Validation and Utility of ARDS Subphenotypes Identified by Machine Learning Models Using Clinical Data: An Observational Multi-Cohort Retrospective Analysis.

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Supplementary Material

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Methods

Study Populations

In the training cohort (ARMA, ALVEOLI, and FACTT) patient were assigned Latent class analysis (LCA) derived phenotype using pre-enrollement data. In EARLI and VALID, patients were followed until death, discharge, or at least 28 days. ARDS was diagnosed with consensus of two board-certified physicians who independently reviewed clinical data and radiographic studies. In EARLI, patients were enrolled into the study once a decision for ICU admission had been made by a physician in the emergency department. For most patients, data on day 1 of hospital admission constituted as study day 1 and this data was used to identify subphenotypes. By contrast, in VALID, patients were enrolled into the study on the morning of day two of ICU admission and consequently their hospital course and ICU may have been longer that the EARLI cohort.

In LUNG SAFE, patients were followed until death, discharge, or 90 days. ARDS was identified using the raw data of individual components of the Berlin Definition (i.e., low partial pressure of oxygen to inspired oxygen ratio, acute pulmonary infiltrates identified on radiographic imaging, and positive end expiratory pressure of at least 5cm H_2O). Data was collected daily in the morning at 10 am. Bicarbonate in LUNG SAFE was derived from arterial blood gas sample, using the Henderson–Hasselbalch equation (whereas it was measured in the serum in EARLI and VALID). For the purposes of this study, the units of bilirubin and creatinine were converted from metric (mmol/L) to imperial (mg/dL).

In all cohorts, samples sizes were dictated by the convenience of data availability. In the validation cohort these were dictated by availability for LCA-derived phenotypes. Power analyses specifically for the presented modelling were not performed, however, all training, testing and validation cohorts were adequately powered for the original LCA studies.

Details of XGBoost

XGBoost is an ensemble implementation of a gradient boosted machine, a type of supervised machine learning algorithm that is trained on a dataset with known labels and can then predict classifications in an evaluation set without known labels. Details of our machine learning approach have been previously published.[1] A decision tree is a simple mathematical algorithm that allows for classification based on a small number of parameters (e.g., is a single variable above a certain threshold?). XGBoost combines numerous decision trees for a final model (i.e., "ensemble") that optimizes model accuracy in classifying the evaluation set. Each subsequent decision tree attempts to correct the error of the previous model (i.e., "gradient boost") such that model accuracy is improved as additional trees are added.

In XGBoost, there are several components ("hyperparameters") that must be tuned to optimize model performance. For example, an accurate model requires identifying the optimal number of trees, as adding many trees risks "over-fitting" the model to the training set with worsened performance in an evaluation set. We tuned the models to optimize the number of trees in the ensemble (*nrounds)*, the depth of branches and complexity in each tree *(max_depth)*, and the "learning rate" at which the model corrects error in each subsequent step (*eta)*. We utilized a grid search using the R package *caret* to identify optimal cutoffs. For *nrounds*, we searched the optimal number of trees between 50 and 1000 trees; for *max_depth*, we searched for optimal tree depth between 2 and 5; and for *eta*, we searched for an optimal learning rate between 0·025 and 0·3 (see below table for final hyperparameters used). Other model hyperparameters were set at their default setting. The gain in classification accuracy associated with each variable across the numerous trees in the XGBoost model was aggregated to calculate a variable's ranking as the most important.

Model	nrounds	max_depth	eta
Vitals and labs	550	2	0·025
Full features	800	3	0·025
Custom LUNG SAFE variables only	250	3	0·05

Another advantage of XGBoost is its in-built (sparsity-aware) algorithm to handle missing values. On the assumption that the values are missing at random, XGBoost models have a unified method of dealing with missing data. When constructing individual decision trees in the event of missing data, at each node, the default direction for missing data is selected based on learning from the data such that algorithm will select the direction with the highest gain to maximize model performance. We chose this approach, as opposed to imputation, because the models can generate probabilities despite missing data and would be a desirable feature in the prospective clinical setting.

Sensitivity analysis for treatment interaction

Several sensitivity analyses were performed to evaluate the heterogeneity of treatment effect that was observed in the PEEP-strategy groups and ARDS subphenotypes. First, PEEP groups were created using quintiles, such that the lower two quintiles served as the low-PEEP group and upper two quintiles served as high-PEEP group with the middle quintile discarded for analysis. Results of these analyses are presented in **Table S13**. Logistic regression model was created with the interaction term of PEEP-group and subphenotype serving as an independent variable and 90-day mortality as the dependent variable. Further treatment interaction was sought in subphenotypes classified using a range of probability cut-offs.

Further, sensitivity analyses were performed to evaluate whether heterogeneity of treatment effect was observed in PEEP groups with other markers of disease severity. For these analyses, we used PaO_2/FiO_2 ratio and SOFA score and PEEP groups were derived using tertile values of the mean PEEP over day 1 to 3, as described in the primary analysis. Treatment interactions were sought using the approach outlined above. PaO_2/FiO_2 ratio stratified groups were created using the severity stratification groups described in the Berlin definition (mild 200 to ≤300, moderate >100 to <200, and severe ≤100). The results of this analysis are presented in **Table S15**. For creating two SOFA subgroups, we used the following strategies: a) equal-sized groups were created using the median SOFA score; and b) based on SOFA score the population was split into proportions similar to the ARDS subphenotypes (75:25) with the smaller sized group having the higher SOFA score. The results of these analyses are presented in **Table S16**.

Reference

1. Sinha P, Churpek MM, Calfee CS. Machine Learning Classifier Models Can Identify Acute Respiratory Distress Syndrome Phenotypes Using Readily Available Clinical Data. *Am J Respir Crit Care Med* 2020; **202**(7): 996-1004.

Supplementary Tables

Model	Feature Set (Variables)
Vital signs and laboratory (Primary Model) ("vitals and labs" model) Training set: - ARMA, ALVEOLI, FACTT (n=2022) Independent Validation sets: - EARLI (n=335) - VALID (n=452) - EARLI, EHR-derived (n=117)	Temperature (C; high), Systolic BP (mmHg; low), Heart Rate (bpm; high), Respiratory Rate (breaths/min; high), Vasopressor use (yes/no), Hematocrit (%; low), WBC Count ($10^3/\mu L$; high), Platelet Count ($10^3/\mu L$; low), Sodium (mmol/L; high), Creatinine (mg/dL; high), Bicarbonate (mmol/L; low), Albumin (g/dL; low), Bilirubin (mg/dL; high)
All available features (Secondary Model) ("full featured" Model) Training set: - ARMA, ALVEOLI, FACTT (n=2022) Validation sets: - EARLI (n=335) - VALID (n=452) -	Age (years), Sex (Female), Ethnicity (White), Risk factor for ARDS (i.e., pneumonia, sepsis, aspiration, trauma, or other), Temperature (C; high), Systolic BP (mmHg; low), Heart Rate (bpm; high), Respiratory Rate (breaths/min; high), Vasopressor use (yes/no), PEEP (cmH_2O), $PaCO_2$ (mmHg), PaO_2/FiO_2 (mmHg), Hematocrit (%; low), WBC Count ($10^3/\mu L$; high), Platelet Count ($10^3/\mu L$; low), Sodium (mmol/L; high), Creatinine (mg/dL; high), Bicarbonate (mmol/L; low), Albumin (g/dL; low), Bilirubin (mg/dL; high)
Features for LUNG SAFE model Training set: - ARMA, ALVEOLI, FACTT (n=2022) Evaluation sets: - SAILS (n=745) - VALID (n=452) - LUNG SAFE (n=2813)	Respiratory Rate (breaths/min), Mean Arterial Pressure (mmHg), Vasopressor Use (yes/no), Platelet Count ($10^3/\mu L$), Creatinine (mg/dL), Bicarbonate (mmol/L), Bilirubin (mg/dL)

Table S1 Description of model characteristics. Features, training (derivation) cohort, and validation or evaluation cohorts used in the analyses. Abbreviations: Acute Respiratory Distress Syndrome (ARDS); Blood Pressure (BP); Positive End Expiratory Pressure (PEEP); Partial pressure of carbon dioxide in arterial blood ($PaCO_2$); Ratio of partial pressure of oxygen in arterial blood to fraction inspired oxygen (PaO_2/FiO_2); White Blood Cell (WBC); Electronic Health Record (EHR).

Characteristic	EARLI (n = 335)	VALID (n=452)	LUNG SAFE (n=2813)
Age	0 (0%)	0 (0%)	0 (0%)
Female	4 (1%)	0 (0%)	0 (0%)
Ethnicity	0 (0%)	0 (0%)	*
Body Mass Index	36 (11%)	*	147 (5%)
Temperature	0 (0%)	2 (0%)	*
Systolic BP	2 (1%)	0 (0%)	*
Mean Arterial Pressure	*	0 (0%)	224 (8%)
Heart Rate	0 (0%)	0 (0%)	*
Respiratory Rate	4 (1%)	1 (0%)	12 (0%)
Vasopressor Use	1 (0%)	0 (0%)	16 (1%)
Tidal Volume	*	125 (28%)	171 (6%)
PEEP	114 (34%)	141 (31%)	0 (0%)
Minute Ventilation	193 (58%)	*	178 (6%)
$PaCO_2$	46 (14%)	121 (27%)	31 (1%)
PaO_2/FiO_2	56 (17%)	125 (28%)	0 (0%)
Hematocrit	1 (0%)	2 (0%)	*
WBC Count	2 (1%)	3 (1%)	*
Platelet Count	1 (0%)	3 (1%)	126 (4%)
Sodium	1 (0%)	0 (0%)	*
Creatinine	2 (1%)	2 (0%)	202 (7%)
Bicarbonate	3 (1%)	0 (0%)	32 (1%)
Glucose	1 (0%)	*	*
Albumin	114 (34%)	219 (48%)	*
Bilirubin	26 (8%)	124 (27%)	674 (24%)

Table S2 Missing data for predictor variables. Values are presented as count and percentage. Abbreviations: Blood Pressure (BP), Positive End Expiratory Pressure (PEEP); Partial pressure of carbon dioxide in arterial blood ($PaCO_2$); Ratio of partial pressure of oxygen in arterial blood to fraction inspired oxygen (PaO_2/FiO_2); White Blood Cell (WBC); * Indicates predictor that was not available in the dataset.

Characteristic	Training (n=2022)	EARLI (n=335)	VALID (n=452)	LUNG SAFE (n=2813)
Number of patients	2022	335	452	2813
Age (years)	50 (± 17)	66 (± 17)	55 (± 16	61 (±17)
Sex (% female)	901 (45%)	147 (44%)	214 (47%)	1084 (39%)
Ethnicity (% White)	1409 (70%)	165 (49%)	401 (89%)	*
Body Mass Index (kg/m^2)	27·9 (± 7·3)	27·1 (± 9·8)	*	27·5 (± 8·7)
Temperature (C)	38·4 (± 1·0)	37·7 (± 1·4)	37·9 (± 1·0)	*
Systolic BP (mmHg)	88 (± 17)	86 (± 21)	87 (± 16)	*
Mean Arterial Pressure (mmHg)	69 (± 16)	*	96 (± 17)	74 (± 16)
Heart Rate (bpm)	125 (± 22)	126 (± 27)	121 (± 21)	*
Respiratory Rate (breaths/min)	32 (26 – 40)	35 (30 – 40)	31 (26 – 37)	20 (16 – 26)
Vasopressor use (%)	647 (32%)	212 (63%)	199 (44%)	1420 (50%)
Tidal Volume (mL)	518 ± 139	*	426 (± 76)	476 (± 123)
PEEP (cmH2O)	10 (5 – 12)	5 (5 – 8)	10 (8 – 12)	8 (5 – 10)
Minute Ventilation (L/min)	12·5 (± 4)	10·4 (± 3·3)	*	10·1 (± 3·9)
$PaCO_2$ (mmHg)	39 (± 10)	43 (± 16)	47 (± 14)	46 (± 16)
PaO_2/FiO_2 (mmHg)	131 (± 61)	138 (± 68)	132 (± 66)	160 (± 67)
Hematocrit (%)	30 (± 6)	30 (± 7)	30 (± 7)	*
WBC Count (10^3/mL)	14·7 (± 11·9)	15·0 (± 12·6)	15·4 (± 11·7)	*
Platelet Count (10^3/mL)	183 (± 125)	169 (± 105)	181 (± 123)	178 (± 131)
Sodium (mEq/dL)	137 (± 6)	135 (± 6)	138 (± 6)	*
Creatinine (mg/dL)	1·5 (± 1·4)	2·1 (± 2·2)	2·0 (± 1·7)	1·7 (± 3·1)
Bicarbonate (mmol/L)	21·4 (± 5·5)	20·5 (± 5·9)	21·6 (± 5·1)	23·5 (± 6·8)
Glucose (mg/dL)	129 (± 60)	121 (± 66)	*	*
Albumin (g/dL)	2·2 (± 0·6)	2·5 (± 0·7)	2·6 (± 0·6)	*
Bilirubin (mg/dL)	0·8 (0·5 – 1·7)	1·0 (0·7 – 1·5)	1·1 (0·7 – 2·2)	0·8 (0·4 – 1·3)
ARDS Risk factor: Trauma	178 (9%)	0 (0%)	0 (0%)	87 (3%)
ARDS Risk factor: Sepsis	478 (24%)	118 (35%)	148 (33%)	455 (16%)
ARDS Risk factor: Aspiration	305 (15%)	51 (15%)	108 (24%)	218 (8%)
ARDS Risk factor: Pneumonia	837 (41%)	145 (43%)	156 (35%)	1540 (55%)
ARDS Risk factor: Other	224 (11%)	21 (6%)	40 (9%)	513 (18%)
Interleukin-6 (pg/mL)	*	191 (51 – 2471)	56 (20 – 260)	*
Interleukin-8 (pg/mL)	*	32 (12 – 208)	19 (8 – 72)	*
Soluble TNF Receptor-1 (pg/mL)	*	4332 (2226 – 10089)	3014 (1819 – 5030)	*
Protein C (% Control)	*	90 (± 68)	62 (± 38)	*
Ventilator Free Days	17 (0 – 23)	21 (0 – 26)	18 (1 – 24)	10 (0 – 22)
Mortality†	575 (28%)	137 (41%)	151 (33%)	1108 (39%)

Table S3 Baseline patient characteristics for training (combined cohort of ARMA, ALVEOLI, FACTT) and three observational cohorts, EARLI, VALID, and LUNG SAFE. Data are presented as count (%), mean (± standard deviation), or as median (interquartile range). †In ARMA, ALVEOLI, FACTT, and LUNG SAFE mortality is reported as 90-day mortality; in EARLI and VALID, mortality is reported as in-hospital mortality. Abbreviations: Blood Pressure (BP), Positive End Expiratory Pressure (PEEP); Partial pressure of carbon dioxide in arterial blood ($PaCO_2$); Ratio of partial pressure of oxygen in arterial blood to fraction inspired oxygen (PaO_2/FiO_2); White Blood Cell (WBC); Acute Respiratory Distress Syndrome (ARDS); Chronic Obstructive Pulmonary Disease (COPD); Tumor Necrosis Factor (TNF). * Indicates missing predictor in the cohort.

A: Vitals and labs model in EARLI				
Probability Cutoff	**Accuracy**	**Sensitivity**	**Specificity**	**Hyperinflammatory Subphenotype**
0·3	0·79	0·92	0·72	52% (173/335)
0·4	0·82	0·87	0·80	45% (151/335)
0·5	0·84	0·85	0·84	41% (139/335)
0·6	0·85	0·79	0·89	36% (122/335)
0·7	0·86	0·73	0·93	31% (104/335)
B: Vitals and labs model in VALID				
Probability Cutoff	**Accuracy**	**Sensitivity**	**Specificity**	**Hyperinflammatory Subphenotype**
0·3	0·78	0·82	0·77	41% (187/452)
0·4	0·79	0·72	0·83	34% (153/452)
0·5	0·80	0·66	0·86	30% (134/452)
0·6	0·82	0·62	0·91	25% (113/452)
0·7	0·82	0·53	0·94	20% (91/452)
C: Full featured model in EARLI				
Probability Cutoff	**Accuracy**	**Sensitivity**	**Specificity**	**Hyperinflammatory Subphenotype**
0·3	0·84	0·88	0·81	44% (149/335)
0·4	0·84	0·83	0·85	40% (135/335)
0·5	0·85	0·80	0·88	37% (124/335)
0·6	0·85	0·74	0·91	33% (110/335)
0·7	0·83	0·67	0·93	29% (98/335)
D: Full featured model in VALID				
Probability Cutoff	**Accuracy**	**Sensitivity**	**Specificity**	**Hyperinflammatory Subphenotype**
0·3	0·78	0·71	0·81	35% (156/452)
0·4	0·80	0·67	0·86	30% (137/452)
0·5	0·81	0·64	0·89	27% (123/452)
0·6	0·82	0·59	0·91	24% (108/452)
0·7	0·81	0·51	0·94	20% (89/452)

Table S4. Model performance metrics for clinical-classifier model over a range of probability cutoffs for class assignment. A: "Vitals and labs" model in EARLI (n=335). **B:** "Vitals and labs" model in VALID (n=452). **C:** "Full featured" model in EARLI (n=335). **D:** "full featured" model in VALID (n=452).

A: Vital signs and labs model in EARLI					
Probability Cutoff	**Outcome**	**Hypoinflammatory**	**Hyperinflammatory**	**Effect size**	**P value**
0·3	Mortality	30% (48/162)	51% (89/173)	2·5 (1·6 – 4·0)	<0·0001
	VFD	25 (0 – 28)	7 (0 – 25)	0·26 (0·15 – 0·38)	<0·0001
0·4	Mortality	28% (52/184)	56% (85/151)	3·3 (2·1 – 5·2)	<0·0001
	VFD	24 (0 – 28)	0 (0 – 25)	0·30 (0·19 – 0·41)	<0·0001
0·6	Mortality	30% (63/213)	61% (74/122)	3·7 (2·3 – 5·9)	<0·0001
	VFD	24 (0 – 28)	0 (0 – 24)	0·31 (0·19 – 0·42)	<0·0001
0·7	Mortality	30% (69/231)	65% (68/104)	4·4 (2·7 – 7·3)	<0·0001
	VFD	24 (0 – 28)	0 (0 – 23)	0·33 (0·21 – 0·45)	<0·0001
B: Vital signs and labs model in VALID					
Probability Cutoff	**Outcome**	**Hypoinflammatory**	**Hyperinflammatory**	**Effect size**	**P value**
0·3	Mortality	23% (61/265)	48% (90/187)	3·1 (2·1 – 4·7)	<0·0001
	VFD	21 (8 – 25)	7 (0 – 22)	0·31 (0·21 – 0·4)	<0·0001
0·4	Mortality	24% (72/299)	52% (79/153)	3·4 (2·2 – 5·1)	<0·0001
	VFD	21 (8 – 25)	4 (0 – 21)	0·36 (0·26 – 0.45)	<0·0001
0·6	Mortality	27% (93/339)	51% (58/113)	2·8 (1·8 – 4·3)	<0·0001
	VFD	20 (5 – 25)	4 (0 – 21)	0·32 (0·20 – 0·42)	<0·0001
0·7	Mortality	28% (102/361)	54% (49/91)	3·0 (1·8 – 4·8)	<0·0001
	VFD	20 (4 – 25)	2 (0 – 21)	0·36 (0·24 – 0·47)	<0·0001

Table S5 Clinical outcomes for the ARDS subphenotypes classified using the Primary ("Vitals and labs") model over a range of probability cutoffs for subphenotype assignment. Outcomes are in-hospital mortality and Ventilator free days censored at day 28 (VFD; median and interquartile range). A: EARLI (n=335). B: VALID (n=452). Effect size was estimated using odds ratio for mortality and rank biserial correlation for VFD, with 95% confidence intervals. P-values are Chi-squared test for mortality and Wilcoxon-rank test for VFD.

A: Full featured model in EARLI					
Probability Cutoff	**Outcome**	**Hypoinflammatory**	**Hyperinflammatory**	**Effect size**	**P value**
0·3	Mortality	27% (51/186)	58% (86/149)	3·6 (2·3 – 5·7)	<0·0001
	VFD	25 (1 – 28)	0 (0 – 24)	0·33 (0·22 – 0·44)	<0·0001
0·4	Mortality	28% (55/200)	61% (82/135)	4·1 (2·6 – 6·5)	<0·0001
	VFD	24 (1 – 28)	0 (0 – 24)	0·35 (0·24 – 0·46)	<0·0001
0·5	Mortality	28% (60/211)	62% (77/124)	4.1 (2.6 – 6.6)	<0·0001
	VFD	24 (0 – 28)	0 (0 – 23)	0.35 (0.24 – 0.46)	<0·0001
0·6	Mortality	29% (66/225)	65% (71/110)	4·4 (2·7 – 7·1)	<0·0001
	VFD	24 (0 – 28)	0 (0 – 22)	0·37 (0·26 – 0·48)	<0·0001
0·7	Mortality	30% (71/237)	67% (66/98)	4·8 (2·9 – 8·0)	<0·0001
	VFD	24 (0 – 28)	0 (0 – 21)	0·37 (0·25 – 0·48)	<0·0001
B: Full featured model in VALID					
Probability Cutoff	**Outcome**	**Hypoinflammatory**	**Hyperinflammatory**	**Effect size**	**P value**
0·3	Mortality	25% (74/296)	49% (77/156)	2·9 (1·9 – 4·4)	<0·0001
	VFD	21 (6 – 25)	7 (0 – 22)	0·28 (0·18 – 0·38)	<0·0001
0·4	Mortality	26% (82/315)	50% (69/137)	2·9 (1·9 – 4·4)	<0·0001
	VFD	21 (6 – 25)	5 (0 – 22)	0·3 (0·19 – 0·4)	<0·0001
0·5	Mortality	27% (88/329)	51% (63/123)	2.9 (1.9 – 4.4)	<0·0001
	VFD	21 (5 – 25)	4 (0 – 21)	0.33 (0.22 – 0.43)	<0·0001
0·6	Mortality	27% (94/344)	53% (57/108)	3·0 (1·9 – 4·6)	<0·0001
	VFD	21 (5 – 25)	4 (0 – 21)	0·35 (0·23 – 0·45)	<0·0001
0·7	Mortality	29% (104/363)	53% (47/89)	2·8 (1·7 – 4·5)	<0·0001
	VFD	20 (4 – 25)	4 (0 – 21)	0·33 (0·21 – 0·45)	<0·0001

Table S6. Clinical outcomes for the ARDS subphenotypes classified using the Secondary ("Full featured") model over a range of probability cutoffs for subphenotype assignment. Outcomes are in-hospital mortality and Ventilator free days censored at day 28 (VFD; median and interquartile range). A: EARLI (n=335). B: VALID (n=452). Effect size represents odds ratio for mortality and rank biserial correlation for VFD, with 95% confidence interval. P-values are Chi-squared test for mortality and Wilcoxon-rank test for VFD.

	EARLI, EHR-derived (n=117)	**Missing Data**
Number of patients	117	N/A
Age (years)	70 (± 15)	N/A
Sex (% female)	47 (40%)	N/A
Ethnicity (% White)	60 (51%)	N/A
Temperature (C)	37·5 (± 1·3)	1 (1%)
Systolic BP (mmHg)	78 (± 18)	0 (0%)
Heart Rate (bpm)	124 (± 27)	0 (0%)
Respiratory Rate (breaths/min)	37 (33 – 42)	0 (0%)
Vasopressor use (%)	82 (70%)	0 (0%)
Hematocrit (%)	30 (± 7)	5 (4%)
WBC Count (10^3/mL)	16·0 (± 10·7)	5 (4%)
Platelet Count (10^3/mL)	181 (± 113)	5 (4%)
Sodium (mEq/dL)	138 (± 6)	0 (0%)
Creatinine (mg/dL)	2·2 (± 2·0)	1 (1%)
Bicarbonate (mmol/L)	19·6 (± 5·9)	1 (1%)
Glucose (mg/dL)	252 (± 121)	0 (0%)
Albumin (g/dL)	2·3 (± 0·8)	56 (48%)
Bilirubin (mg/dL)	1·1 (0·7 – 1·8)	7 (6%)
Hyperinflammatory Subphenotype (by LCA)	48 (41%)	N/A
Ventilator Free Days	10 (0 – 25)	N/A
In-hospital mortality	56 (48%)	N/A

Table S7 Baseline patient characteristics for Electronic Health Record (EHR)-derived EARLI cohort and missing data per variable. Missing data are specific to the data for this cohort that was derived from EPIC EHR. Data are presented as count (%), mean (± standard deviation) or as median (interquartile range). Abbreviations: Blood Pressure (BP); White Blood Cell (WBC); Latent Class Analysis (LCA). N/A = Not applicable as these parameters were obtained from the original EARLI cohort database and not from the EHR.

Validation Cohort	Outcome	Hypoinflammatory	Hyperinflammatory	P value
EARLI, EHR-derived n=117	Mortality	33% (21/64)	66% (35/53)	0·0007
	VFD	24 (0 – 26)	0 (0 – 21)	0·0005

Table S8 Clinical outcomes for Electronic Health Record (EHR)-derived observational cohort (n=117) stratified by subphenotypes. ARDS subphenotypes were classified by the "vital and labs" model using a probability cutoff of 0·5. Outcomes are in-hospital mortality and Ventilator free days censored at day 28 (VFD; median and interquartile range). P-values are Chi-squared test for mortality and Wilcoxon-rank test for VFD.

Probability Cutoff	Accuracy	Sensitivity	Specificity	Youden Index	Hyperinflammatory Subphenotype
0·3	0·79	0·68	0·83	0·51	32% (146/452)
0·4	0·81	0·64	0·89	0·53	27% (121/452)
0·5	0·82	0·55	0·93	0·48	22% (98/452)
0·6	0·82	0·51	0·96	0·47	18% (83/452)
0·7	0·80	0·40	0·97	0·37	14% (64/452)

Table S9 Model performance metrics of the custom classifier ("LUNG SAFE") model in VALID (n=452). Includes percentage of patients classified into the Hyperinflammatory subphenotype for each cut-off. The Youden index is defined as sensitivity + sensitivity – 1.

Probability Cutoff	Outcome	Hypoinflammatory	Hyperinflammatory	Effect size	P value
0·3	Mortality	32% (629/1951)	56% (479/862)	2·6 (2·2 – 3·1)	<0·0001
	VFD	15 (0 – 23)	0 (0 – 19)	0·23 (0·19 – 0·28)	<0·0001
0·5	Mortality	34% (753/2222)	60% (355/591)	2·9 (2·4 – 3·5)	<0·0001
	VFD	14 (0 – 23)	0 (0 – 18)	0·25 (0·20 – 0·30)	<0·0001
0·6	Mortality	35% (817/2338)	61% (291/475)	2·9 (2·4 – 3·6)	<0·0001
	VFD	13 (0 – 23)	0 (0 – 18)	0·24 (0·19 – 0·30)	<0·0001
0·7	Mortality	36% (864/2433)	64% (244/380)	3·2 (2·6 – 4·1)	<0·0001
	VFD	13 (0 – 23)	0 (0 – 17)	0·25 (0·19 – 0·31)	<0·0001

Table S10 Clinical outcomes for ARDS subphenotypes in LUNG SAFE (n=2813) across a range of probability cutoffs for the "LUNG SAFE" model. Mortality was assessed at day 90 and Ventilator free days (VFD) censored at day 28 (median and interquartile range). Effect size was estimated using odds ratio for mortality and rank biserial correlation for VFD, with 95% confidence intervals. P-values are Chi-squared test for mortality and Wilcoxon-rank test for VFD. Abbreviations: Acute Respiratory Distress Syndrome (ARDS).

Clinical feature	Hypoinflammatory	Hyperinflammatory	P value
ARDS Diagnosis on Day 2	65% (937/1447)	72% (340/469)	0·0024
Prevalence of chronic liver disease	2% (44/2088)	9% (68/725)	<0·0001
Prevalence of Chronic Obstructive Pulmonary Disease	24% (500/2088)	15% (107/725)	<0·0001
Prevalence of immunosuppression	12% (249/2088)	14% (104/725)	0·10

Table S11 ARDS resolution and underlying disease prevalence in ARDS subphenotypes in LUNG SAFE (n=2813). ARDS subphenotypes were classified by the LUNG SAFE model using a probability cutoff of 0·4 for subphenotype assignments. Abbreviations: Acute Respiratory Distress Syndrome (ARDS).

Characteristic	Hyperinflammatory Low PEEP subgroup	Hyperinflammatory High PEEP subgroup
Age (years)	66 ± 15	59 ± 16
Female (% female)	74 (36%)	117 (37%)
Body Mass Index (kg/m^2)	27·0 ± 6·3	27·8 ± 7·0
PaO_2/FiO_2 ratio (mmHg)	186 ± 63	135 ± 53
SOFA Score	13 (11 – 15)	13 (11 – 15)
ARDS Risk factor: Trauma	2 (1%)	5 (2%)
ARDS Risk factor: Sepsis	51 (25%)	73 (23%)
ARDS Risk factor: Aspiration	15 (7%)	26 (8%)
ARDS Risk factor: Pneumonia	87 (42%)	165 (53%)
ARDS Risk factor: Other	50 (24%)	44 (14%)

Table S12 Comparison of baseline characteristics between the Hyperinflammatory low-PEEP (n=205) and high-PEEP (n=313) subgroups in LUNG SAFE. ARDS subphenotypes were classified by the LUNG SAFE model using a probability cutoff of 0·4 for subphenotype assignments. PEEP subgroups were assigned based on tertiles of the mean PEEP usage over days 1-3, such that the upper tertile was the High PEEP group and lower tertile the Low PEEP group, with the middle tertile discarded. Data are presented as count (%), mean (± standard deviation), or median (interquartile range). Abbreviations: Positive end-expiratory pressure (PEEP); Sequential Organ Failure Assessment (SOFA); Acute Respiratory Distress Syndrome (ARDS).

Probability Cutoff	Mortality in Hypoinflammatory subphenotype		Mortality in Hyperinflammatory subphenotype		P value
	Low PEEP	High PEEP	Low PEEP	High PEEP	
0·3	31% (214/699)	34% (210/618)	61% (146/240)	51% (190/370)	0·009
0·4	32% (233/734)	34% (231/675)	62% (127/205)	54% (169/313)	0·041
0·5	32% (247/764)	35% (259/739)	65% (113/175)	57% (141/249)	0·048
0·6	34% (267/794)	36% (288/790)	64% (93/145)	57% (112/198)	0·075
0·7	34% (282/825)	37% (302/823)	68% (78/114)	59% (98/165)	0·069

Table S13 Mortality at Day 90 in tertile-derived PEEP subgroups stratified by ARDS subphenotypes over a range of probability cutoff for subphenotype classification in LUNG SAFE (n = 2813). ARDS subphenotypes were classified by the LUNG SAFE model. PEEP subgroups were assigned based on tertiles of the mean PEEP usage over days 1-3, such that the upper tertile was the High PEEP group (n=992; median 11 cm H_2O [10 – 12]) and lower tertile the Low PEEP group (n=943; median 5 cm H_2O [5 – 6]). Abbreviations: Positive End Expiratory Pressure (PEEP); Acute Respiratory Distress Syndrome (ARDS). P-value is for the interaction term of PEEP subgroups and ARDS subphenotypes with mortality as the dependent variable and was derived using the Wald test.

Probability Cutoff	Mortality in Hypoinflammatory subphenotype		Mortality in Hyperinflammatory subphenotype		P value
	Low PEEP	High PEEP	Low PEEP	High PEEP	
0·3	31% (234/753)	35% (244/701)	61% (159/262)	52% (206/399)	0·006
0·4	32% (256/792)	35% (267/763)	61% (137/223)	54% (183/337)	0·045
0·5	33% (271/824)	36% (298/830)	64% (122/191)	56% (152/270)	0·041
0·6	34% (292/856)	37% (331/887)	64% (101/159)	56% (119/213)	0·053
0·7	35% (308/890)	38% (348/924)	68% (85/125)	58% (102/176)	0·032

Table S14 Mortality at Day 90 in quintile-derived PEEP subgroups stratified by ARDS subphenotypes over a range of probability cutoff for subphenotype classification in LUNG SAFE (n = 2813). ARDS subphenotypes were classified by the LUNG SAFE model. PEEP subgroups were assigned based on quintiles of the mean PEEP usage over days 1-3, such that the upper two quintiles were the High PEEP group (n=1104; median 10 cm H_2O [9 – 12]) and the lower two quintiles were the Low PEEP group (n=1019; median 5 cm H_2O [5 – 6]). P-value is for the interaction term of PEEP subgroups and ARDS subphenotypes with mortality as the dependent variable and was derived using the Wald test.

ARDS Severity by PaO_2/FiO_2	Mortality in Low PEEP	Mortality in High PEEP	P value
Mild (PaO_2/FiO_2 200 – 300) n=828	35% (133/384)	34% (59/173)	0·96
Moderate (PaO_2/FiO_2 100 – < 200) n=1341	39% (172/441)	39% (174/449)	
Severe ($PaO_2/FiO_2 \leq$ 100) n=644	48% (55/114)	46% (167/366)	

Table S15. Mortality at Day 90 in tertile-derived PEEP subgroups stratified by ARDS severity defined by PaO_2/FiO_2 in LUNG SAFE (n = 2813). PEEP subgroups were assigned based on tertiles of the mean PEEP usage over days 1-3, such that the upper tertile was the High PEEP group (n=992; median 11 cm H_2O [10 – 12]) and lower tertile the Low PEEP group (n=943; median 5 cm H_2O [5 – 6]). Abbreviations: Positive End Expiratory Pressure (PEEP); Acute Respiratory Distress Syndrome (ARDS). P-value is for the interaction term of PEEP subgroups and ARDS severity groups with mortality as the dependent variable and was derived using the Wald test.

A: SOFA subgroups based on mean SOFA score			
ARDS Severity by SOFA score	**Mortality in Low PEEP**	**Mortality in High PEEP**	**P value**
Low SOFA (≤ 10) n=1314	30% (139/457)	30% (132/441)	0·51
High SOFA (> 10) n=1063	54% (165/308)	50% (230/464)	
B: SOFA subgroups split into proportions similar to ARDS subphenotypes (~75:25)			
ARDS Severity by SOFA score	**Mortality in Low PEEP**	**Mortality in High PEEP**	**P value**
Low SOFA (≤ 13) n=1857	34% (209/614)	34% (232/677)	0·30
High SOFA (> 13) n=520	63% (95/151)	57% (130/228)	

Table S16. Mortality at Day 90 in tertile-derived PEEP subgroups stratified by Sequential Organ Failure Assessment (SOFA) score subgroups in LUNG SAFE (n = 2813). PEEP subgroups were assigned based on tertiles of the mean PEEP usage over days 1-3, such that the upper tertile was the High PEEP group (n=992; median 11 cm H_2O [10 – 12]) and lower tertile the Low PEEP group (n=943; median 5 cm H_2O [5 – 6]). A: Two SOFA subgroups derived by splitting at the median value. B: Two SOFA subgroups derived to achieve proportions similar to ARDS subphenotypes (~75:25), with the smaller subgroup comprising the higher SOFA scores. Abbreviations: Sequential Organ Failure Assessment (SOFA); Acute Respiratory Distress Syndrome (ARDS); Positive End Expiratory Pressure (PEEP). P-value is for the interaction term of PEEP subgroups and SOFA subgroups with mortality as the dependent variable and was derived using the Wald test.

Supplementary Figure Legends

Figure S1 Feature importance of the ten most important features of the clinical-classifier models in the training data cohort (ARMA, ALVEOLI, and FACTT; n=2022). A: Primary ("vital and labs") model. **B:** Secondary (full-feature) model. Abbreviations: Blood Pressure (BP); White Blood Cell (WBC).

Figure S2 Probabilities generated by the new clinical-classifier models developed for this study plotted against the probabilities generated by the corresponding models developed in our prior study.[1] A: Primary ("vital and labs") model. **B:** Secondary ("full feature") model. R = represents Pearson's correlation coefficient.

Figure S3 Calibration plot for the primary ("vital and labs") and secondary ("full featured") models. The model generated probabilities for Hyperinflammatory subphenotype with LCA-derived subphenotype as the gold-standard classification. **A:** EARLI (n=335). **B:** VALID (n=452). CI = 95% Confidence interval.

Figure S4 Receiver operating characteristic (ROC) curve for secondary ("full-feature") model in EARLI (n=335) and VALID (n=452). AUC = Area under the ROC curve. EARLI AUC = 0.92; VALID AUC = 0.87

Figure S5 Differences in protein biomarkers when patients are stratified by "full feature" model, for EARLI (n=335) and VALID (n=452) cohorts. Y-axis was limited to aid better data visualization. Consequently, in EARLI, 9, 10, 13, and 4 observations were censored, and in VALID, 13, 16, 17, and 3 observations were censored for Interleukin-6, Interleukin-8, Soluble tumor necrosis factor receptor-1, and Protein C, respectively.

Figure S6 Alluvial plot showing ARDS subphenotype assignments by LCA (left), hand-curated cohort (middle) and EHR-derived cohort (right). All three cohorts were subsets of the EARLI cohort and comprised 117 patients. The "vitals and labs" clinical classifier model was used to assign subphenotype for both EHR cohorts. Abbreviations: Latent Class Analysis (LCA); Area Under Receiver Operating Characteristic Curve (AUC); Electronic Health Record (EHR); Hyperinflammatory subphenotype (Hyper); Hypoinflammatory subphenotype (Hypo).

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