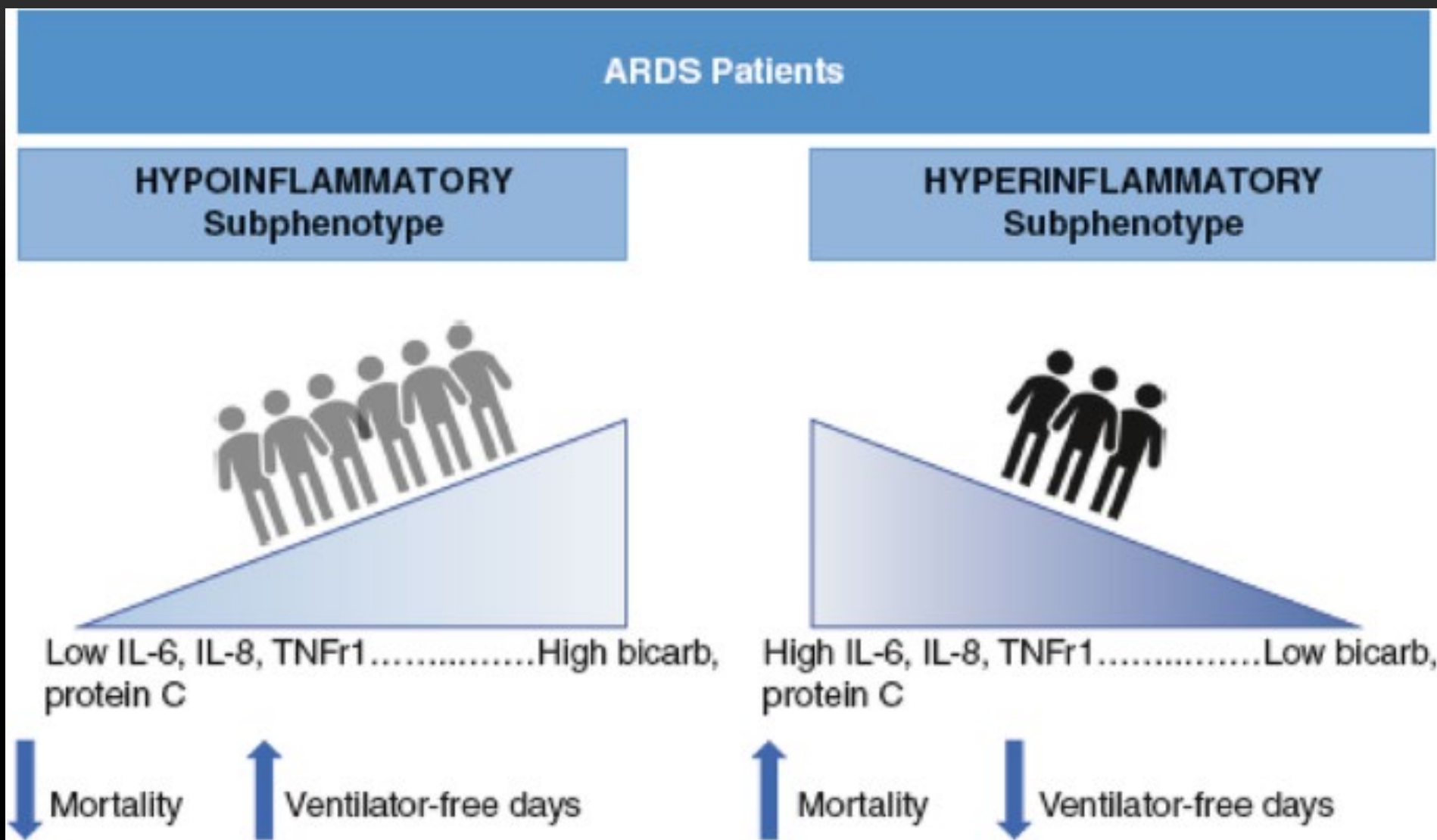


Figure 2: Differences in standardised values of each continuous variable by phenotype in the ARMA cohort (A) and the ALVEOLI cohort (B)

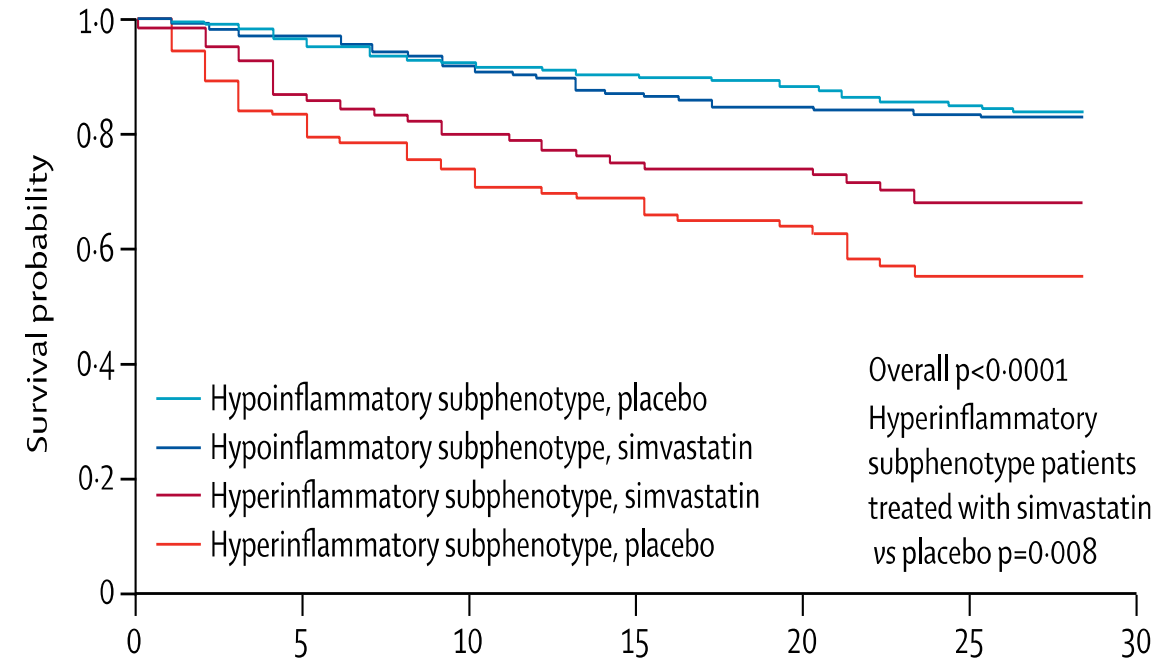
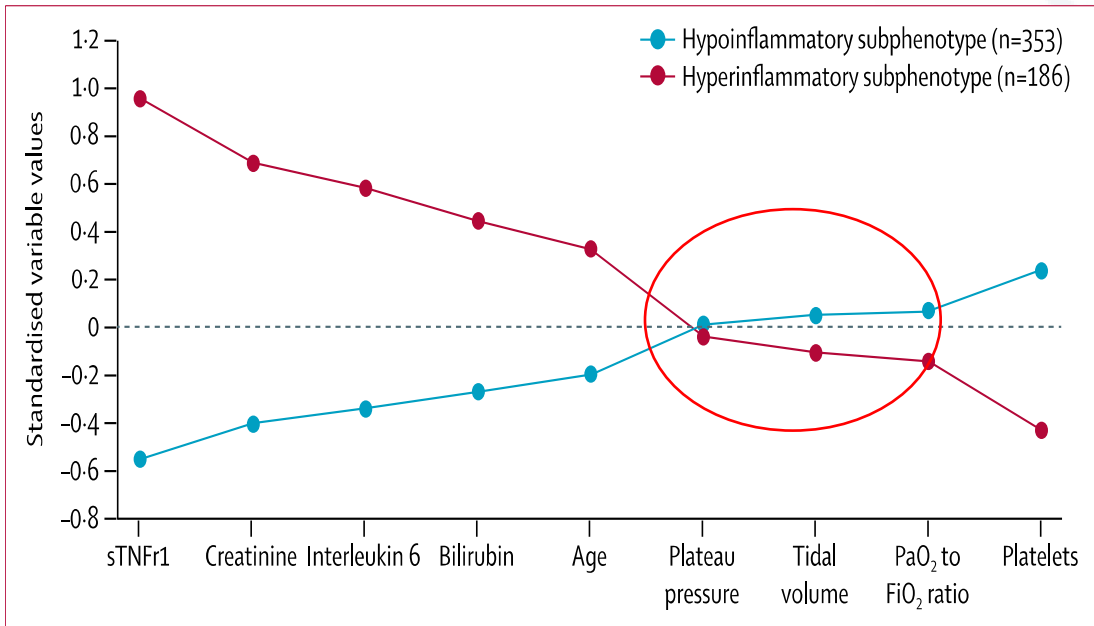
The variables are sorted on the basis of the degree of separation between the classes from maximum positive separation on the left (ie, phenotype 2 higher than phenotype 1) to maximum negative separation on the right (ie, phenotype 2 lower than phenotype 1). Variable standardisation, in which all means are scaled to zero and SDs to one, is described in the appendix. A value of +1 for the standardised variable signifies that the mean value for a given phenotype was one SD higher than the mean value in the cohort as a whole. TNF α =tumour necrosis factor receptor-1. PAI-1=plasminogen activator inhibitor-1. MinVent=total minute ventilation. ICAM-1=intercellular adhesion molecule-1. MAP=mean airway pressure. VWF= von Willebrand factor. PEEP=positive end-expiratory pressure. Urine=urine output over prior 24 h. BMI=body-mass index. SBP=systolic blood pressure. SPD=surfactant protein D. PaCO $_2$ =partial pressure of carbon dioxide in arterial blood.



ARDS endotypes and resolution

Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial

Carolyn S Calfee, Kevin L Delucchi, Pratik Sinha, Michael A Matthay, Jonathan Hackett, Manu Shankar-Hari, Cliona McDowell, John G Laffey, Cecilia M O'Kane, Daniel F McAuley, on behalf of the Irish Critical Care Trials Group



DIRECT (PULMONARY) & INDIRECT(ENDOTHELIAL)ETIOLOGY

Higher mortality rate of indirect such as sepsis etiology vs direct etiology.

Increased levels of endothelial markers such as IL6, IL8 , angiopoettin 2 in parallel to increased levels of sRAGE(soluble Receptor form of the for Advanced Glycation End products) originated from pneumocyte type 1 injury ,indicative of severe derangement of edema clearance are seen in non focal type.

sRAGE > 1188pg/lit is elevated before appearance of nonfocal ARDS by CT.

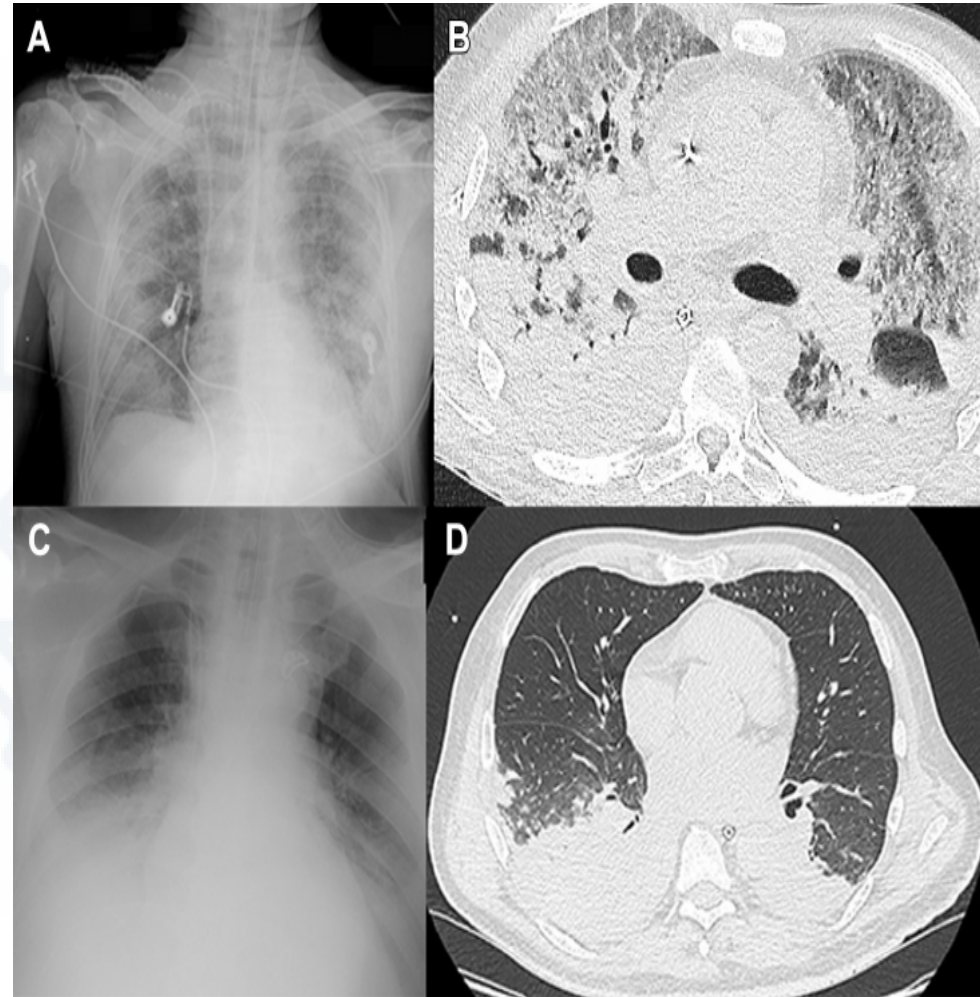
ARDS PHENOTYPES BASED ON LUNG MORPHOLOGY



Elevated Plasma Levels of sRAGE Are Associated With Nonfocal CT-Based Lung Imaging in Patients With ARDS

A Prospective Multicenter Study

Segolene Mrozek, M.D., Matthieu Jabaudon, M.D., Samir Jaber, M.D., Ph.D., Catherine Paugam-Burtz, M.D., Ph.D., Jean-Yves Lefrant, M.D., Ph.D., Jean-Jacques Rouby, M.D., Ph.D., Karim Asehnoune, M.D., Ph.D., Bernard Allaouchiche, M.D., Ph.D., Olivier Baldesi, M.D., Marc Leone, M.D., Ph.D., Qin Lu, M.D., Ph.D., Jean-Etienne Bazin, M.D., Ph.D., Laurence Roszyk, Pharm D, Vincent Sapin, PharmD Ph.D., Emmanuel Futier, M.D., Ph.D., Bruno Pereira, Ph.D., Jean-Michel Constantin, M.D., Ph.D., for Azurea network



distinguish patient groups with different incidences of postoperative pulmonary complications.⁴

In *The Lancet Respiratory Medicine*, Pratik Sinha and colleagues⁵ reported the results of a retrospective analysis of data pooled from cohorts of large ARDS randomised controlled trials, aimed at developing a simple model to facilitate phenotypic identification in patients with ARDS at the bedside. In an elegant, hypothesis-driven study with sophisticated statistical analyses, the authors tested the prognostic validity of their models in two external ARDS clinical trial datasets (START⁶ and HARP-2⁷). The two ARDS phenotypes, hyperinflammatory and hypoinflammatory, could be accurately identified with a simple logistic regression model using three or four variables (interleukin-8, bicarbonate, and protein C, with the optional addition

of interleukin-6 and interleukin-10). However, multiple

factors contribute to disease progression. Thus, even if individual phenotypes are identified correctly, this might not ensure the efficacy of specific treatment. In this context, recent evidence suggests that individualised mechanical ventilation strategies might not be effective to improve outcomes both in perioperative medicine⁸ and in ARDS.⁹ Care must be taken to refrain from prematurely positive interpretations of analyses of

previously collected data, which have not been validated in prospective patient cohorts nor in randomised controlled trials. To date, no guidelines that include different ARDS phenotypes have been published. For personalised medicine to be applied to the clinical care of ARDS, clear experimental and clinical action plans must be developed. First, the development and

COVID 19 SUBTYPES(L, H)

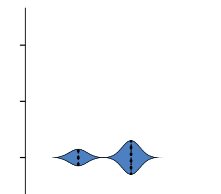
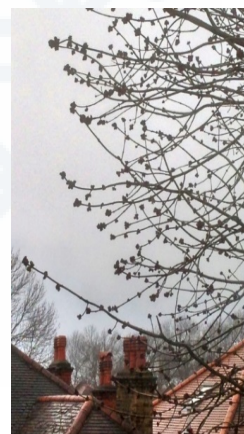
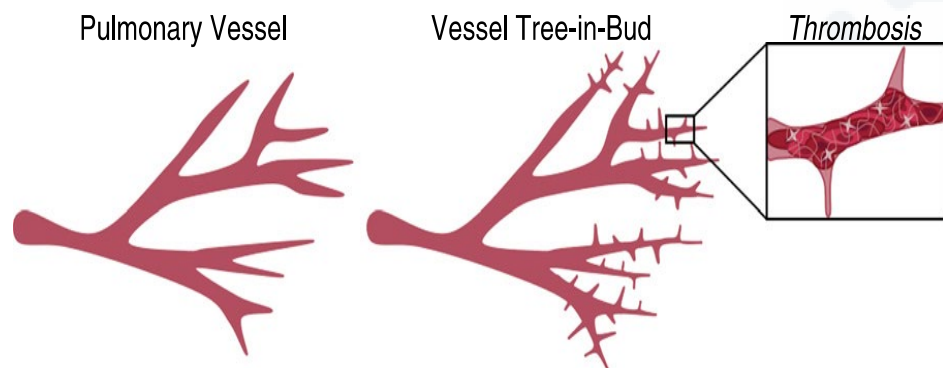
- **L type:** Cs is normal or near normal, increased VD/Vt, lesser CT GGOs and lesser PEEP requirement, thrombotic angiopathy.
- **H type:** more extensive GGOs , Lowest lung compliance , higher PEEP requirements .
- **Postmortem :** DAD +widespread thrombosis +striking new vascular growth (Intessusceptive angiogenesis)

Vascular tree-in-bud

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Vascular Tree in Bud:

- '....a manifestation of pulmonary thrombotic angiopathy.'
- 'neoangiogenesis'
- increases in incidence with duration of disease.



Thank You

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