ARDS, RESPIRATORY FAILURE AND BLOOD BIOMARKERS

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Angela Rogers, MD, MPH, received her medical degree from Harvard Medical School, and her Masters in public health from the Harvard School of Public Health, and pursued post-graduate training at the Brigham and Women's Hospital and Harvard Combined fellowship. She is an Assistant Professor in Pulmonary and Critical Care Medicine at Stanford University, where her research focuses on using genetics and genomics to identify novel biology in ARDS.

Precision medicine & the role for biomarkers in ARDS

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California Thoracic Society
January 18, 2019

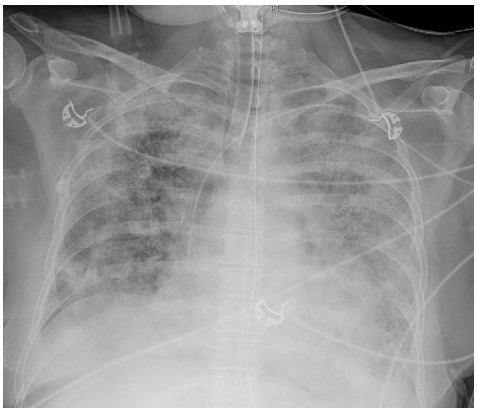
Conflicts of Interest

- I have no conflicts of interest

Learning objectives

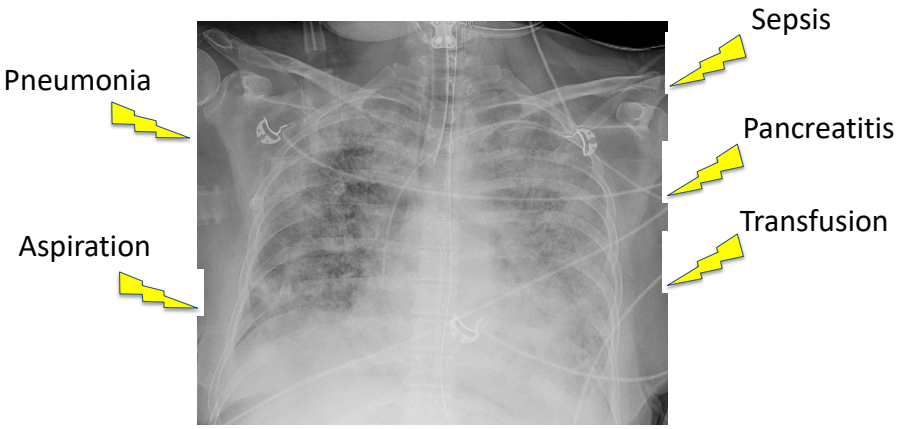
- To understand the need for biomarkers in ARDS
- PaO2:FIO2: A biomarker that works in ARDS
- Biomarkers for endotyping or "splitting" ARDS:
  - Latent class modeling of plasma
  - Molecular phenotyping of edema fluid

ARDS is defined very simply

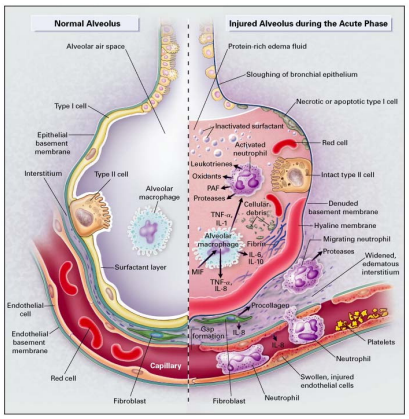


- Intubated
- Acute
- P:F ratio <300
- Bilateral opacities
- Not explained by hydrostatic edema

Diverse underlying risk factors



ARDS pathophysiology is complex

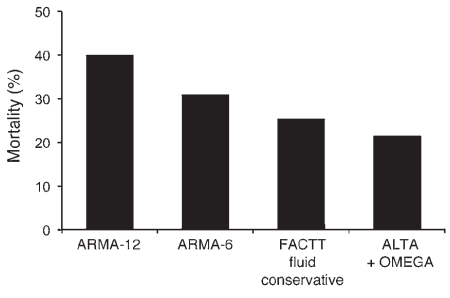


Ware & Matthay, NEJM 2000

"Lumping" vs "Splitting"

What have we learned from lumping?

- ARDS is common
  - 10% of all ICU & 23% of acute respiratory failure admissions
- In real world carries high mortality rate
- Major benefit of low tidal ventilation



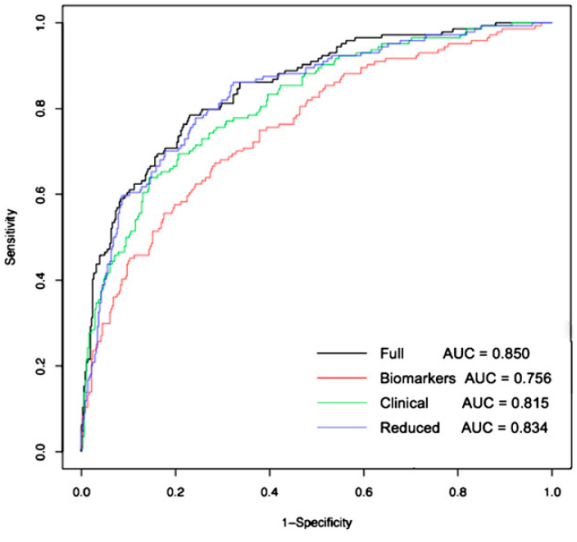
Bellani et al, *JAMA* 2016
ARDSNET *NEJM* 2000
Matthay et al. *JCI* 2012

Biomarkers in all of ARDS

		90-day mortality		
Pathway	**Biomarker**	**Alive**	**Die**	**p-value**
Inflammation	IL-6	209	322	0.004
	IL-8	35	64	<0.001
	TNFR	3668	6914	<0.001
Coagulation & fibrinolysis	Protein C	82	68	.011
	PAI-1	54	111	<0.001
Endothelial injury	ICAM	854	1072	<0.001
	VWF	370	477	<0.001
Epithelial injury	SP-D	92	124	.01

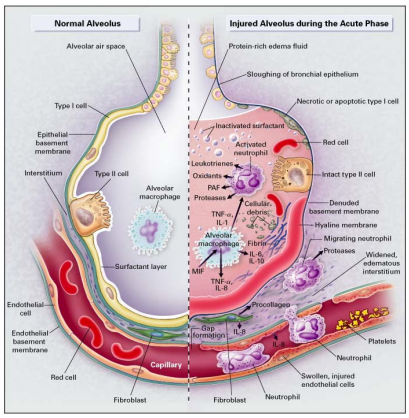
Ware LB, *Chest* 2010

Combining biomarkers to improve prediction based on ALVEOLI trial



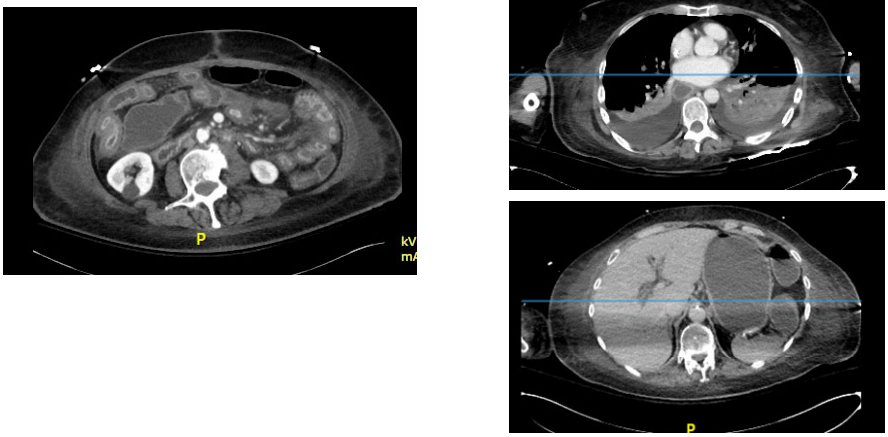
Ware LB, *Chest* 2010

Is it possible that lumping all of ARDS together is harming ARDS clinical trials & science?

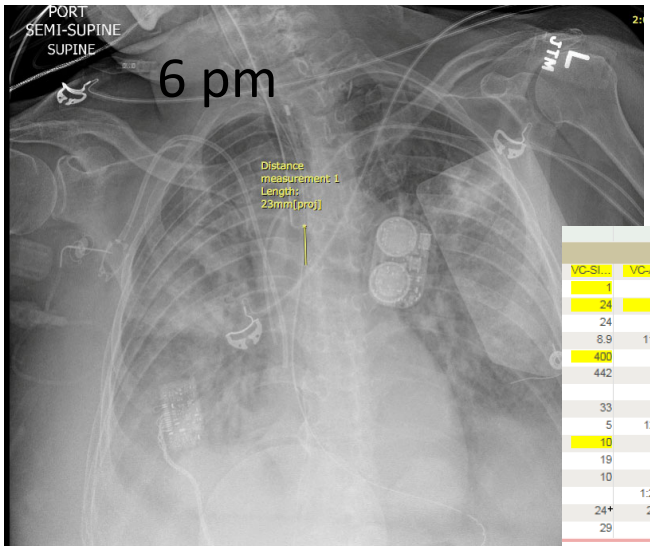


Why splitting matters: a case to classify

- 70 yo F with colon CA on chemo, recently discharged after 1 week admission for failure to thrive
- Per husband, was nauseated, ”gurgling” all night
- Returns to ED critically ill



10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	
			None			None	None	Nor	
			None			None	None		
36.3 ...	35.8 ...		36 (9...	36.5...+			--≡	-	
24+	24+	24+	24+	26+			26		
95	76	85	80	87	87	83	92	8	
	76/53		105/70	113/72+	57/41	140/79	88/63	90/7	
	63		52	88+	77	105	73	79	
107/61	87/68	74/50	101/72	120/71+					
	67		54						
		80 kg...				79.4 ...			
	89		86	82	88	85		83	
								83	
38									
				1 mg/...		1 mg/...	1 mg/...	1 mg/	amiodarone Do...
			0.1 ...+	0.03...+	0.3 m...	0.24...+	0.2 ...+	0 mc...	epinephrine Do...
					0.5 m...	1 mg...+	1 mg/hr≡	1 mg/l	hydromorphone...
					1 mg/hr	2 mg...+	2 mg/hr≡	2 mg/l	midazolam Dos...
5 mc...+	15 m...+	20 mc...	20 m...+			20 mc...	20 mc...	20 m...	norepinephrine...
					100 m...	100 m...	100 m...	100 m	phenylephrine...
			*1 U...+			0.04 ...	0.04 ...	0.04	vasopressin Do...
			VC-SI...	VC-AC		VC-AC			
			1			1			



VC-SI...	VC-AC		VC-AC
1			1
24	28	32	32
24			32
8.9	11.2	11.2	10.8
400		350	350
442			
			0
33	35	36	37
5	12	16	18
10			
19	27	28	33
10			24
	1:2.3	1:2.1	1:2.1
24+	23+	27+	22
29			21

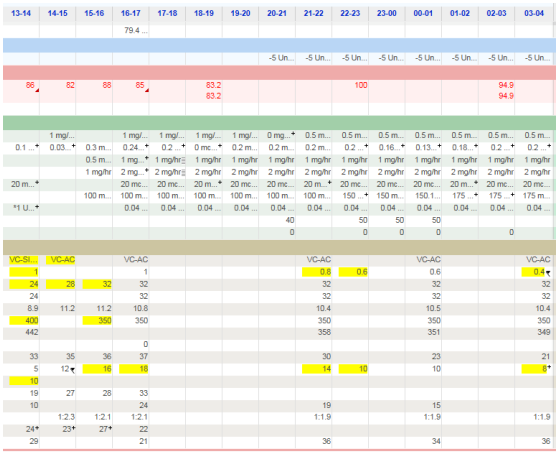
ARDS clinical trial enrollment

	Live	Die
Paralytic		
Placebo		

ARDS biobank

	ARDS	Not ARDS
Patient #1		

Overnight respiratory improvement



- 6 pm: FIO2 1.0, PEEP 18, Pplat 37, ABG 7.23/60/55
- 3 am: FIO2 0.4, PEEP 8, Pplat 21, ABG 7.23/60/90
- 9 am: MAP falls to 40, pH 6.8/55/80, c/w bowel perforation

What does this case do to our clinical trial and biobank?

	Live	Die
Paralytic		
Placebo		

	ARDS	Not ARDS
Patient #1		

Misclassification in ARDS really matters for clinical trials

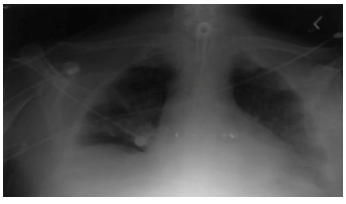
- Inter-rater CXR interpretation varies from κ ~.4-.9

K = 1

	ARDS	Not ARDS
ARDS	50	
Not		50

K = .6

	ARDS	Not ARDS
ARDS	40	10
Not	10	40



K = .4

	ARDS	Not ARDS
ARDS	40	20
Not	10	30

Rubenfeld et al. *Chest* 1999

Power for clinical trials dramatically falls with misclassification

RCT power estimate when ARDS enrollment is imperfect from a patient cohort with 25% ARDS prevalence

Inter-observer Agreement	Kappa	Power in 1500 patient trial	Sample size for 90% power
Perfect	1.00	0.92	1402
Almost perfect	0.85	0.87	1664
Substantial	0.72	0.81	1968
	0.61	0.74	2320
Moderate	0.51	0.67	2726
	0.42	0.60	3198

Sjoder et al. *Annals ATS* 2016

A major role for biomarkers may be in "Splitting" ARDS

- Prognostic: Identify patients at highest risk of bad outcomes and death
- Predictive: Identify patients who would benefit most from treatment

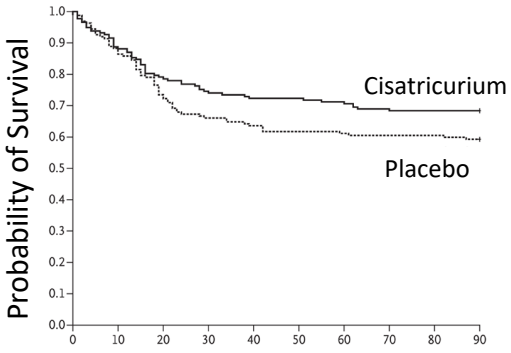
PaO2:FIO2 ratio as a critical ARDS biomarker

- PaO2:FIO2
  - P:F ratio defines disease severity
    - Prognostic, outperforms other, more complex models
  - Enriches clinical trials: recruiting based on more stringent thresholds
    - Predictive enrichment

AECC consensus conf, *AJRCCM* 1994
Berlin definition, *JAMA* 2014

P:F <150 → positive clinical trials

Neuromuscular blockade

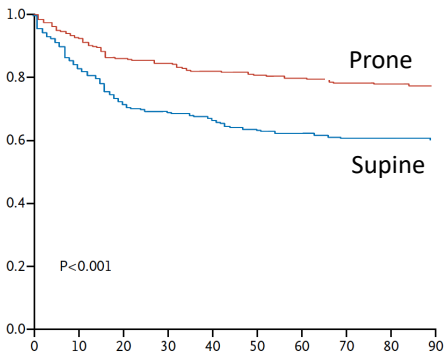


Lower hazard for death (.68, p=.04)

31.6% vs 40.7% 90-day mortality (p=.08)

NEJM. 2010, 373: 1107-16

Prone positioning

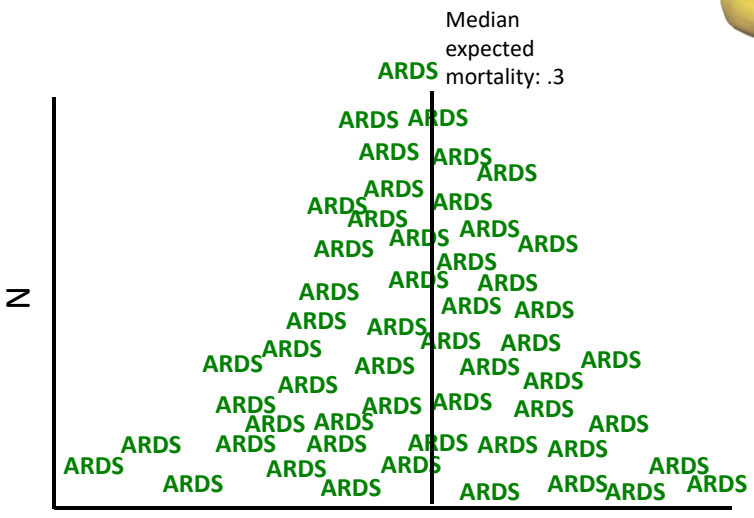


16% vs 32.8% 28d mortality (p<.001)

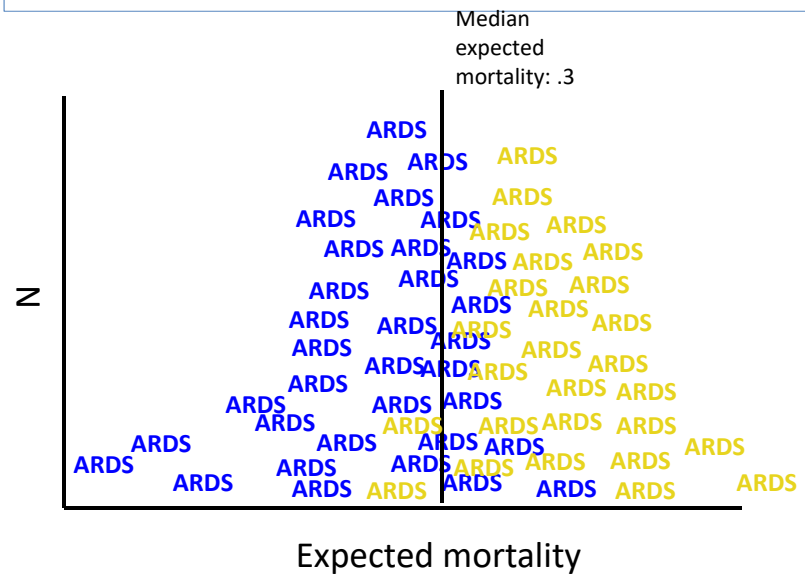
23.6 vs 41% 90d mortality (p<.001)

NEJM. 2013, 368: 2159-67

Biomarkers for splitting



Biomarkers for splitting



2 examples

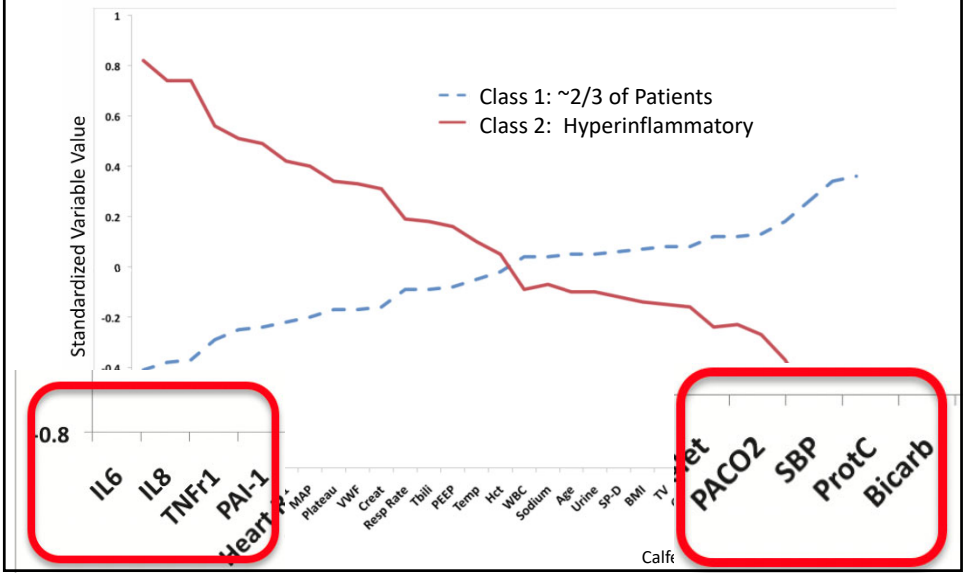
- Latent class modeling, identified plasma biomarkers
- Metabolomics of pulmonary edema fluid

Latent Class Analysis: Are There Distinct Subtypes of ARDS?

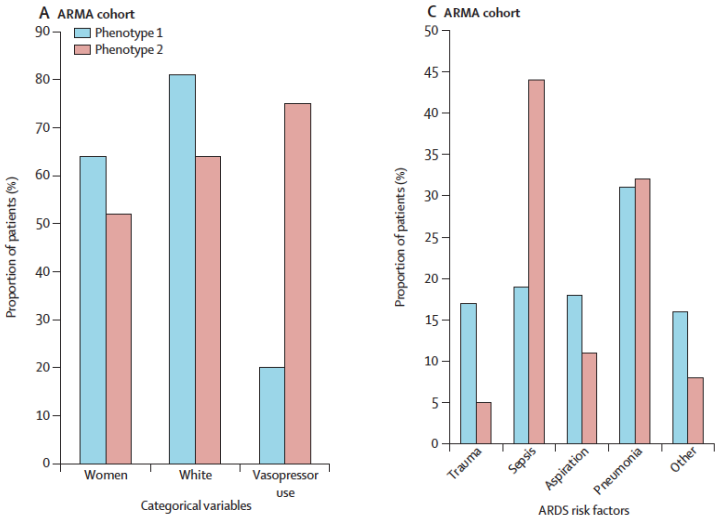
- Study population: Three ARDSnet clinical trials
  - First cohort: ARMA (low tidal volume only; n=479)
  - Second cohort: ALVEOLI (low vs. high PEEP; n=549)
  - Third cohort: FACCT (conservative vs liberal fluid; n=1000)
- Clinical and biomarker data from baseline in each study as inputs that "identify" class (endotype)
  - Analysis conducted independently in each cohort
  - Outcomes not considered in class modeling

Calfee CS et al, *Lancet Resp Med* 2014
Famous K et al, *AJRCCM* 2016

What variables are important in class definition?



Classes differ by clinical variables



Calfee CS et al, *Lancet Resp Med* 2014

Mortality differs by class

	90-day mortality		
Study	**Class 1 (~2/3) ARDS**	**Class 2 (~1/3) ARDS**	**p-value**
ARMA	23%	44%	0.006
ALVEOLI	19%	51%	<0.001
FACTT	22%	45%	<0.0001

Class could be defined w/ >90% AUC with 3 factors: IL8, TNFr1, bicarbonate

Calfee CS et al, *Lancet Resp Med* 2014
Famous K et al, *AJRCCM* 2016

Response to Therapy differs by class

ALVEOLI ($p_{interaction}$=.049)

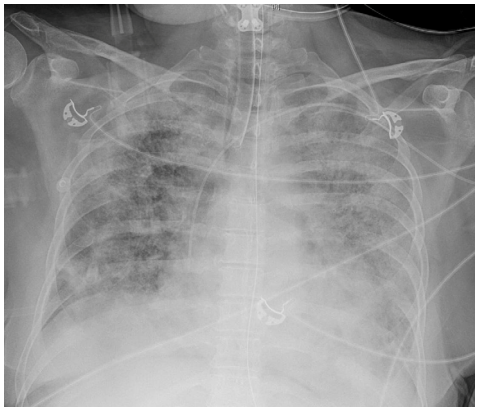
	Mortality in Class 1 ARDS (n=404)	Mortality in Class 2 ARDS (n=145)
Low PEEP	16%	51%
High PEEP	24%	40%

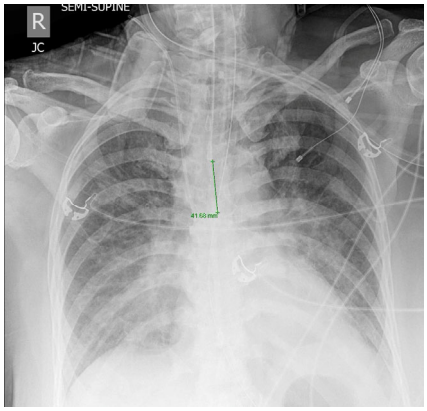
FACCT ($p_{interaction}$=.004)

	Mortality in Class 1 ARDS (n=727)	Mortality in Class 2 ARDS (n=273)
Liberal fluid	18%	50%
Conservative fluid	26%	40%

Calfee CS et al, *Lancet Resp Med* 2014
Famous K et al, *AJRCCM* 2016

Metabolomics of pulmonary edema fluid: ARDS vs CHF





Pulmonary edema fluid metabolomics

- Undiluted pulmonary edema fluid in ARDS
  - High edema: plasma protein ratio (>.65) associated with ARDS (AUC >.8)
- Pulmonary edema fluid at time of intubation
  - 16 ARDS vs 13 CHF
  - Collected at Vanderbilt and UCSF

Rogers et al. *AJP Lung* 2017

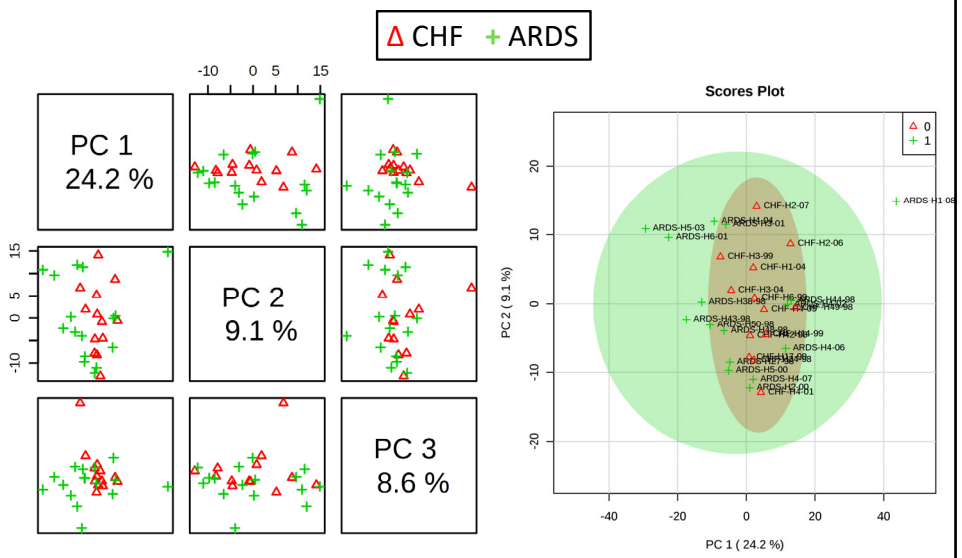
CHF vs ARDS Phenotyping

	ARDS (N=16)	CHF (N=13)	P value
Age	43.7	50.5	.3
Gender (%M)	50%	62%	.7
Sepsis	44%	0%	.008
Mortality	44%	15%	.12
Primary Diagnosis	Pneumonia (4) Sepsis (4) Anaphylaxis (2) Aspiration (1) TRALI (2) Fulm Hep Fail (1) Reperfusion edema (1) Tumor lysis (1)	Vol overload/CHF (5) MI/Ischemia (2) Cardiac arrest (1) Post-obstructive (2) Cardiogenic shock (1) TRALI (1) Neurogenic (1)	.01

Metabolic profiling strategy

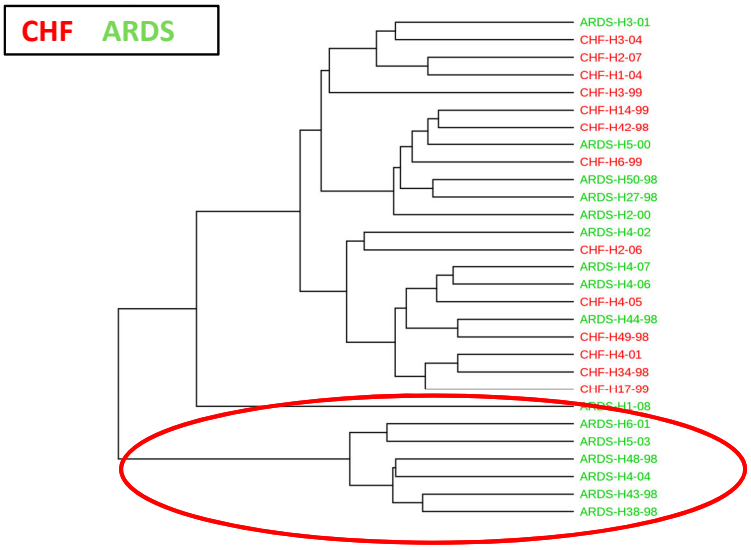
- Undiluted pulmonary edema fluid profiled by Metabolon
- Tests up to 3000 human plasma metabolites with high accuracy
- Metabolite levels $\log_2$ normalized and auto scaled
- Differences in classes assessed using machine learning
  - Principle components analysis
  - Partial least squares-discriminant analysis
  - Hierarchical clustering

No separation of CHF vs ARDS



Rogers et al. *AJP Lung* 2017

Hierarchical clustering: A subset separates



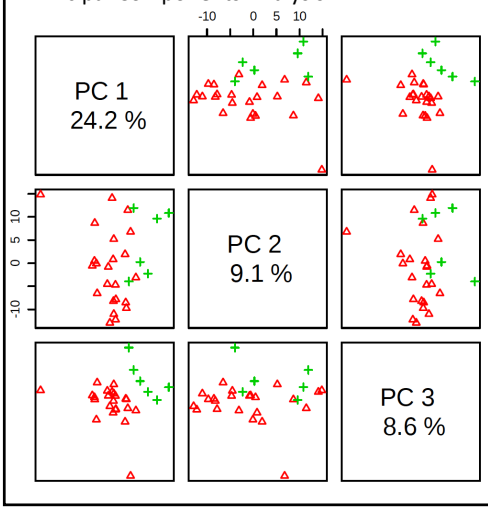
6 Separate ARDS

	6 Distinct ARDS	10 Remaining ARDS	CHF
Age	36	49	51
Gender (%M)	33	60%	62%
Sepsis	66%	30%	0%
Mortality	66%	30%	15%
Primary Diagnosis	Sepsis (3) Fulm Hep Fail (1) Anaphylaxis (1) Aspiration (1)	Pneumonia (4) Sepsis (1) Anaphylaxis (1) TRALI (2) Reperfusion edema (1) Tumor lysis (1)	Vol overload/CHF (5) MI/Ischemia (2) Cardiac arrest (1) Post-obstructive (2) Cardiogenic shock (1) TRALI (1) Neurogenic (1)

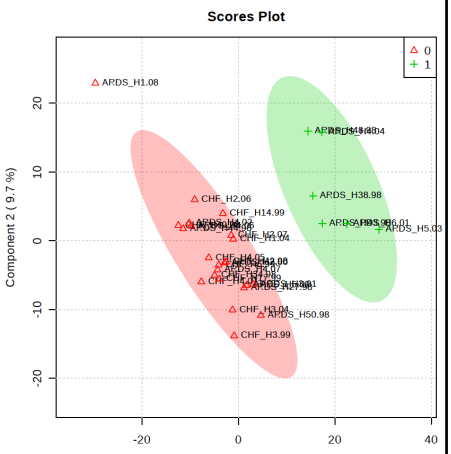
These 6 separate

Δ CHF & 10 ARDS + 6 distinct ARDS

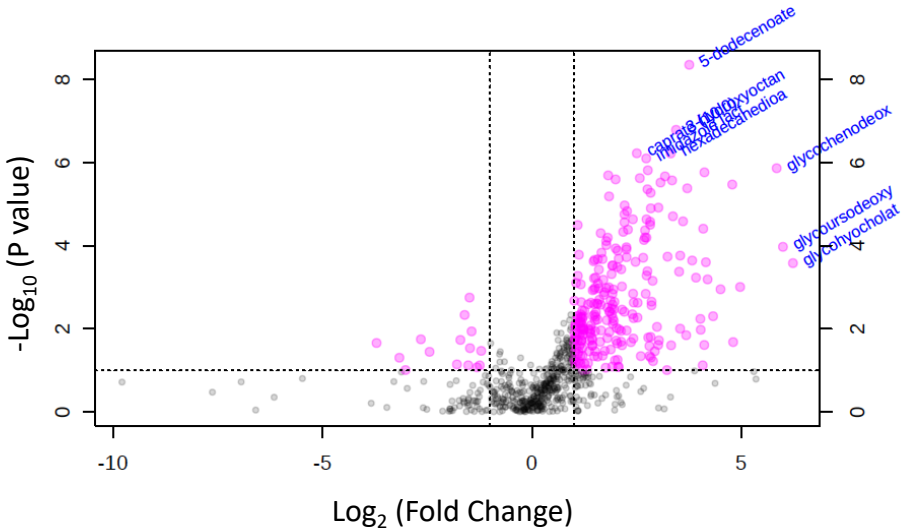
Principal Components Analysis



Partial Least Squares DA

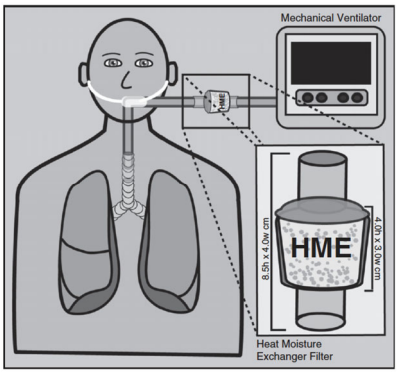


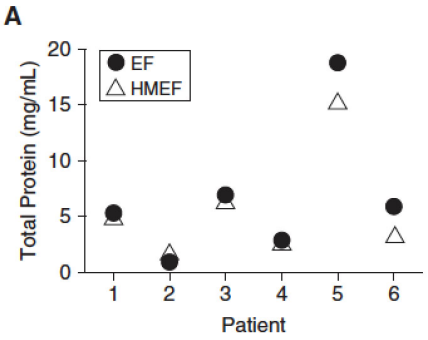
These 6 are highly metabolically active



Rogers et al. *AJP Lung* 2017

Pulmonary edema: A newly attainable biomarker?





McNeil et al. *AJRCCM* 2018

Should we be lumping or splitting ARDS?

Should we be lumping AND splitting ARDS?

Should we be lumping AND splitting ARDS?

Low tidal volume, lung protective ventilation

- Clearly helps mortality in ARDS
- Little downside in some misclassification

Should we be lumping AND splitting ARDS?

ARDS clinical trials

- Genomics tells us we need to be careful with lumping
  - Endotypes
  - Frank misclassification
- Kills power of trial & puts patients who can't benefit at risk

Conclusions

- Lumping all of ARDS as a single phenotype has been very successful for lung protective ventilation and reduced mortality
- For moving toward precision medicine:
  - To date our only established biomarker in ARDS is the P:F ratio, which is prognostic and predictive
  - Biomarkers will likely be critical in endotyping ARDS & moving toward personalized medicine in practice and clinical trials