CHEST Online Supplement

Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials

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e-Appendix 1. Methods

Estimation of prevalence of rapidly improving acute respiratory distress syndrome (riARDS)
Patient-level data from six ARDSNet trials (namely, ARMA, ALVEOLI, FACTT, ALTA, EDEN and SAILS) were harmonized, including patient demographic, clinical, and outcome data. We studied the prevalence of riARDS in each trial, and changes over time in such. Changes over time were studied in two ways. First, we estimated the prevalence of riARDS in each study, and graphically depicted this prevalence by publication date. The line of best fit was found using a univariate linear regression using studies as the unit of observation, the year of publication as the independent variable, and the percentage of participants with riARDS as dependent variable. We used weights to account for the heteroscedasticity created by difference in precision in the estimates of riARDS prevalence due to differing study sample sizes.[1] These weights were the inverse of the sample size, normalized to sum to one.[2] Second, to understand whether this secular trend could be explained by changes in patient severity or ventilator practices, we explored a patient-level multivariate logistic regression estimating the prevalence of riARDS. In this model we included study publication date as the predictor of interest and we controlled for both individual [Acute Physiology and Chronic Health Evaluation (APACHE) III and number of days from diagnosis of ARDS to trial enrollment] and study-level (standard ventilator practice) characteristics.

Development of a predictive model of riARDS
Having explored the differences between patients with riARDS and ARDS> 1 day in terms of baseline characteristics and outcomes, we strove to develop a predictive model that maximized the ability to effectively rule out the chance of subsequent development of riARDS.

As a first step we randomly separated the 1909 unique patients available in the three most recently published ARDSNet trials (namely, ALTA, EDEN and SAILS) into a derivation dataset (n=1357) and a validation dataset (n=552); a commonly used statistical approach in the literature.[3] The validation dataset was put aside to test the validity of the chosen models without bias.

Over 150 variables were extracted across trials, although missingness was an important issue for many, as some measurements were trial-specific. Several additional variables were created based on clinical experience. In terms of intensive care unit (ICU) admission source, each location was treated individually. Patients in the medical ICU who were transferred in from either "Another Special Care Unit", "Another Hospital" or "Stepdown Unit" could be at increased risk for worse outcomes, thus we wanted to capture this situation. For our purposes having an ARDS risk factor that is respiratory-related could be more important than whether it is pneumonia or aspiration. We also wanted to capture patients who did not have any organ failure beyond the pulmonary system. Finally, as partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) data were available at screening and immediately before enrollment, we added variables indicating the change from screening to enrollment, the direction of the change, and a categorization of whether the patient

increased by at least 50 mmHg, decreased by at least 50 mmHg, or did not change substantially. The APACHE III score, while available, was intentionally not included as a potential predictor as it cumbersome and not routinely calculated at the bedside, or during trial enrollment decisions.

Using the derivation dataset only, we first limited ourselves to variables that were available for at least 85% of patients, which nevertheless included 87 variables. These included demographics, enrollment, clinical, and disease specific information. All patients with complete data were used to fit the prediction models.

Even with the restriction of sufficiently complete data for each predictor, the number of predictors was much greater than traditional regression methods can handle. Given the large number of predictors available and the relative scarcity of events, we turned to machine learning (data mining) techniques to allow the data to tell us which of these potential predictors may be best suited to predict riARDS. Random Forest[4] is a well-established ensemble non-parametric technique well suited for our classification problem. It does not assume a particular distribution for either the predictors or their association with the outcome and is able to handle a large number of predictors. The algorithm works by fitting a set of classification trees, each of which is based on a bootstrapped sample of patients (random sample with replacement the same size as the original data). The algorithm chooses the best predictor to divide the data into two subgroups more homogeneous in their respective probability of riARDS. A strong advantage of Random Forests (and classification trees in general) is that for continuous parameters, all possible dichotomization points are considered without having to define these *a priori*. Once these two subgroups are divided at a *node split*, the procedure is repeated within each subgroup, recursively continuing until each group is either all riARDS or all ARDS> 1 day. A tree is created for each bootstrapped sample. At each node the algorithm selects from a random subset of predictors, thus differences across the trees comes from both the bootstrapping of each sample as well as the options for predictors at each node. This procedure leads to a set of trees, which are then combined in such a way as to reduce prediction error[4]. The R package *randomForest*[5] was used to fit 500 trees, with 8 predictors considered at any particular node split.

Improvement of the model at each node split can be measured by the decrease in misclassification, here quantified by the Gini impurity index. This measure of improvement is summed across trees for each predictor to calculate the improvement afforded to the model by that measure. By ranking all predictors available according to the gain each contributed, we can obtain a measure of the relative importance of each potential predictor, and thus discard those which will not improve results. Results of this variable importance measure are shown in the supplementary figure below. It is important to keep in mind that this measure of relative importance assumes all other predictors are included, and thus may not be reflective of importance of a variable in a more parsimonious model.

The flexibility and potential increased accuracy of random forests comes at the cost of interpretability, as the algorithm is a "black box" and therefore is difficult to use at the bedside or to gain scientific

understanding of the phenomenon at hand. We thus used the variable importance measures in combination with clinical experience to select several reasonably sized subsets of potential predictors to test using models in line with our practical and scientific goals. We based our selective combinations of variables that were easily available at the bedside, captured several unique components of physiology and had a track record of association with ARDS progression.[6,7]

For each given set of predictors, we fit a logistic regression model. For the logistic regression, predictors were added one at a time using forward selection minimizing the Akaike information criterion (AIC), a measure of goodness of fit that also incorporates a penalty for the number of parameters used. The procedure arrives at an optimal parsimonious model for that set of potential predictors.

The logistic algorithm produces a continuous prediction for the probability that each patient will have riARDS. The accuracy of these predictions was estimated using the area under the receiver operating curve (AUC). Youden's index was then used to dichotomize these predictions at an optimal point to maximize sensitivity plus specificity. The accuracy of this binary prediction was then studied using sensitivity, specificity, negative predictive value and positive predictive value.

Several models were chosen that performed well, combined appropriate physiological characteristics that could be assessed easily at the bedside and would not be burdensome to incorporate into a predictive algorithm. Among these, we then chose our final set of predictors that when used in the logistic regression model effectively ruled out riARDS and maximized the negative predictive value. We used this set and refit the logistic regression using all patients with sufficient data for the select variables in these models (PaO_2:FiO_2 at screening, change in PaO_2:FiO_2 from screening to enrollment, usage of vasopressors, FiO_2 at enrollment and bilirubin level). In total, 1080 patients were available for derivation of this model.

Having chosen and estimated a single logistic prediction model, we applied these models to all patients with sufficiently complete data in validation dataset, which to this point had not been used. No other models were tested in the validation dataset, ensuring proper inference would be possible. The coefficients and cut points established in the derivation dataset were used to predict a continuous probability of patient having riARDS. The accuracy was tested in a similar fashion as in the derivation dataset, with AUC, sensitivity, specificity, negative predictive value, and positive predictive value.

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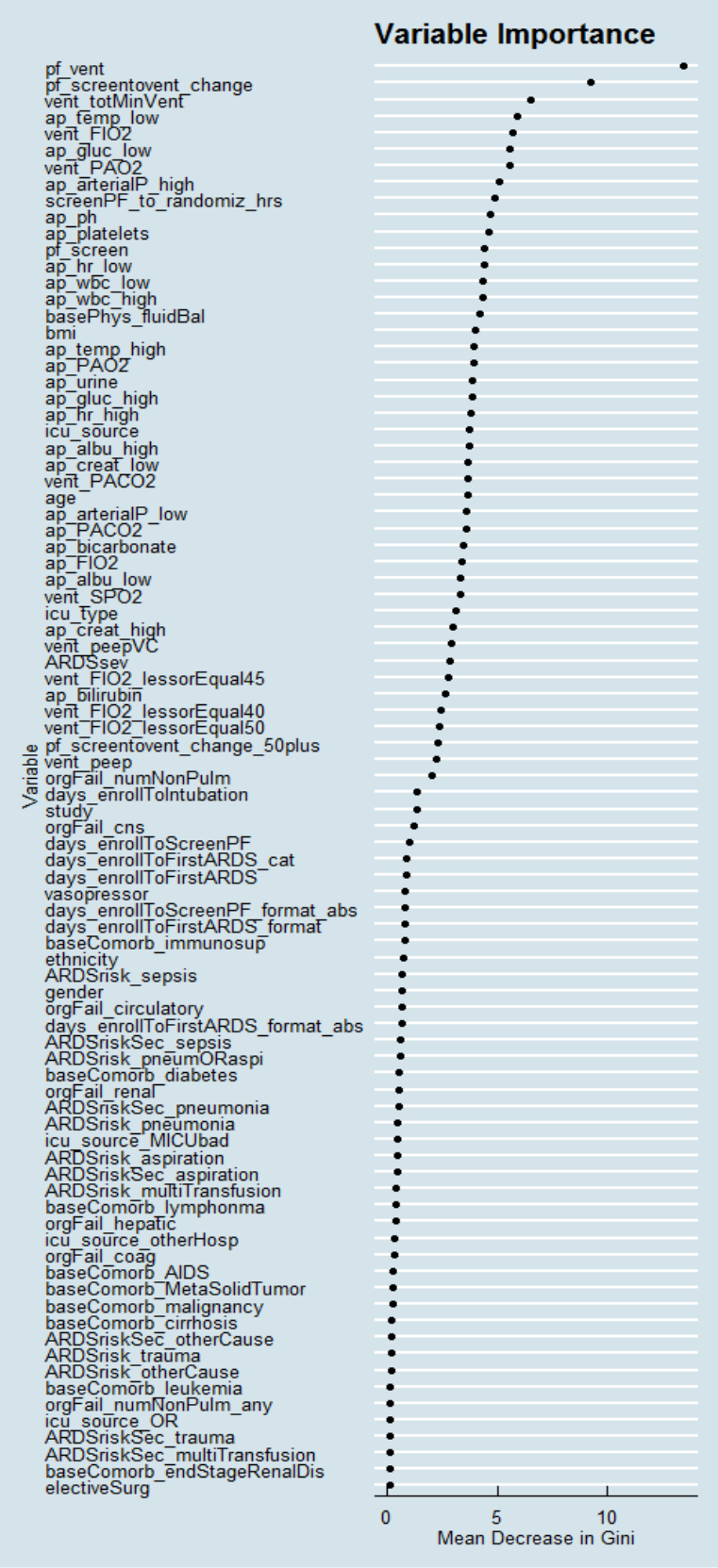
Methods e-Figure: Relative variable importance in a random forest using all predictors available for at least 85% of patients.



e-Table 1. Characteristics of ARDSNet trials.

Trial name	Period of enrollment	Sample size	Interventions	PEEP	Days from ARDS diagnosis to enrollment	Primary outcome	Number of unique patients (Number of patients used in the logistic regression model)
ARMA	3/1996-3/1999	861	Higher tidal volume vs Lower tidal volume	8.44 (3.87)	1 [0-1]	60-day mortality	861
ALVEOLI	10/1999-2/2002	549	Lower PEEP vs Higher PEEP	9.54 (4.27)	1 [0-1] 0 [-2-73]	60-day mortality	549
FACTT	6/2000-10/2005	1000	Liberal fluid therapy vs Conservative fluid therapy	9.45 (3.98)	1 [0-1]	60-day mortality	1000
ALTA	8/2007-7/2008	282	Placebo vs Albuterol	9.17 (3.59)	1 [0-1]	Ventilator-free days	282 (203)
EDEN	1/2008-3/2011	1000	Full feeding vs Trophic feeding	9.48 (4.13)	1 [0-1]	Ventilator-free days	963* (720)
SAILS	3/2010-9/2013	745	Placebo vs Rosuvastatin	9.20 (3.74)	1 [0-1]	60-day mortality	664** (521)

Abbreviations: ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; vs, versus.
Data on PEEP on the first day of enrollment are reported as mean (standard deviation). Data on days from ARDS diagnosis to enrollment are reported as median [interquartile range].
The American-European Consensus Conference definition of ARDS was used in all trials.
*37 patients in EDEN were co-enrolled in ALTA.
**81 patients in SAILS were co-enrolled in EDEN.
For the prediction model, data of a total of 1909 unique patients enrolled in ALTA, EDEN and SAILS were used, divided in a derivation dataset (2/3; *i.e.*, 1357 patients) and in a validation dataset (1/3; *i.e.*, 552 patients). For the random forest, data on 889 patients in derivation dataset who had complete data for all variables with 85% completion rate were used. Logistic regression was fit using 1023 patients (140 patients from ALTA, 503 from EDEN, 380 from SAILS) in derivation dataset who had partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) at screening, change in PaO_2:FiO_2 from screening to enrollment, usage of vasopressors, FiO_2 at enrollment and serum bilirubin. Validation dataset used 421 patients (63 from ALTA, 217 from EDEN, 141 from SAILS) with complete data.

e-Table 2. Logistic regression analysis of the prevalence of rapidly improving ARDS over time.				
	Univariate analysis		**Multivariate analysis**	
	Odds ratio (95% CI)	**p value**	**Odds ratio (95% CI)**	**p value**
Year of publication of ARDSNet trial	1.06 (1.04-1.08)	<0.0001	1.08 (1.04-1.13)	0.0003
Study-wide ventilator practice	1.07 (1.04-1.10)	<0.0001	0.99 (0.93-1.05)	0.67
Days from diagnosis of ARDS to trial enrollment	1.03 (0.89-1.20)	0.66	0.89 (0.76-1.04)	0.14
APACHE III score	0.98 (0.98-0.99)	<0.0001	0.98 (0.98-0.99)	<0.0001

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence intervals; APACHE, acute physiology and chronic health evaluation.
Median number of ventilator-free days among patients without rapidly improving ARDS was used to assess study-wide ventilator practice.

e-Table 3. Risk factors in mild, moderate and severe ARDS.				
Primary risk factor of ARDS	**Mild (n=348)**	**Moderate (n=939)**	**Severe (n=622)**	**p value**
Pneumonia	204 (59%)	601 (64%)	408 (66%)	0.088
Sepsis	77 (22%)	168 (18%)	100 (16%)	0.062
Aspiration	31 (9%)	98 (10%)	57 (9%)	0.598
Trauma	14 (4%)	27 (3%)	23 (3%)	0.504
Multiple Transfusions	6 (2%)	12 (1%)	7 (1%)	0.717
Other	19 (5%)	36 (4%)	28 (5%)	0.435

Abbreviation: ARDS, acute respiratory distress syndrome.
Data are presented as n (%).
Severity of ARDS was categorized based on the Berlin definition.

e-Table 4. Outcomes of patients with rapidly improving ARDS vs ARDS> 1 day in each ARDSNet trial.			
	Rapidly improving ARDS	**ARDS> 1 day**	**p value**
ALTA	44 (16%)	238 (84%)	
60-day mortality	3 (7%)	55 (23%)	0.024
Ventilator-free days	27 (22-27)	19 (0-23)	<0.001
ICU-free days	23 (17-25)	16 (0-21)	<0.001
Non-pulmonary organ failure-free days	24 (13-27)	17 (1-23)	0.008
EDEN	129 (13%)	871 (87%)	
60-day mortality	11 (9%)	216 (25%)	<0.001
Ventilator-free days	27 (24-27)	18 (0-23)	<0.001
ICU-free days	25 (21-26)	16 (0-21)	<0.001
Non-pulmonary organ failure-free days	25 (3-28)	15 (0-25)	<0.001
SAILS	108 (15%)	637 (85%)	
60-day mortality	13 (12%)	186 (29%)	<0.001
Ventilator-free days	27 (25-27)	18 (0-24)	<0.001
ICU-free days	24 (21-26)	16 (0-21)	<0.001
Non-pulmonary organ failure-free days	26 (3-28)	15 (0-25)	<0.001

Abbreviations: vs, versus; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Data are presented as n (%) or median (interquartile range).

Patients discharged from hospital with unassisted breathing before 60 days considered to be alive at 60 days. Ventilator-free days, ICU-free days and non-pulmonary organ failure-free days were calculated by the number of days in the first 28 days that a patient was alive and not on a ventilator, not in the ICU, or free of non-pulmonary organ failure, respectively.

e-Table 5. Cox proportional hazards regression of 60-day mortality, accounting for rapidly improving ARDS and individual patient and trial characteristics.		
	Multivariate analysis	
	Hazard ratio (95% CI)	**p value**
ARDS> 1 day (vs rapidly improving ARDS)	2.86 (1.95-4.12)	<0.0001
APACHE III	1.02 (1.02-1.02)	<0.0001
PaO_2:FiO_2 at enrollment (10 points change)	0.98 (0.97-0.99)	0.005
Study (reference ALTA)		
EDEN	1.12 (0.84-1.48)	0.43
SAILS	1.35 (1.01-1.81)	0.041

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence intervals; vs, versus; APACHE, acute physiology and chronic health evaluation; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio.
Patients discharged from hospital with unassisted breathing before 60 days considered to be alive at 60 days.

e-Table 6. Treatment effects overall and within subgroups defined by rapidly improving ARDS in each ARDSNet trial.

	Treatment		p value	Risk Ratio (95% CI)	p value
ARMA	**Higher tidal volume**	**Lower tidal volume**			
riARDS	34 (8%)	29 (7%)	0.581		
60-day mortality	167 (39%)	130 (30%)	0.007	0.77 (0.64-0.93)	0.007
ARDS> 1 day	162 (41%)	128 (32%)	0.008	0.77 (0.64-0.93)	0.008
riARDS	5 (15%)	2 (7%)	0.437	0.47 (0.00-2.34)	0.437
Ventilator-free Days	4 (0-22)	13 (0-23)	0.004		
ARDS> 1 day	0 (0-21)	11 (0-22)	0.003		
riARDS	27 (18-27)	27 (27-27)	0.009		
ICU-free days	2 (0-19)	9 (0-20)	0.006		
ARDS> 1 day	0 (0-17)	8 (0-19)	0.002		
riARDS	24 (16-26)	24 (22-26)	0.654		
Non-pulmonary organ failure-free days	12 (0-24)	18 (2-25)	0.008		
ARDS> 1 day	11 (0-23)	17 (1-25)	0.003		
riARDS	26 (17-28)	25 (22-28)	0.803		
ALVEOLI	**Lower PEEP**	**Higher PEEP**			
riARDS	25 (9%)	26 (9%)	0.999		
60-day mortality	68 (25%)	76 (28%)	0.498	1.11 (0.83-1.48)	0.498
ARDS> 1 day	65 (26%)	72 (29%)	0.548	1.10 (0.83-1.47)	0.548
riARDS	3 (12%)	4 (15%)	0.999	1.28 (0.24-NA)	0.999
Ventilator-free days	18 (0-24)	18 (0-24)	0.422		
ARDS> 1 day	16 (0-23)	16 (0-23)	0.561		
riARDS	27 (27-27)	27 (19-27)	0.556		
ICU-free days	14 (0-22)	15 (0-21)	0.821		
ARDS> 1 day	13 (0-20)	14 (0-20)	0.825		
riARDS	25 (22-26)	22 (14-25)	0.092		
Non-pulmonary organ failure-free days	20.5 (13-25)	21 (12-25)	0.637		
ARDS> 1 day	20 (12-25)	20 (11-25)	0.760		
riARDS	24 (23-26)	25 (14-26)	0.621		
FACTT	**Liberal fluid therapy**	**Conservative fluid therapy**			
riARDS	29 (6%)	45 (9%)	0.079		

60-day mortality	141 (28%)	128 (25%)	0.318	0.90 (0.73-1.09)	0.318
ARDS> 1 day	138 (29%)	122 (27%)	0.343	0.90 (0.74-1.11)	0.343
riARDS	3 (10%)	6 (13%)	0.999	1.29 (0.32-NA)	0.999
Ventilator-free days	15 (0-22)	19 (0-24)	<0.0001		
ARDS> 1 day	14 (0-21)	18 (0-23)	0.0002		
riARDS	27 (19-27)	27 (22-27)	0.318		
ICU-free days	11 (0-19)	15 (0-21)	<0.0001		
ARDS> 1 day	11 (0-19)	14 (0-21)	0.0008		
riARDS	24 (12-25)	24 (21-25)	0.395		
Non-pulmonary organ failure-free days	20 (5-24)	19 (3-24)	0.953		
ARDS> 1 day	19 (4-24)	18 (3-24)	0.895		
riARDS	25 (18-26)	24.5 (16-26)	0.941		
ALTA	**Placebo**	**Albuterol**			
riARDS	20 (15%)	24 (16%)	0.999		
60-day mortality	23 (18%)	35 (23%)	0.303	1.30 (0.81-2.08)	0.270
ARDS> 1 day	22 (20%)	33 (26%)	0.355	1.29 (0.80-2.07)	0.293
riARDS	1 (5%)	2 (8%)	0.999	1.67 (0.16-17.06)	0.665
Ventilator-free Days	21 (8-24)	20 (0-24)	0.195		
ARDS> 1 day	20 (2-23)	17 (0-23)	0.191		
riARDS	27 (23-27)	27 (20-27)	0.401		
ICU-free days	19 (9-22)	16 (0-22)	0.049		
ARDS> 1 day	18 (7-22)	14 (0-21)	0.047		
riARDS	23 (20-25)	22 (14-26)	0.943		
Non-pulmonary organ failure-free days	18 (8-24)	16 (0-23)	0.299		
ARDS> 1 day	18 (7-24)	16 (0-23)	0.207		
riARDS	24 (14-27)	23 (13-26)	0.862		
EDEN	**Full feeding**	**Trophic feeding**			
riARDS	58 (12%)	71 (14%)	0.349		
60-day mortality	109 (22%)	118 (23%)	0.706	1.05 (0.83-1.32)	0.685
ARDS> 1 day	106 (24%)	110 (25%)	0.814	1.03 (0.82-1.30)	0.799
riARDS	3 (5%)	8 (11%)	0.343	2.18 (0.61-7.84)	0.219

Ventilator-free days	20 (0-24)	20 (0-25)	0.711		
ARDS> 1 day	18 (0-23)	18 (0-24)	0.674		
riARDS	27 (25-27)	27 (22-27)	0.300		
ICU-free days	18 (1-22)	17 (0-23)	0.846		
ARDS> 1 day	16 (0-21)	15 (0-22)	0.868		
riARDS	25 (22-26)	25 (20-26)	0.992		
Non-pulmonary organ failure-free days	16 (0-25)	17 (0-26)	0.462		
ARDS> 1 day	15 (0-25)	15 (0-25)	0.488		
riARDS	26 (2-28)	25 (3-27)	0.691		
SAILS	**Placebo**	**Rosuvastatin**			
riARDS	60 (16%)	48 (13%)	0.180		
60-day mortality	91 (25%)	108 (28%)	0.282	1.15 (0.90-1.46)	0.263
ARDS> 1 day	84 (27%)	102 [31%]	0.383	1.12 (0.88-1.43)	0.351
riARDS	7 (12%)	6 (12%)	0.999	1.07 (0.39-2.98)	0.895
Ventilator-free days	20 (0-25)	20 (0-25)	0.663		
ARDS> 1 day	18 (0-24)	19 (0-23)	0.628		
riARDS	27 (25-27)	27 (24-27)	0.763		
ICU-free days	17 (0-23)	17 (1-22)	0.659		
ARDS> 1 day	16 (0-21)	16 (0-21)	0.834		
riARDS	24 (22-26)	25 (21-26)	0.477		
Non-pulmonary organ failure-free days	18 (0-26)	17 (0-25)	0.331		
ARDS> 1 day	12 (0-25)	15 (0-25)	0.848		
riARDS	26 (20-28)	26 (0-27)	0.375		

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence intervals; riARDS, rapidly improving ARDS; ICU, intensive care unit; PEEP, positive end-expiratory pressure; NA: not applicable.

Data are presented as n (%) or median (interquartile range).

Patients discharged from hospital with unassisted breathing before 60 days considered to be alive at 60 days. Ventilator-free days, ICU-free days and non-pulmonary organ failure-free days were calculated by the number of days in the first 28 days that a patient was alive and not on a ventilator, not in the ICU, or free of non-pulmonary organ failure, respectively.

e-Table 7. Baseline characteristics and outcomes of patients with ARDS achieving unassisted breathing on the first study day vs patients with ARDS> 1 day (sensitivity analysis).			
	Rapidly improving ARDS	**ARDS> 1 day**	**p value**
Number of patients	197 (10%)	1712 (90%)	
Age, years	54 (41-65)	53 (42-64)	0.729
Male sex	105 (53%)	861 (50%)	0.469
Race			0.610
White	164 (83%)	1376 (80%)	
Black	27 (14%)	269 (16%)	
Other	6 (3%)	67 (4%)	
Body mass index	28 (24-33)	29 (24-35)	0.501
Comorbidity			
Diabetes Mellitus	44 (22%)	442 (26%)	0.327
Malignancy	16 (8%)	122 (7%)	0.715
Cirrhosis	5 (3%)	90 (5%)	0.139
End-stage renal disease	4 (2%)	51 (3%)	0.597
Immunosuppression	28 (14%)	211 (12%)	0.519
Usage of vasopressors	62 (32%)	903 (53%)	<0.001
APACHE III score	78 (60-96)	92 (73-112)	<0.001
Primary risk factor of ARDS			
Pneumonia	111 (56%)	1102 (64%)	0.033
Sepsis	37 (19%)	308 (18%)	0.861
Aspiration	24 (12%)	162 (10%)	0.275
Trauma	8 (4%)	56 (3%)	0.708
Multiple Transfusions	6 (3%)	19 (1%)	0.037
Other	12 (6%)	71 (4%)	0.279
Non-Pulmonary Organ Failure			
Circulatory	118 (60%)	1236 (72%)	<0.001
Coagulation	24 (12%)	319 (19%)	0.027
Hepatic	18 (10%)	255 (16%)	0.032
Renal	40 (20%)	424 (25%)	0.173
Neurological	159 (81%)	1541 (90%)	<0.001
Days from intubation to enrollment	1 (1-2)	1 (1-2)	0.422
Days from diagnosis of ARDS to enrollment	1 (0-1)	1 (0-1)	0.548
Severity of ARDS at screening			<0.001
Mild	62 (32%)	286 (17%)	
Moderate	99 (50%)	840 (49%)	
Severe	36 (18%)	586 (34%)	

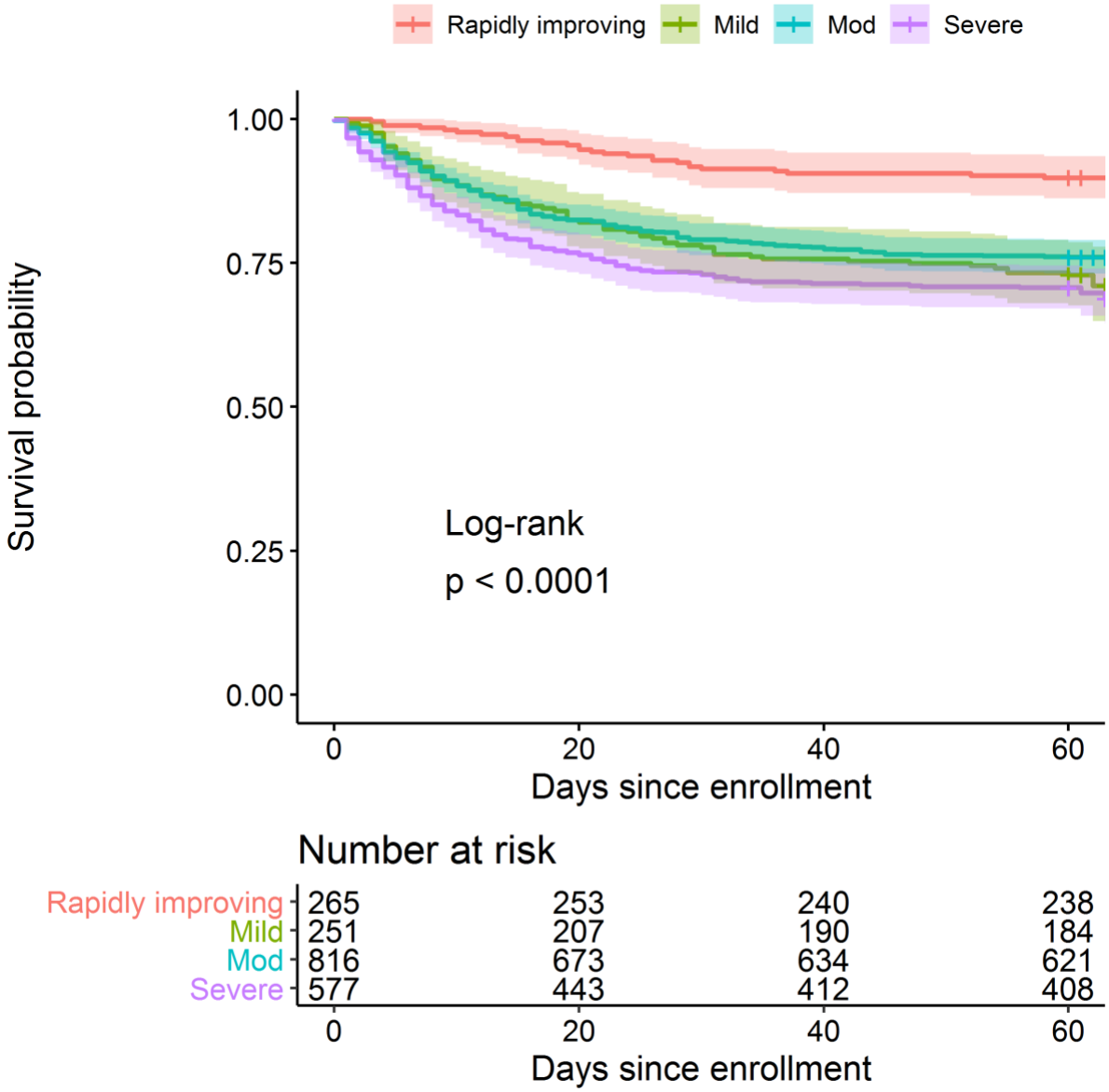
PaO_2:FiO_2 at screening	144 (97-204)	120 (80-173)	<0.001
Change in PaO_2:FiO_2 from screening to enrollment	56 (0-119)	28 (-6-77)	<0.001
Driving pressure	13 (11-15)	14 (11-18)	0.043
Plateau pressure	20 (17-24)	24 (20-28)	<0.001
Positive end-expiratory pressure	8 (5-10)	10 (7-12)	<0.001
Minute ventilation	10 (7-12)	11 (9-13)	<0.001
Outcomes:			
60-day mortality	15 (8%)	445 (26%)	<0.001
Ventilator-free days	27 (27-27)	18 (0-23)	<0.001
ICU-free days	25 (23-26)	16 (0-21)	<0.001
Non-pulmonary organ failure-free days	26 (19-28)	15 (0-25)	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; vs, versus; APACHE, acute physiology and chronic health evaluation; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; ICU, intensive care unit.
Data are presented as n (%) or median (interquartile range).
Severity of ARDS was categorized based on the Berlin definition.
Patients discharged from hospital with unassisted breathing before 60 days considered to be alive at 60 days. Ventilator-free days, ICU-free days and non-pulmonary organ failure-free days were calculated by the number of days in the first 28 days that a patient was alive and not on a ventilator, not in the ICU, or free of non-pulmonary organ failure, respectively.

e-Table 8. Baseline characteristics and outcomes of patients with rapidly improving ARDS vs patients with ARDS> 1 day after excluding intubated patients with missing oxygenation data on the first study day (sensitivity analysis).			
	Rapidly improving ARDS	**ARDS> 1 day**	**p value**
Number of patients	265 (16%)	1369 (84%)	
Age, years	54 (44-66)	53 (41-63)	0.138
Male sex	132 (50%)	717 (52%)	0.486
Race			0.377
White	40 (15%)	229 (17%)	
Black	218 (82%)	1083 (79%)	
Other	7 (3%)	57 (4%)	
Body mass index	28 (24-34)	29 (24-35)	0.365
Comorbidity			
Diabetes Mellitus	65 (25%)	339 (25%)	0.993
Malignancy	22 (8%)	92 (7%)	0.428
Cirrhosis	10 (4%)	73 (5%)	0.371
End-stage renal disease	8 (3%)	35 (3%)	0.825
Immunosuppression	39 (15%)	154 (11%)	0.134
Usage of vasopressors	98 (37%)	744 (55%)	<0.001
APACHE III score	80 (64-100)	93 (74-113)	<0.001
Primary risk factor of ARDS			
Pneumonia	147 (56%)	886 (65%)	0.005
Sepsis	59 (22%)	238 (17%)	0.072
Aspiration	28 (11%)	129 (9%)	0.643
Trauma	9 (3%)	52 (4%)	0.889
Multiple Transfusions	8 (3%)	15 (1%)	0.023
Other	16 (6%)	54 (4%)	0.169
Non-Pulmonary Organ Failure			
Circulatory	166 (63%)	994 (73%)	0.001
Coagulation	49 (19%)	248 (18%)	0.994
Hepatic	27 (11%)	212 (17%)	0.023
Renal	64 (24%)	327 (24%)	0.999
Neurological	220 (83%)	1236 (90%)	0.001
Days from intubation to enrollment	1 (1-2)	1 (1-2)	0.622
Days from diagnosis of ARDS to enrollment	1 (0-1)	1 (0-1)	0.481
Severity of ARDS at screening			<0.001
Mild	97 (37%)	191 (14%)	
Moderate	123 (46%)	662 (48%)	
Severe	45 (17%)	516 (38%)	

PaO_2:FiO_2 at screening	149 (99-205)	116 (79-166)	<0.001
Change in PaO_2:FiO_2 from screening to enrollment	80 (16-149)	25 (-8-71)	<0.001
Driving pressure	13 (11-16)	14 (11-18)	0.046
Plateau pressure	20 (17-25)	24 (20-28)	<0.001
Positive end-expiratory pressure	8 (5-10)	10 (8-12)	<0.001
Minute ventilation	10 (8-12)	11 (9-13)	<0.001
Outcomes:			
60-day mortality	27 (10%)	369 (27%)	<0.001
Ventilator-free days	27 (24-27)	18 (0-23)	<0.001
ICU-free days	24 (20-26)	15 (0-21)	<0.001
Non-pulmonary organ failure-free days	25 (3-27)	14 (0-25)	<0.001

Abbreviations: ARDS, acute respiratory distress syndrome; vs, versus; APACHE, acute physiology and chronic health evaluation; PaO_2:FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; ICU, intensive care unit.
Data are presented as n (%) or median (interquartile range).
Severity of ARDS was categorized based on the Berlin definition.
Patients discharged from hospital with unassisted breathing before 60 days considered to be alive at 60 days. Ventilator-free days, ICU-free days and non-pulmonary organ failure-free days were calculated by the number of days in the first 28 days that a patient was alive and not on a ventilator, not in the ICU, or free of non-pulmonary organ failure, respectively.



e-Figure 1. Kaplan Meier curves of survival probability for patients with rapidly improving acute respiratory distress syndrome (ARDS) and ARDS> 1 day stratified by ARDS severity (mild, moderate and severe). Patients discharged home considered alive at 60 days.

Protocol

Note: During the peer review process, the term "rapidly resolving ARDS (RRARDS)" (used below in the Protocol, which was submitted to Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung and Blood Institute to request raw data for this secondary analysis) was replaced by the term "rapidly improving ARDS".

Background/Rationale:

The Acute Respiratory Distress Syndrome, ARDS is a common and morbid intensive care unit (ICU) condition.[1] Despite initial characterization 50 years ago,[2] there remains unresolved heterogeneity in the definition of the clinical syndrome and its pathologic correlates.[3] This remains despite the most recently updated clinical definition of the syndrome.[4,5] State of the art care for ARDS is targeted at protecting the lung from injurious forces applied by mechanical ventilation and vigorous respiratory efforts.[6] Most pharmacologic therapeutics for this syndrome have universally failed in large clinical trials despite exciting early stage clinical studies.[7] A recent study of the modern epidemiology of this syndrome revealed that up to 25 % of patients meeting all clinical criteria for the syndrome will no longer meet criteria following 24 hours.[1] In addition, the most recent formal clinical/research definition of ARDS does not offer guidance as to how long the criteria must be met before a patient should be categorized as having the syndrome.[8]

Significance:

It is unclear whether this group of patients with rapidly resolving ARDS (RRARDS), i.e. ARDS resolving within 24 hours after its onset, represents a similar pathophysiologic process as those with ARDS which persists for more than 24 hours or is another syndrome altogether.[4,9] RRARDS deserves attention in order to improve our understanding of the epidemiology of this syndrome. In addition to more nuanced understanding correctly classifying this phenotype, this distinction carries great import for the appropriate inclusion of subjects into prospective clinical trials. Past ARDSnet, the North American ARDS clinical trials consortium, studies have allowed for the recruitment of subjects who meet clinical criteria for ARDS even if it only lasts for 24 hours.[10-16] Other multicenter clinical trials have used prolonged clinical criteria, e.g. > 12-24 hours, in order to be enrolled.[17,18] Earlier enrollment may allow for more effective therapy and alteration of pathophysiology before lung injury has set in, however enrollment of subjects in whom therapy is not needed exposes an increased population to risks without offering benefit.[19] We hypothesize that RRARDS subjects in ARDSnet prospective trials will have different baseline characteristics and better clinical outcomes (including lower overall mortality) when compared to those with prolonged lung injury.

Design:

A secondary analysis of data from published prospective clinical therapeutic studies of ARDS

Primary Objective:

This study will characterize the epidemiology of RRARDS in previously published high quality prospective clinical trials.

a. We will define the point prevalence of rapidly resolving ARDS in these trials in the immediate time period following enrollment.
b. We will analyze the crude overall 60 day mortality of subjects with RRARDS compared to prolonged ARDS.

Secondary Objectives:

We will characterize the phenotypic characteristics of RRARDS in this study population. We analyze baseline characteristic differences between RRARDS and prolonged ARDS, including risk factors for the syndrome and other important comorbidities and effect modifiers. We will compare severity of illness and analyze important secondary outcomes including: burden of additional organ failure as defined by baseline and change in SOFA score, ventilator free days, and ICU free days.

Subject Population:

Subjects for this analysis will be drawn from the ARMA, ALVEOLI, FACTT, EDEN, ALTA, and SAILS trials.[10-16] Subjects from the OMEGA trial were not included because they had already been included in the EDEN trial. Full details of the included trials have been published. Briefly these trials have enrolled 4438 subjects (2188 patients were in the control group and the rest in an experimental group) meeting clinical criteria for ARDS within 48 hours prior to enrollment over the past 20 years. Each trial was a randomized interventional clinical trial comparing various therapies for ARDS. Each trial collected clinical data at the time of enrollment prior to randomization in addition to data regarding interventions and clinical response.

Statistical Plan:

In the recent LUNG SAFE epidemiologic study, 13% of patients with severe ARDS had RRARDS.[1] We therefore conservatively estimate that between 5-10 % of enrolled subjects in these clinical trials will have RRARDS. With this relative population we will have a greater than 85 % power to detect a 10 % difference in our primary outcome, 60 day mortality with an alpha level of 0.05.

Expected Contribution:

This analysis will provide important data as to the relative prevalence of RRARDS in the clinical trial population and provide an estimate of their outcomes. This will inform future decisions about whether to include these subjects in randomized trials.

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Variable list

SAILS

ARDSNET_010

Some overlap with EDEN

New inclusion criteria

Had to have sepsis

Value for us

All data in **SAS**

READ me file has sas code for derived variables which are recorded in sas tmp "derive"

Also descriptives are completed in a pdf

However big difference

Organ failure only tracked through day 14

VFD ICU free through day 28

Definition of RR vs Sustained ARDS

Composite any one of the following

Sas tmp: study_term variable If yes, day of UAB (first day with no AB)= 1,2

sas tmp: brussall variable: Day 0,1 PaO2/FiO2 >/= 300

Similar definition of UAB date as ARDSNET_04 in full → **Date of first UAB (from Study Termination form**): Defined as the first day that the subject is on UAB from midnight to midnight. Example: if subject meets UAB at 1900 on
6/1/06, then the date of first UAB would be 6/2/06, as long as subject does not return to AB on 6/2/06.

In addition ARDSNET_10 kept y, n to 1, 0

Baseline demographics and severity of illness

A. Rapid Resolving vs Sustained ARDS

(1) Age (Mean SD) sas tmp: enroll1 variable: age (age > 89 reported as 89 to de-identify)

(2) Sex (No %) sas tmp: enroll1 variable: gender (1 male 2 female)

(3) Ethnicity (No %) sas tmp: enroll1 variable: Hispanic or Not Hispanic 1 = Hispanic 2 = non-hispanic then further ID'ed variables white y = 5 n = sysmis black or African American y = 3 n = sysmis Other Race Category y = 99 n = sysmis Race Not Reported y = 5 n =sysmis

(4) BMI (Mean SD) sas tmp: base_vs variable: Measured Weight / (Measured Height x 100)^2

(5) ARDS risk factor (No %)

(a) Pneumonia sas tmp: enroll1 variable: Pneumonia 1 primary 2 secondary 0 none

(b) Sepsis sas tmp: enroll1 variable: Sepsis 1 primary 2 secondary 0 none

(c) Aspiration sas tmp: enroll1 variable: Aspiration 1 primary 2 secondary 0 none

(d) Trauma sas tmp: enroll1 variable: Trauma 1 primary 2 secondary 0 none

(e) Other Causes sas tmp: enroll1 variable: Other Lung Injury 1 primary 2 secondary 0 none

(f) Multiple Transfusion sas tmp: enroll1 variable: Multiple Transfusions 1 primary 2 secondary 0 none

(6) APACHEIII score (Mean SD) (of note sas tmp: bypt variable apache: I assume I can't open this on my sas!)

(7) Baseline Vasopressor Use (No %) sas tmp: brussall (brussdt0) variable: Day 0 Vasopressor = 1 Y 0 N

(8) Baseline non-pulmonary organ failure (mean SD) sas tmp: brussall variable:

Y N for each organ failure definition below

1. Circulatory failure = defined as a systolic blood pressure of 90 mm Hg or less or the need for treatment with any vasopressor Day 0 Systolic BP <=90 + Vasopressor = 1
2. Coagulation failure = a platelet count of < 80,000 Day 0 Platelets x 1000 < 80
3. Hepatic failure bilirubin of at least 2 Day 0 Bilirubin >/= 2
4. Renal failure creatinine least 2 Day 0 Creatinine >/= 2
5. Neurological failure Day 0 Glascow Coma Score of </= 12

Comment on organ failure free days
followed for 28 days of non-pulmonary organs and systems calculated the number of days without organ or system failure by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death. Organs and systems were considered failure-free after patients were discharged from the hospital.

(9) PF ratio at baseline (mean SD) sas tmp: brussall variable: Day 0 PaO2/FiO2
  (a) No % Mild ARDS (200< pf ratio </=300)
  (b) No % Moderate ARDS (100< pf ratio </=200)
  (c) No % Severe ARDS (pf ratio </=100)
(10) Rx assignment (No %) sas tmp: study_term variable: sails (rosuvastatin vs placebo)

Outcomes
Rapid Resolving vs Sustained ARDS 90 day mortality (No %)
sas tmp: study_term variable: status 1 alive dc'ed home unassisted breathing 2 dead 3 other

Only one row for each individual and one time documented if > 90 days to be recorded as 90, with censoring.

Home with UAB, date = date dc alive
Dead prior to home with UAB, day = date death
Other, day of last known status = date other (last contact date is recorded if remains 3 at day 90)

(11) Non pulmonary organ failure free days (median IQR) see above sas tmp: brussall
(12) ICU length of stay (median IQR) sas tmp: study_term If yes, day of ICU DC date of ICU DC following enrollment
(13) ICU free days

B. Sustained ARDS by Rx Assignment (rosuvastatin vs placebo)
(1) 90 day mortality (No %)
(2) Non pulmonary organ failure free days (median IQR)
(3) Ventilator-free days

The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Of

note please check sas tmp: study_term variable: If yes, day of UAB (first day with no AB) following extubation to be included calculating from day 28 for total vent free days.
If yes, day of return to AB = date of reintubation = If yes, day of UAB (2nd day with no AB) date off ventilator for the second time
only last time off vent counts for VFD's

(4) ICU length of stay (median IQR)

(5) ICU free days

APACHEIII scoring system

Physiology (0-252) take the largest apache value for each variable set and add together

Notes: If a physiologic measurement is not obtained during this initial 24-h period, no risk points are assigned. The most abnormal arterial blood gas measurement is the one associated with the widest P(A-a)O2 or the lowest PaO2. If a patient is heavily sedated and/or paralyzed, so that his neurologic status cannot be evaluated, and no reliable evaluation prior to sedation is available, the neurologic status should be recorded as normal.

1. Pulse high or low sas tmp: apache_phys variables: Lowest Heart Rate (beats/min) Highest Heart Rate (beats/min)
    a. <= 39 = 8
    b. 40-49 = 5
    c. 50-99 = 0
    d. 100-109 = 1
    e. 110-119 = 5
    f. 120-139 = 7
    g. 140-154 = 13
    h. >= 155 = 17

2. Mean blood pressure sas tmp: apache_phys variables: Lowest Mean Arterial Pressure Highest Mean Arterial Pressure
    a. <= 39 = 23
    b. 40-59 = 15
    c. 60-69 = 7
    d. 70-79 = 6
    e. 80-99 = 0
    f. 100-119 = 4
    g. 120-129 = 7
    h. 130-139 = 9
    i. >= 140 = 10
3. Temperature high or low sas tmp: apache_phys variables: Lowest Temperature in Celcius Highest Temperature in Celcius
    a. <= 32.9 = 20
    b. 33-33.4 = 16
    c. 33.5-33.9 = 13
    d. 34-34.9 = 8
    e. 35-35.9 = 2
    f. 36-39.9 = 4

4. Respiratory Rate high or low sas tmp: apache_phys variables Lowest Respiratory Rate (breaths/min) Highest Respiratory Rate (breaths/min) (if sas tmp: apache_phys variable: Paitent ventilated at lowest resp. rate = 1 and Lowest Respiratory Rate (breaths/min) = 6-13 then no value is given)
    a. <= 5 = 17
    b. 6-11 = 8
    c. 12-13 = 7
    d. 14-24 = 0
    e. 25=34 = 6
    f. 35-39 = 9
    g. 40-49 = 11
    h. >= 50 = 18

Notes on selecting the APACHE III ABG (sails gives us APACHE max abg which choses the max abg for us… very useful to QI any algorithm)
Sas tmp: apache_abg2

The most abnormal arterial blood gas measurement is the one associated with the widest P(A-a)O2 (fio2>= 50%) or the lowest PaO2 (fio2 < 50%). Once selected use the ph and pco2 of that abg for the acid base calculation.

5. Pao2 if fio2 < 50% than use lowest Pao2
    a. <= 49 = 15
    b. 50-69 = 5
    c. 70-79 = 2
    d. >= 80 = 0

6. if fio2 >= 50 % then use AaDo2 formula (713 x FiO_2) – (pCO_2 / 0.8) – (paO_2)
    a. <100 = 0
    b. 100-249 = 7
    c. 250-349 = 9
    d. 350-499 = 11
    e. >= 500 = 14
7. White blood cell count sas tmp: apache_phys variables: WBC: Lowest mm^3 WBC: Highest mm^3
    a. <1000 = 19
    b. 1000-2900 = 5
    c. 3000-19900 = 0
    d. 20000-24900 = 1
    e. >= 25000 = 5
8. Creatinine no acute renal failure (defined as creatinine >= 1.5 sas tmp: apache_phys variable Serum Creatinine Highest (mg/dl)+ urine output < 410 sas tmp: apache_phys variable Urine output for 24 hours preceding randomization + no chronic dialysis sas tmp: apache_demog variable Patient on chronic or peritoneal dialysis 1 y 0 n)
    a. <= 0.4 = 3
    b. 0.5-1.4 = 0
    c. 1.5-1.94 = 4
    d. >= 1.95 = 7

9. Creatinine with acute renal failure (defined as creatinine >= 1.5 sas tmp: apache_phys variable Serum Creatinine Highest (mg/dl)+ urine output < 410 sas tmp: apache_phys variable Urine output for 24 hours preceding randomization + no chronic dialysis sas tmp: apache_demog variable Patient on chronic or peritoneal dialysis 1 y 0 n)
    a. 0-1.4 = 0
    b. >= 1.5 = 10
10. Urine output sas tmp: apache_phys variable Urine output for 24 hours preceding randomization
    a. <= 399 = 15
    b. 400-599 = 8
    c. 600-899 = 7
    d. 900-1499 = 5
    e. 1500-1999 = 4
    f. 2000-3999 = 0
    g. >= 4000 = 1
11. Serum BUN sas tmp: apache_phys variable: Serum BUN (highest)(mg/dl)
    a. <= 16.9 = 0
    b. 17-19 = 2
    c. 20-39 = 7
    d. 40-79 = 11
    e. >= 80 = 12
12. Serum sodium sas tmp: apache_phys variable: Serum Sodium: Highest (mEq/L) Serum Sodium: Lowest (mEq/L)
    a. <= 119 = 3
    b. 120-134 = 2
    c. 135-154 = 0
    d. >= 155 = 4
13. Serum Albumin sas tmp: apache_phys variable: Serum Albumin Highest (g/dl) Serum Albumin Lowest (g/dl)
    a. <= 1.9 = 11
    b. 2.0-2.4 = 6
    c. 2.5-4.4 = 0
    d. >= 4.5 = 4

14. Serum Bilirubin sas tmp: apache_phys variable: Serum Bilirubin Highest (mg/dl)
    a. <= 1.9 = 0
    b. 2.0-2.9 = 5
    c. 3.0-4.9 = 6
    d. 5.0-7.9 = 8
    e. >= 8 = 16
15. Serum Glucose sas tmp: apache_phys variable: Serum Glucose Highest (mg/dl) Serum Glucose Lowest (mg/dl)
    a. <= 39 = 8
    b. 40-59 = 9
    c. 60-199 = 0
    d. 200-349 = 3
    e. >= 350 = 5

Age (score 0-24)

Sas tmp: enroll1 variable: Age as appesrs on screening form (in years):

<= 44 = 0
45-59 = 5
60-64 = 11
65-69 = 13
70-74 = 16
75-84 = 17
>= 85 = 24

Chronic health comorbidities (score 0-23) highest score only **do not sum**

Elective post op if 1 then leave out chronic health eval
Sas tmp: apache_demog variable: Patient post-operative elective surgery? 1 yes 0 no if yes leave out chronic health eval

Sas tmp: apache_demog variable: if yes

Aids (does not include only HIV+) 23

leuk (AML, CML, ALL, multiple myeloma) 10

lymph (Non-Hodgekins Lymphoma) 13

tumor (Solid tumor with metastasis) 11

immune (Immune Suppression w/in past 6 mths) 10

hepa (hepatic Failure with coma or encephalo.) 16

cirr (Cirrhosis) 4

GCS component values sas tmp: gcs variable: visit = 0

ARDSNET used a best guess if the patient was sedated! Not according to APACHE rules but hey

See matrix

All remaining sas tmp: glascow_coma

Eyes open to painful (variable: Eye opening score: >= 2)/No eye opening to painful (variable: Eye opening score: = 1)

Verbal values sas tmp: glascow_coma variable: Verbal response score:

Oriented = 5

Confused = 4

Inappropriate words/Incomprehensible sounds = 3-2

No response = 1

Motor values sas tmp: glascow_coma variable: Motor response score:

Obeys verbal command = 6

Localizes to pain = 5

Flexor/decorticate = 4-3

Decerebrate/No Response = 2-1

Motor (Verbal) see ‡	Oriented, Converses	Confused Conversation	Inappropriate Words & Incomprehensible Sounds	No Response
Obeys verbal command	0 / NA	3 / NA	10 / NA	15 / 16
Localizes pain	3 / NA	8 / NA	13 / NA	15 / 16
Flexion withdrawal/decorticate rigidity	3 / NA	13 / NA	24 / 24	24 / 33
Decerebrate rigidity/no response	3 / NA	13 / NA	29 / 29	29 / 48

Acid Base

Above chosen ABG for oxygenation (Pao2 or AdDo2) will be used with the following table:

Acute Physiology	pCO_2 < 25	25 to < 30	30 to < 35	35 to < 40	40 to < 45	45 to < 50	50 to < 55	55 to < 60	pCO_2 ≥ 65
pH < 7.15	12								4
7.15 to < 7.20									
7.20 to < 7.25	9		6	3					2
7.25 to < 7.30									
7.30 to < 7.35			0					1	
7.35 to < 7.40	5								
7.40 to < 7.45									
7.45 to <7.50			0	2					
7.50 to < 7.55	3								
7.55 to < 7.60							12		
7.60 to < 7.65									
pH ≥ 7.65	0								