

SUPPLEMENTAL DATA

Stability of ARDS Subphenotypes Over Time in Two Randomized Controlled Trials

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Supplementary Methods

The variables included in the analyses included both categorical (race, gender, primary ARDS risk factor, and vasopressor use) as well as continuous variables (age, (Interleukin (IL)-8, IL-6, Plasminogen Activator Inhibitor 1 (PAI-1), soluble Tumor Necrosis Factor 1 (sTNF α 1), soluble Intercellular Adhesion Molecule-1 (ICAM-1), von Willebrand factor antigen (vWF), Surfactant Protein D (SP-D), Protein C, total minute ventilation, heart rate, mean airway pressure, temperature, respiratory rate, bilirubin, plateau pressure, creatinine, tidal volume, hematocrit, body mass index, white blood cell count, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO $_2$: FiO $_2$), partial pressure of arterial carbon dioxide (PaCO $_2$), platelets, and systolic blood pressure).

Table S1: Sample Sizes Available for Analysis at Day 0 and Day 3 in Each Study.

	ARMA	ALVEOLI
Day 0 N	473	549
Day 3 N	458 (97%)	525 (96%)
No Day 3 Data		
Died	13	23
No data collected	2	1

Table S2: Latent Class Analysis of Subjects Enrolled in ARMA at Day 0

N Classes	Bayesian Information Criterion	entropy	Number Assigned to Each Subphenotype				p-value*
			Class 1	Class 2	Class 3	Class 4	
1	32693.8		473				
2	32193.9	.80	338	135			<.01
3	32006.8	.88	322	107	44		.61
4	31941.9	.91	323	98	42	10	.76

* P-value represents the Vuong-Lo-Mendell-Rubin (VLMR) test, which tests if k classes confer an improved model fit over $k-1$ classes.

Table S3: Latent Class Analysis of Subjects Enrolled in ALVEOLI at Day 0

N Classes	Bayesian Information Criterion	entropy	Number Assigned to Each Subphenotype				p-value*
			Class 1	Class 2	Class 3	Class 4	
1	41360.7		549				
2	40579.1	.85	403	146			.04
3	40215.5	.91	399	146	4		.33
4	39961.3	.93	379	136	4	20	.55

* P-value represents the Vuong-Lo-Mendell-Rubin (VLMR) test, which tests if k classes confer an improved model fit over $k-1$ classes.

Table S4: Effect of Active Study Drugs on Day 3 Levels of Key Class-Defining Biomarkers in ARMA

Study	Day 3 Measure	Day 3 Value, Active Drug	Day 3 Value, Placebo	p-value, Drug vs. Placebo*
Keto	IL-6, pg/ml	96 (61, 188)	96 (67, 144)	.03
	IL-8, pg/ml	62 (40, 121)	53 (35, 93)	.77
	Protein C, % control	53 (36, 68)	53 (37, 74)	.81
Liso	IL-6, pg/ml	82 (24, 145)	78.5 (45, 164)	.87
	IL-8, pg/ml	20 (20, 35)	26 (20, 40)	.35
	Protein C, % control	73 (47, 101)	62 (44, 85)	.05
	TNFr1, pg/ml	3512 (2227, 4711)	3263 (2099, 7031)	.21

* P-value based on parametric test of log-transformed values.

All values displayed as median (25%-75% range).

Table S5: Effect of Active Study Drugs on Day 3 Levels of Key Class-Defining Biomarkers in ARMA, Stratified By Day 0 Class*

Study	Day 3 Measure	Day 3 Median, Class 1, Active Drug	Day 3 Median, Class 1, Placebo	Day 3 Median, Class 2, Active Drug	Day 3 Median, Class 2, Placebo	p-value, Class-by-Drug Interaction**
Keto	IL-6, pg/ml	83	90	208	138	.02
	IL-8, pg/ml	50	51	128	80	.58
	Protein C, % control	60	62	41	39	.72
Liso	IL-6, pg/ml	71	66	110	163	.77
	IL-8, pg/ml	20	20	37	72	.23
	Protein C, % control	80	67	36	52	.07
	TNFr1, pg/ml	3051	2539	3961	7032	.13

* All classes assigned for this table by Day 0 data

** P-value based on parametric test of log-transformed values.

Table S6: Clinical and Biological Phenotype of Each Class at Day 0 and Day 3 in ARMA, Selected Variables

	Day 0		Day 3	
	Class 1 (N = 338)	Class 2 (N = 135)	Class 1 (N = 321)	Class 2 N = 137)
Minute ventilation, L/min	12.3 ± 3.5	15.9 ± 4.7	12.1 ± 3.3	14.8 ± 3.4
Plateau pressure, cm H2O	28 ± 7	33 ± 8	24 ± 6	29 ± 7
PF ratio, mm Hg	139 ± 60	115 ± 57	176 ± 70	129 ± 63
Systolic BP, mm Hg (lowest)	93 ± 19	78 ± 17	107 ± 23	90 ± 26
Heart rate, bpm (highest)	87 ± 16	99 ± 20	97 ± 18	102 ± 16
Platelets, thousands	178 ± 127	130 ± 100	168 ± 116	106 ± 90
PaCO ₂ , mm Hg	38 ± 8	34 ± 9	43 ± 11	42 ± 12
Creatinine, mg/dL	1.0 (0.7, 1.5)	1.6 (1.0, 2.6)	0.8 (0.6, 1.1)	1.9 (1.2, 3.7)
Bilirubin, mg/dL	0.9 (0.6, 1.8)	1.4 (0.7, 3.2)	0.4 (0, 1.0)	1.1 (0, 3.1)
ICAM-1, ng/mL	523 (302, 845)	878 (607, 1382)	514 (336, 898)	1017 (636 1943)
vWF, % control	249 (163, 396)	388 (251, 599)	283 (167, 416)	387 (290, 529)
PAI-1, ng/mL	56 (37, 94)	130 (71, 342)	46 (33, 89)	73 (41, 171)
Protein C, % control	53 (39, 70)	30 (23, 44)	60 (47, 81)	37 (26, 50)

IL-8, pg/mL	28 (20, 62)	113 (57, 360)	20 (20, 46)	86 (38, 161)
IL-6, pg/mL	172 (83, 426)	1343 (403, 3027)	68 (39, 116)	271 (137, 695)
TNFr-1, pg/mL	2655 (1932, 3846)	5983 (3916, 10320)	2339 (1873, 3440)	8142.5 (5064, 14169)
SP-D, ng/mL	84 (41, 175)	81 (39, 146)	118 (60, 212)	192 (106, 283)

Values represent mean \pm SD or median (25th-75th percentile).

Table S7: Clinical and Biological Phenotype of Each Class at Day 0 and Day 3 in ALVEOLI, Selected Variables

	Day 0 Value		Day 3 Value	
	Class 1 (N = 403)	Class 2 (N = 146)	Class 1 (N = 394)	Class 2 (N = 131)
Minute ventilation, L/min	11.1 ± 3.1	14.7 ± 4.2	11.2 ± 3.3	13.5 ± 3.6
Plateau pressure, cm H2O	26 ± 7	29 ± 7	24 ± 6	27 ± 6
PF ratio, mm Hg	133 ± 58	113 ± 52	196 ± 77	155 ± 64
Systolic BP, mm Hg (lowest)	91 ± 16	79 ± 13	105 ± 19	93 ± 19
Heart rate, bpm (highest)	120 ± 22	139 ± 24	91 ± 18	103 ± 17
Platelets, thousands	195 ± 125	128 ± 107	212 ± 126	115 ± 115
PaCO ₂ , mm Hg	40 ± 9	36 ± 8	43 ± 12	41 ± 12
Creatinine, mg/dL	1.0 (0.7, 1.7)	1.4 (0.9, 2.6)	0.9 (0.6, 1.4)	1.5 (0.9, 3.2)
Bilirubin, mg/dL	0.7 (0.4, 1.2)	1.4 (0.6, 2.6)	0.6 (0.4, 1.3)	2.3 (0.8, 6.5)
ICAM-1, ng/mL	821 (562, 1165)	1390 (854, 1856)	951 (672, 1379)	1369 (1038, 2051)
vWF, % control	359 (223, 54)	538 (341, 765)	418 (251, 632)	565 (367, 817)
PAI-1, ng/mL	46 (27, 88)	164 (80, 250)	37 (21, 74)	73 (42, 174)
Protein C, % control	89 (59, 133)	37 (22, 70)	111 (77, 160)	66 (34, 106)

IL-8, pg/mL	16 (16, 53)	162 (81, 552)	16 (16, 34)	107 (62, 268)
IL-6, pg/mL	155 (67, 368)	1535 (528, 3968)	69 (41, 128)	302 (131, 774)
TNFr-1, pg/mL	3462 (2372, 6346)	7985 (4472, 14692)	3440 (2481, 5569)	7786 (4476, 18973)
SP-D, ng/mL	111 (53, 242)	77 (43, 159)	196 (93, 339)	180 (101, 340)

Values represent mean \pm SD or median (25th-75th percentile).

Table S8. Mean probabilities of day 0 latent class membership by whether subject changed class from Day 0 to Day 3.

	Day 0 Class		Mean	SD	p-value
ARMA	1	Changed Class	0.99	0.23	.09
		Stayed in Class	0.89	0.24	
	2	Changed Class	0.73	0.37	.11
		Stayed in Class	0.94	0.08	
ALVEOLI	1	Changed Class	0.98	0.05	.50
		Stayed in Class	0.95	0.16	
	2	Changed Class	0.77	0.34	.21
		Stayed in Class	0.90	0.20	

Figure Legends:

Figure S1a: Differences in standardized values of each continuous variable by class in the ARMA cohort on Day 3 by latent class. The variables are sorted on the basis of the degree of separation between the classes. The y-axis represents standardized variable values, in which all means are scaled to zero and SDs to one. A value of +1 for the standardized variable signifies that the mean value for a given phenotype was one SD higher than the mean value in the cohort as a whole. Mean values are joined by lines to facilitate displaying class profiles. TNFr1=tumor necrosis factor receptor-1. PAI-1=plasminogen activator inhibitor-1. ICAM-1=intercellular adhesion molecule-1. MAP=mean airway pressure. VWF= von Willebrand factor. BMI=body-mass index. SBP=systolic blood pressure. SPD=surfactant protein D. PaCO₂=partial pressure of carbon dioxide in arterial blood. Plateau=plateau pressure.

Figure S1b: Differences in standardized values of each continuous variable by class in the ALVEOLI cohort on Day 3 by latent class. The variables are sorted on the basis of the degree of separation between the classes. The y-axis represents standardized variable values, in which all means are scaled to zero and SDs to one. A value of +1 for the standardized variable signifies that the mean value for a given phenotype was one SD higher than the mean value in the cohort as a whole. Mean values are joined by lines to facilitate displaying class profiles. TNFr1=tumor necrosis factor receptor-1. PAI-1=plasminogen activator inhibitor-1. ICAM-1=intercellular adhesion molecule-1. MAP=mean airway pressure. VWF= von Willebrand factor. BMI=body-mass index. SBP=systolic blood pressure. SPD=surfactant protein D. PaCO₂=partial pressure of carbon dioxide in arterial blood. Plateau=plateau pressure.

Figure S2a: Sankey chart depicting change in class from Day 0 to Day 3, ARMA Cohort.

Figure S2b: Sankey chart depicting change in class from Day 0 to Day 3, ALVEOLI Cohort

Figure S1A.

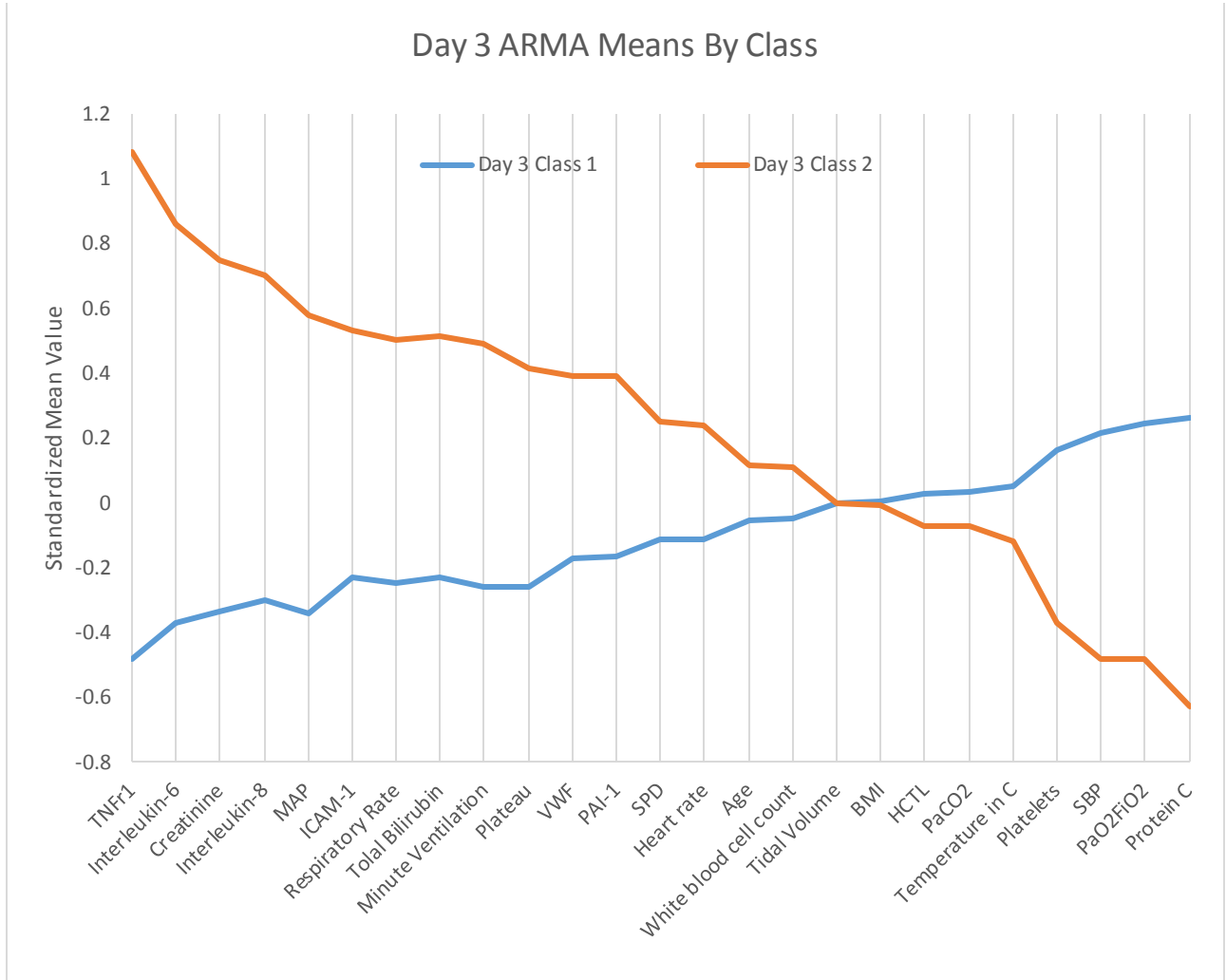


Figure S1B.

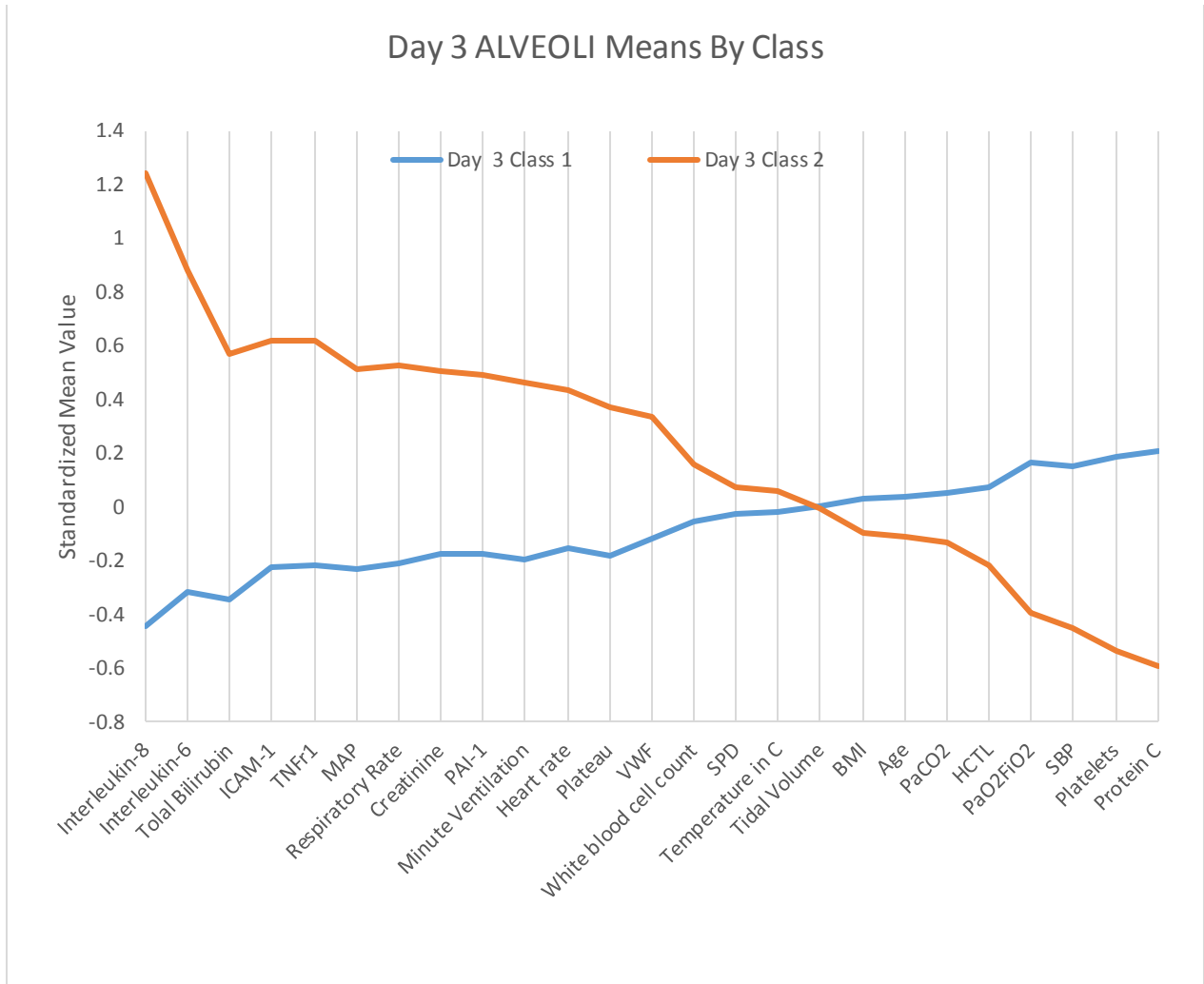


Figure S2a.

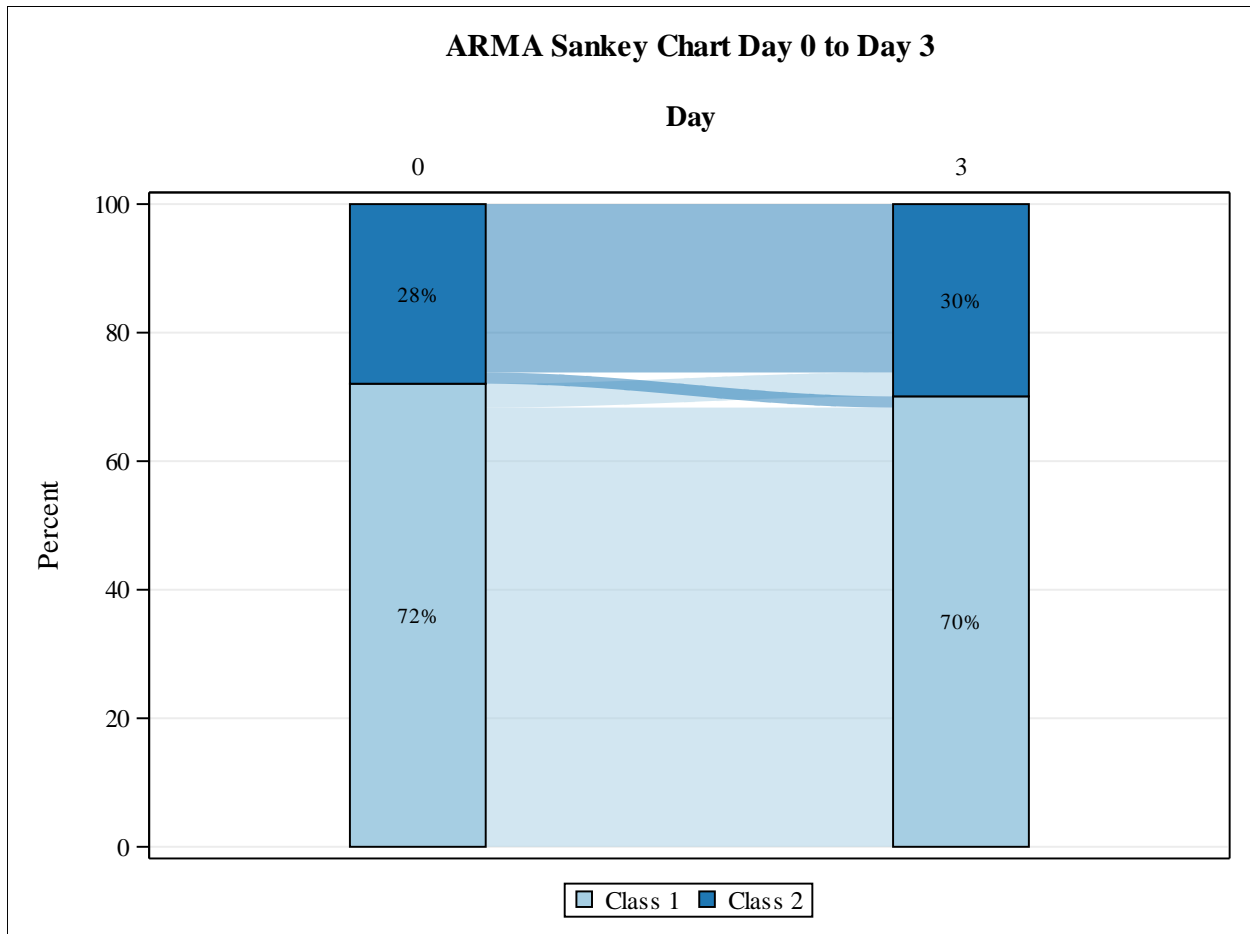


Figure S2b.

