*SUPPLEMENTAL FILE\**

# Predicting length of mechanical ventilation in ARDS using machine learning: The PIONEER Study

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*For the PredictION of duration of mEchanical vEntilation in ARDS (PIONEER) Network\**

*This Supplemental File has been provided by the authors for additional information about their work.

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# The PIONEER Study

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**SUPPLEMENTARY METHODS**

This comprehensive analysis was an investigator-initiated study from multicenter, clinical observational studies conducted in a network of intensive care units (ICUs) from several geographical areas of Spain.

The purpose of the study was to develop and validate an early prediction model for duration of mechanical ventilation (MV) longer than 14 days in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) using machine learning (ML) techniques.

**Ethics Approval**

This study was approved by the Ethics Committee for Clinical Research at the Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain (Reference CEI/CEIm 2021-321-1). The need for informed consent was waived based on Spanish legislation for biomedical research (Royal Decree 1090/2015 December 2015, and Royal Decree 957/2020 November 2020) due to the retrospective nature of the secondary analysis, the anonymization/dissociation of data, and no potential for harm or benefit to patients.

This study was conducted in accordance with the principles of the Declaration of Helsinki approved by the World Medical Association [1], the Convention of the European Council related to human rights and biomedicine, the International Code of Medical Ethics of the World Medical Association [2], and within the requirements established by the Spanish legislation for biomedical research, the protection of personal data, and bioethics. None of the findings reported in the present study have been published elsewhere.

The study followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines for prediction models [3].

**Patient population**

This study is an extension of the *S*panish *I*nitiative for *E*pidemiology, *S*tratification and *T*herapies of *A*cute Respiratory Distress Syndrome (SIESTA) Program [4-7] (*members are listed in Appendix 1 and Appendix 2 of this Supplemental File*). We performed a comprehensive analysis, termed the PIONEER ("PredictION of duration of mEchanical vEntilation in aRds") Study (registered on August 14th 2023 at ClinicalTrials.gov: NCT NCT05993377), of an unrestricted dataset derived from 1,303 adult (>17 years) patients with moderate-to-severe ARDS [8] treated with lung-protective MV in a network of ICUs from several geographical areas of Spain.

**Study design**

This study was conducted in three steps. In the first two steps (model development and testing), we analyzed data derived from 1,000 patients included in three independent, prospective, multicenter, observational, and non-interventional cohorts, enrolling consecutive patients meeting current criteria for moderate/severe ARDS [8]. In the ALIEN cohort [4], 22 participating ICUs included 300 patients from September 2008 to May 2010 (NCT00736892). In the STANDARDS cohort [9,10], 24 participating ICUs included 300 patients from September 2013 to July 2015 (NCT02288949). The STANDARDS-2 cohort [11], 21 participating ICUs admitted 400 patients from August 2015 to April 2017 (NCT02836444).

In the third step, we tested the performance of the model in an independent cohort of 303 patients with moderate/severe ARDS included in the multicenter observational PANDORA study [7]. Patients were admitted in a network of 22 ICUs from May 2017 to March 2018 (NCT03145974). With this approach, we studied the temporal aspect and external validity of predicting prolonged duration of MV days as primary endpoint in future observational studies and clinical trials, since the new cohort contains recently treated ARDS patients. The external validation cohort has sufficient number of events required for external validation [12], recommended by recent guidelines [13].

Patients admitted to participating ICUs were screened daily during the study periods. All patients were intubated and mechanically ventilated. All consecutive patients (in the ALIEN cohort) meeting the American-European Consensus Conference (AECC) criteria for ARDS [14] on positive end-expiratory pressure (PEEP) ≥5 $cmH_2O$, and the Berlin criteria for moderate or severe ARDS [8] (in the STANDARDS, STANDARDS-2, and PANDORA cohorts) were included for this analysis. Of note, by leaving the assessment of $PaO_2/FiO_2$ essentially unchanged, the AECC definition and the Berlin criteria are basically identical. The requirement of a minimum PEEP level of 5 $cmH_2O$ has no impact on the definition since all patients with ARDS were managed with PEEP ≥5 $cmH_2O$. Our screening applies only to patients with moderate-to-severe ARDS, which include: (i) having an initiating clinical condition (pneumonia, aspiration, overdose, sepsis, trauma, acute pancreatitis, etc.), (ii) within one week of a known clinical insult or new or worsening respiratory symptoms, (iii) bilateral pulmonary infiltrates on chest imaging, (iv) absence of left atrial hypertension or no clinical signs of left heart failure, and (v) hypoxemia (as defined by a $PaO_2/FiO_2$≤100 mmHg on PEEP≥5 $cmH_2O$ for severe ARDS, and 100 mmHg<$PaO_2/FiO_2$≤200 mmHg on PEEP≥5 $cmH_2O$ for moderate ARDS, regardless of $FiO_2$). We only included patients with moderate/severe ARDS. We did not enroll patients with persistent mild ARDS

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during the entire ICU stay. However, no patients with mild ARDS were excluded if they moved to a more severe category, although we do not have data on the precise number of those patients. We excluded patients <18 years old, with severe chronic pulmonary disease, acute heart failure, with a do-not-resuscitate orders, brain death, or patients receiving MV for <24 hours.

For the purpose of this study and to avoid selection bias, we only analyzed patients with MV data from the first three ICU days after diagnosis of moderate/severe ARDS: data captured at the time of diagnosis of moderate/severe ARDS (T0), at 24 hours (T24), and at 72 hours (T72). Data from day 2 were not collected in the parent studies. Therefore, we only considered patients on MV for ≥3 days with data at T0, T24, and at T72 to compare patients with data at those time-periods. As a result, we excluded 130 patients on MV for <3 days (80 from 1,000 patients included in the development/testing cohort and 50 from the 303 patients included in the validation cohort), and finally analyzed data from 920 patients in the derivation/testing cohort, and 253 patients from the external validation cohort.

T0 was defined as the day in which the patient first met moderate/severe ARDS criteria, irrespective of the day of ICU admission or initiation of MV, as mandated by the Berlin definition [8]. All patients had arterial blood gases at study inclusion. We did not use peripheral capillary oxygen saturation ($SpO_2$) as a surrogate for $PaO_2$ for enrolling patients. At T24, values of gas-exchange and lung mechanics [including $PaO_2$, $PaCO_2$, $PaO_2/FiO_2$, inspiratory plateau pressure (Pplat), among others] were assessed in all patients under standardized ventilator settings [positive end-expiratory pressure (PEEP) of 10 $cmH_2O$ and $FiO_2$ of 0.5] [7]. When patients required PEEP>10 or $FiO_2$>0.5 and could not tolerate a decrease in PEEP or $FiO_2$, a set of rules for setting PEEP and $FiO_2$ were applied *only* during the standardized assessment, as described and validated previously by our group [11,15]. At other times, PEEP and $FiO_2$ levels were set at the discretion of managing clinicians. For T72, we used representative data at 72 hours after diagnosis of moderate/severe ARDS.

For appropriate identification of patients with moderate/severe ARDS, attending physicians considered qualifying blood gases only while patients were clinically stable, and did not consider transient falls in $PaO_2$ resulting from acute events unrelated to the disease process (such as obstruction of endotracheal tube by secretions, endotracheal suctioning, ventilator disconnection, or sudden pneumothorax). Also, because diagnostic inclusion could occur with other diseases that cause hypoxemia and have bilateral pulmonary infiltrates on radiographs, clinicians excluded lymphangitic

carcinomatosis, acute eosinophilic pneumonia, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis [16].

**General Care**

Attending clinicians followed current guidelines for general critical care management, which included the following: (i) in case of sepsis, physicians were urged to ensure early identification of causative microorganism, intravenous administration of antibiotics as soon as bacterial sepsis was suspected or recognized, and to optimize antibiotic selection and timely administration on the bases of antibiogram; (ii) fluid resuscitation and vasopressor use were individualized with the goal of maintaining a systolic blood pressure ≥90 mmHg or a mean arterial pressure ≥65 mmHg; (iii) to maintain hemoglobin between 7-10 g/dL. For ventilatory management, clinicians followed current recommendations for lung-protective ventilation with a tidal volume (VT) of 4-8 mL/kg predicted body weight (PBW), a Pplat <30 cmH$_2$O, a ventilatory rate (RR) to maintain a PaCO$_2$ between 35-50 mmHg (permissive hypercapnia was allowed to target VT), and PEEP and FiO$_2$ combinations according to the PEEP-FiO$_2$ table of the ARDSnet protocol [17], ensuring that among the PEEP and FiO$_2$ combinations, clinicians should use the PEEP levels that allowed the reduction of FiO$_2$ to the lowest levels for maintaining a PaO$_2$ within a target range of 60 to 100 mmHg or a SpO$_2$ within a target range of 90 to 98%. Routine blood parameters were left to the discretion of the responsible physician, but it was not mandatory to record them, although clinicians used routinely that information for diagnosis and magamen5t of the underlying disease process, for scoring organ dysfunction, and as mandated by SOF scale and for APACHE II score.

The choice of drugs for sedation and analgesia, early neuromuscular blockade, prone positioning, recruitment maneuvers, hemodynamic management modalities, and the decision to perform a tracheostomy were left to the discretion of the attending physician. PBW was calculated using the following formula: 50 + 0.91 x [height (cm) – 152] for men, and 45.5 + 0.91 x [height (cm) – 152] for women [17]. Although prone positioning and recruitment maneuvers were used in some patients, we do not have data on timing of prone positioning, or whether prone ventilation and recruitment maneuvers were applied as a rescue therapy, as a routine practice, or following any specific protocol. Features highly dependent on ICU variability, such as active treatment and chronic conditions reporting, were not recorded to improve usability across health systems.

Weaning off MV was not strictly protocolized, but could be started when the attending physician considered it clinically appropriate. Patients were assessed daily for readiness for a spontaneous

breathing trial (SBT) based on the ARDSnet protocol [17]. In general, prerequisites for the SBT included a partial reversal of the underlying cause of ARDS, a $PaO_2/FiO_2$ >200 mmHg with PEEP <10 $cmH_2O$ and $FiO_2$ ≤0.4, no vasopressors, continuous sedation minimized, and ability to cough during tracheal aspirations. Spontaneous ventilation was tested with a T-piece or with pressure support at 8 $cmH_2O$. The duration of the SBT was at least 30 min and no longer than 120 min. If the patient passed the trial, a decision for extubation was taken, unless there was a specific reason not to extubate. Weaning and the decision to extubate were left to the discretion of the responsible physician. Since the rate of reintubation after extubation for all indications is estimated at about 20% [18], patients at high risk for reintubation [>65 years of age, or hypercapnic ($PaCO_2$ >45 mmHg after extubation), ineffective cough and excessive secretions, ≥1 weaning failure, with more than one comorbid condition, upper airway obstruction, or APACHE II score >12 on the day of extubation], non-invasive ventilatory support for 24 to 48 hours was indicated until stable or requiring reintubation [19].

**Variables and Outcomes**

Data were collected in each participating ICU using standardized case report forms and transmitted to the coordinating center (Hospital Universitario Dr. Negrin) when the patient was discharged from hospital. Before exporting the data into a computerized database, a trained data collector from the coordinating center checked the completeness and the quality of information. Logical checks were performed for missing data and for finding inconsistences, especially regarding clinical diagnosis, dates, and severity scores. If necessary, the data collector contacted the investigator to validate the data or reformat the data for entry into the database.

Selection of clinically relevant variables was based on our previous studies [11,20]. To build the models, we analyzed information from 165 variables including demographics, comorbidities, and data from ventilator settings and lung mechanics [VT, RR, PEEP, Pplat, driving pressure (calculated as Pplat minus PEEP) and gas exchange ($PaO_2$, $PaCO_2$, $FiO_2$, $PaO_2/FiO_2$, pH)] at T0, T24 and T72. Attending physicians recorded the most common comorbidities (we only considered comorbidities with a prevalence >5%), as reported in our previous work [20]: neoplastic diseases, liver disease, cardiac disease, immunosuppression, diabetes, and morbid obesity. Neoplastic diseases included cancer in solid organs and hematological malignancies. Being immunosuppressed or immunocompromised was a result of certain diseases or conditions, or because of medication or treatment for a disease or condition, including, but not limited to cancer or organ transplantation. We also recorded the APACHE

II (Acute Physiology And Chronic Health Evaluation II) score [21] during the first 24 hours of ARDS diagnosis, the Sequential Organ Failure Assessment (SOFA) score [22], and the occurrence of extrapulmonary organ system failures included in the SOFA scale (cardiovascular system, liver, kidney, coagulation system, and central nervous system). Since the term "organ dysfunction" is unclear and because organ dysfunction may emerge from reasons other than sepsis, extrapulmonary organ failure was defined as an acute change in organ-specific SOFA score ≥2 [23,24]. The baseline SOFA score was assumed to be zero in patients not known to have preexisting organ dysfunction. Sepsis was defined according to 2001 International Consensus Conference criteria [25]. We recorded the actual duration of MV, the length of stay in the ICU, and date and status (alive or dead) at ICU and hospital discharge.

Our primary goal was to compare the performance of three machine learning (ML) methods and conventional statistics in predicting prolonged duration of MV after the diagnosis of moderate/severe ARDS over time. We examined the performance of each method with respect to T0, T24, and T72. For the purpose of this study, prolonged MV was defined as being ventilated for >14 days after diagnosis of moderate/severe ARDS, based on previous work by our group [26].

**Statistical analysis plan**

***Predefined rules, pre-specified statistical analysis, and variable selection***

We defined and specified in advance rules and expectations before the final statistical and machine learning analysis was conducted, realizing that overly detailed analysis could produce overoptimistic results due to a combination of reduced statistical power to detect real differences, or due to an increase in the variance around the mean estimates, and/or an increased statistical likelihood of a false finding when too many variables are examined.

Since feature selection is important in building a prediction model that is easily actionable and interpretable in clinical decision making, we collected data from 165 variables in each patient during their ICU stay. We focused on variables collected at T0, T24 and T72 to estimate the probability of duration of MV>14 days, independent of the underlying disease or whether the patient died (**Figure S1**) based on previous work by our group [9-11]. Our aim for variable selection was to incorporate clinically relevant variables while avoiding noise/redundant variables.

We *first* described the full dataset of patients with moderate-to-severe ARDS ventilated for at least three days (n=920). Thus, we listed the values of each variable for all 920 patients at T0, T24, and

T72. The distribution of values for all variables identified a wide range of duration of MV. *Second*, we initially considered the following features as potential predictors of prolonged MV: age, sex, comorbidities (neoplastic diseases, liver disease, cardiac disease, immunosuppression, diabetes, morbid obesity), SOFA score, number of extrapulmonary OF, $PaO_2$, $PaO_2/FiO_2$, $PaCO_2$, pH, $FiO_2$, VT, RR, PEEP, Pplat, and driving pressure. We did not include respiratory compliance in the model because it shares collinearity with three Independent variables needed for its calculation (VT, Pplat, and PEEP). According to the panel of experts of the Berlin definition [8], respiratory compliance did not contribute to the predictive validity of severe ARDS for mortality and it was removed from the ARDS definition. Although we have the APACHE II score [21] reported at T0 and T24, we did not include it in the model because it is a cumbersome score designed for the first 24 hours of ICU admission, made of 12 physiological variables and two disease-related variables, it is not routinely calculated at the bedside in most ICUs worldwide or during trial enrollment decisions, it requires numerous data elements, and relies on laboratory data that are not uniformly collected. In addition, at least half of the variables needed to calculate the APACHE II score are included in the list of selected variables, such as age, $PaO_2$, $FiO_2$, respiratory rate, pH, renal function, neurological function, and comorbidities.

  *Third*, we identified potential variables that could be included in the prediction models based on our redefined rules and their contribution to the area under the receiver operating characteristic (ROC) curve (AUC), and their p-values in relation to duration of MV (**Table S1**). A ROC curve essentially has two components represented by the sensitivity and 1-specificity [27]. AUC is an effective way to summarize the overall prognostic accuracy of a variable or test, and it is most useful for assessing relevance of treatment effects. When representing and reporting the AUC, the point corresponding to no change (AUC=0.5) is represented by a diagonal line (45-degree line or no discriminatory ability for the outcome of interest).

  *Fourth*, although several variables could share collinearity with other independent variables ($FiO_2$ and $PaO_2$ for the calculation of the $PaO_2/FiO_2$ ratio; Pplat and PEEP for the calculation of driving pressure), we considered all variables at the initial steps of our analysis. Whether driving pressure relates causally to outcome remains to be established in randomized controlled trials, despite we valued Pplat in our previous studies [10,11,28]. Other variables seemed to have redundancy (the value of SOFA score and the number of extrapulmonary OF). To avoid multicollinearity, we built correlation matrices at T0, T24, and T72 as a statistical tool to calculate the linear relationship between two variables in the

dataset [29-31] for excluding features with multicollinearity (**Figure S3**). The matrix shows how all possible pairs of values in a table that are related to each other. It is a powerful tool for summarizing a large data set and showing patterns in the data. The correlation coefficient ranges from -1 to +1, where 1 is considered a strong positive relationship between variables, 0 means a neutral relationship, and -1 means a negative correlation. We also performed a principal component analysis (PCA) as a statistical procedure that allows summarizing the information content by means of a smaller set of "summary indices" that can be more easily visualized and analyzed [31-33] (**Figure S4**). It is a popular multivariate statistical technique used in pattern recognition and signal processing based on projection methods. The goal of PCA is to extract the important information from the data and to express this information as a set of summary indices called principal components [31-33]. The first and second principal component provide an approximation of what model or projection is better. The first principal component represents the maximum variance direction in the data. The second principal component reflects the second largest source of variation in the data. When the two principal components are derived, they define a plane. In the specific context of our study, adding the numerical values of both components provides a tendency in the direction of data in favor of which day seems better positioned to predict MV>14 days.

*Fifth*, variable selection or feature subset selection is a common task in machine learning (ML) or data mining models. ML is a branch of artificial intelligence (AI) encompassing two major approaches: supervised and unsupervised learning [34]. The objective of supervised ML is to develop an algorithm capable of predicting a unique output when provided with a specific input. The expectations are that the resulting algorithm would deliver accurate predictions when exposed to new and never before data. Since the inclusion of all available variables in a ML model could produce noisy results which are difficult to interpret, we screen variables employing a genetic algorithm (GA) variable selection method [35] as a technique to achieve parsimony and to identify a subset of relevant and significant variables (subset selection) for a potential accurate prediction model, while excluding noise/redundant variables. GA variable selection is a technique that helps to identify a subset of the measured variables that are, for a given problem, the most useful for a precise and accurate regression model. Although many variables may be of use in a prediction, several considerations may preclude measuring all the variables originally considered for a prediction model. In these cases, it is useful to identify a subset of variables that allow sufficient prediction accuracy and precision while minimizing the number of variables to be measured. GA provide a straightforward method based on a "survival of the fittest" approach to modelling data. GA

is a heuristic search algorithm mimicking the process of biological evolution and natural selection [36]. GA creates random populations of artificial individuals that are evaluated by a mathematical fitness function. GAs have been successfully applied to solve optimization problems, both for continuous and discrete functions. In this sense, variable selection for logistic regression models can be regarded as an optimization problem, and thus can be solved by GAs [37,38]. Our findings indicate that for the purpose of our study, the GA approach is appropriate for finding an efficient subset of variables for combinations that are optimal for solving high dimensional classification problems. Duration of MV can be treated as a classification problem. The selection of an optimized set of variables in our three early scenarios (T0, T24, T72) is key in the PIONEER study for predicting prolonged duration of MV, especially when the search is large, complex or poorly understood, as in the setting of moderate/severe ARDS. We decided to use GA for feature/variable selection due to our previous successful experience with it [39].

*Sixth*, when applying GA for variable selection, we optimize the subset of selected variables by minimizing the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) [40] (**Figure S2**). AIC is an estimator of prediction error and thereby relative quality of statistical models for a given set of data. BIC is a criterion for model selection among a finite set of models. For both criteria, lower values are preferred. We also calculated the variance inflation factor (VIF), a measure of multicollinearity in regression logistic analysis. Multicollinearity exists when there is a correlation between multiple independent variables in a multiple regression model. For the purpose of our study, only variables with a VIF<5 were included in the model [30]. We searched in the data for model specification since the model was not pre-specified. For building the PIONEER prediction model for moderate/severe ARDS patients, we considered the model with the minimum number of variables that provided a similar or better performance as the full-variable predictor model (**Tables S4-S10**).

*Seventh*, we evaluated the final model with the minimum number of variables at each time scenario using three supervised ML techniques: Random Forest (RF), Support Vector Machine (SVM) and Multilayer Perceptron (MLP) [41-45]. RF is a supervised ML algorithm, which combines the output of multiple decision trees to reach a single result. The RF algorithm is made up of a collection of decision trees, and each tree in the ensemble is comprised of a data sample drawn from a training set with replacement [43]. While decision trees consider all the possible feature split, RF only select a subset of those features, resulting in precise predictions. SVM is one of the prevailing algorithms because the data in biomedical research are often limited. One of the main strengths of the SVM is the ability to

efficiently construct complex decision boundaries from limited samples [41,44]. The deep learning MLP is a feed for forward neural network with a basic architecture comprising fully connected layers [44,45]. The input layer has the same number of inputs that the total predictor variables. The middle layer looks for characteristics associated with the data. The output layer had the same number of outputs as the categories to predict. The R packages for ML that we used are the following: Caret, pROC, randomForest, Keras, and e1071.

For ML techniques, input data were randomly split into training data (train), made up of 80% of the 920 records (736 rows), and the remaining 20% (184 rows) were used as test data. With the intention of reducing noise, each of the selected variables was normalized using the following formula:

$$Z = X - min (X) / [max (X) - min (X)]$$

Where X is one of the selected genes, min (X) is the minimum value, max (X) is the maximum value, and Z is the resulting variable that was used for the ML process.

### *Building the development and validation datasets*

A popular approach is to randomly split the data into two parts: one to develop the model (training cohort) and another to measure its performance (validation cohort). However, this split-sample method is often inefficient [46,47]. We used a 5-fold cross-validation for splitting randomly the 920-patient dataset as 736 patients for development (training) and 184 patients for testing (validating). This computerized technique replicates the process of sample generation by drawing samples with replacement from the original dataset [48], which means that the data set is divided into 5 folds, and in each run, 4 (80%) were used for training (n=736) and the remaining 1 (20%) was used for testing (n=184). We repeated the 5-fold cross-validation 100 times for obtaining a stable estimate with the mean values of 500 validation samplings.

Calculations were performed using the R Core Team software 2023 (R version 4.3.1) (https://www.r-project.org) (R Foundation for Statistical Computing, Vienna, Austria).

We compared the predictive performance of the three ML methods using the following parameters: accuracy, sensitivity, specificity, from the confusion matrix for both the validation and the

test dataset [49]. These values were calculated using the indicators true positive, false positive, false negative and true negative.

### *External validation*

As the third step, and for solving the complexity of validation of our prediction model, we tested the performance of the model in fully new patients. We analyzed a cohort of 253 consecutive patients ventilated ≥3 days with moderate-to-severe ARDS included in the multicenter PANDORA study [7]. With this approach, we studied the temporal aspect of external validity of the model since this independent cohort contains recently treated patients. The external validation cohort had a sufficient number of events (≥100 patients ventilated >14 days) required for external validation [12]. As recommended by recent guidelines [13], we avoided the retraining on the external dataset.

### *Data analysis*

We calculated the mean, standard deviation (SD), median and the interquartile range (IQR) of quantitative variables. We used the Kolmogorov-Smirnov test to examine the normal distribution of data. We calculated the frequency and percentage of qualitative variables. We reported data as percentages or mean ± SD, unless otherwise specified. We reported the odds ratio and 95% confidence intervals (CI). We assessed differences in the values of clinically relevant features in the three scenarios (T0, T24, T72), and across the development/testing cohort and the external validation cohort. We analyzed differences between distributions of categorical variables with the Fisher's exact test. We identified potential variables that could be included in the prediction model based on our predefined rules, the AUC, and their p-values. For all comparisons, a two-sided significance level of p-value <0.005 was considered a real effect size, as recommended [50].

We measured the mean decrease in Gini coefficient as a measure of how each variable contributes to the homogeneity in the resulting RF algorithm model [51]). We also calculated three measures (intercept, calibration slope, and *c*-statistic) to assess the validity of the prediction models, related to calibration and discrimination, and plotted graphically, by studying the external validity of the models developed in 920 patients and tested in 253 patients [47,52].

**SUPPLEMENTARY RESULTS**

ICU and hospital mortalities of development and validation cohorts were similar [307/920 (33.4%) vs. 77/253 (30.4%), p=0.420; and 347/920 (37.7% vs. 87/253 (34.4%, p=0.368, respectively] (**Table S2**). From the original derivation/testing cohort of 1000 patients, 80 patients (8%) were on MV for <3 days, and most of them (68/80, 85%) died in the ICU due mainly to multisystem organ failure (n=47, 69.1%), refractory sepsis/septic shock (n=10, 14.7%), and refractory hypoxemia (n=8, 11.8%). Only 12 patients out of 80 (15%) on invasive MV for <3 days from the derivation cohort survived at ICU discharge.

Considering ICU mortality in relation to duration of MV, ICU mortality rates of both subgroups (MV>14 days vs. MV 3-14 days) were similar in the derivation [152/441 (34.5%) vs. 155/479 (32.4%), OR 1.10 (95%CI 0.84-1.45) (p=0.529), respectively] and validation cohorts [25/100 (25.0%) vs. 52/153 (34.0%), OR 1.54 (95%CI 0.88-2.71) (p=0.162), respectively] (**Table S3**).

Median duration of MV in 920 patients from the derivation cohort was 14 days (IQR: 8-25 days): 441 patients (47.9%) were on MV>14 days and 479 (52.1%) were ventilated for 3-14 days. From 479 patients on MV for 3-14 days, almost a third of them (n=155, 32.4%) died in the ICU, mainly due to multisystem organ failure (n=68, 43.9%), refractory hypoxemia (n=38, 24.5%), and refractory sepsis/septic shock (n=24, 15.5%). In the validation cohort of 253 patients, where the median duration of MV was 13 days (IQR: 7-21 days): 100 patients (39.5%) were on MV>14 days and 153 (60.5%) were ventilated for 3-14 days.

Using a correlation matrix at T0, T24, and T72, we identified that $PaO_2/FiO_2$ was highly correlated with $FiO_2$ and $PaO_2$, Pplat with driving pressure, and SOFA score with the number of extrapulmonary OF (**Figure S3**). As a result, we eliminated from the analysis the following variables: $PaO_2$, $FiO_2$, SOFA score, and driving pressure. The principal component analysis (PCA) supported the finding that the two clusters (MV>14 days vs. MV 3-14 days) differed more at T72 than at baseline or at T24 (**Figure S4**).

The final model minimizing AIC and BIC for prediction of duration of MV>14 days was based on values of variables at T72. We found that $PaO_2/FiO_2$, $PaCO_2$, pH, and PEEP at T72 were among the most predictive features (**Figures S5, S6**), suggesting that most features collected at baseline or at 24h were irrelevant or useless for early prediction of duration of MV>14 days in patients with moderate/severe ARDS. Models developed at one time period are not transferable to other time periods.

**Table S1. Univariate logistic regression of 20 clinically relevant variables in 920 patients with moderate-to-severe ARDS ventilated ≥3 days, in relation to prediction of duration of mechanical ventilation >14 days.**

| Variables | b | SE | OR (95%CI) | P-value | AUC |
|---|---|---|---|---|---|
| Age | 0 | 0 | 1 (1.0 – 1.01) | 0.29 | 0.52 |
| Sex (male) | 0.28 | 0.14 | 1.32 (1.0 – 1.75) | 0.05 | 0.53 |
| Cardiac disease | -0.35 | 0.26 | 0.71 (0.42 – 1.18) | 0.186 | 0.51 |
| Diabetes | -0.04 | 0.19 | 0.96 (0.66 – 1.38) | 0.818 | 0.50 |
| Immunosuppressed | 0.27 | 0.22 | 1.3 (0.84 – 2.03) | 0.234 | 0.51 |
| Morbid obesity | 0.38 | 0.23 | 1.47 (0.93 – 2.33) | 0.098 | 0.52 |
| Liver disease | -0.04 | 0.29 | 0.96 (0.54 – 1.71) | 0.886 | 0.50 |
| Neoplastic disease | 0.06 | 0.17 | 1.06 (0.76 – 1.48) | 0.730 | 0.50 |
| SOFA at T0 | 0.04 | 0.02 | 1.04 (1.0 – 1.08) | 0.055 | 0.55 |
| SOFA at T24 | 0.05 | 0.02 | 1.05 (1.01 – 1.09) | 0.011 | 0.56 |
| SOFA at T72 | 0.05 | 0.02 | 1.05 (1.01 – 1.08) | 0.007 | 0.57 |
| VT at T0 | 0.02 | 0.06 | 1.02 (0.9 – 1.15) | 0.791 | 0.50 |
| VT at T24 | -0.05 | 0.07 | 0.95 (0.82 – 1.1) | 0.474 | 0.51 |
| VT at T72 | -0.04 | 0.06 | 0.96 (0.85 – 1.09) | 0.527 | 0.51 |
| $FiO_2$ at T0 | 0.16 | 0.35 | 1.17 (0.59 – 2.32) | 0.649 | 0.51 |
| $FiO_2$ at T24 | 0.73 | 0.38 | 2.07 (0.99 – 4.36) | 0,055 | 0.54 |
| $FiO_2$ at T72 | 1.33 | 0.34 | 3.79 (1.96 – 7.37) | <0.001 | 0.59 |
| Respiratory rate at T0 | 0.02 | 0.01 | 1.02 (1.0 – 1.05) | 0.093 | 0.54 |
| Respiratory rate at T24 | 0.03 | 0.01 | 1.03 (1.0 – 1.06) | 0.033 | 0.54 |
| Respiratory rate at T72 | 0-04 | 0.01 | 1.04 (1.02 – 1.07) | 0.001 | 0.56 |
| PEEP at T0 | 0.04 | 0.02 | 1.04 (1.0 – 1.08) | 0.037 | 0.54 |
| PEEP at T24 | 0.04 | 0.02 | 1.05 (1.0 -1.09) | 0.047 | 0.54 |
| PEEP at T72 | 0.08 | 0.02 | 1.09 (1.04 – 1.13) | <0.001 | 0.58 |
| Plateau pressure at T0 | 0.02 | 0.01 | 1.02 (0.99 – 1.05) | 0.122 | 0.53 |
| Plateau pressure at T24 | 0.03 | 0.01 | 1.03 (1.0 – 1.06) | 0.033 | 0.54 |
| Plateau pressure at T72 | 0.05 | 0.01 | 1.06 (1.03 – 1.09) | <0.001 | 0.58 |
| Driving pressure at T0 | 0 | 0.01 | 1 (0.98 – 1.03) | 0.844 | 0.51 |
| Driving pressure at T24 | 0.01 | 0.01 | 1.01 (0.99 – 1.04) | 0.32 | 0.52 |
| Driving pressure at T72 | 0.02 | 0.01 | 1.02 (0.99 – 1.05) | 0.309 | 0.53 |
| $PaO_2$ at T0 | -0.01 | 0 | 0.99 (0.99 – 1.0) | 0.016 | 0.55 |
| $PaO_2$ at T24 | 0 | 0 | 1 (0.99 – 1.0) | 0.061 | 0.52 |
| $PaO_2$ at T72 | 0 | 0 | 1 (0.99 – 1.0) | 0.101 | 0.53 |
| $PaO_2/FiO_2$ at T0 | 0 | 0 | 1 (0.99 – 1.0) | 0.017 | 0.54 |
| $PaO_2/FiO_2$ at T24 | 0 | 0 | 1 (0.99 -1.0) | 0.012 | 0.55 |
| $PaO_2/FiO_2$ at T72 | 0 | 0 | 1 (0.99 – 1.0) | <0.001 | 0.59 |
| $PaCO_2$ at T0 | 0.01 | 0.01 | 1.01 (1.0 – 1.02) | 0.074 | 0.54 |
| $PaCO_2$ at T24 | 0-02 | 0.01 | 1.02 (1.01 – 1.04) | <0.001 | 0.57 |
| $PaCO_2$ at T72 | 0.03 | 0.01 | 1.03 (1.02 – 1.05) | <0.001 | 0.59 |
| pH at T0 | -0.18 | 0.62 | 0.84 (0.25 – 2.85) | 0.776 | 0.50 |
| pH at T24 | -1.82 | 0.8 | 0.16 (0.03 -0.78) | 0.023 | 0.54 |
| pH at T72 | -0.04 | 0.84 | 0.96 (0.18 – 5.02) | 0.958 | 0.51 |
| No. extrapulmonary OF at T0 | 0.14 | 0.06 | 1.15 (1.01 – 1.3) | 0.033 | 0.55 |
| No. extrapulmonary OF at T24 | 0.14 | 0.06 | 1.15 (1.02 – 1.3) | 0.019 | 0.55 |
| No. extrapulmonary OF at T72 | 0.11 | 0.06 | 1.11 (1.0 – 1.24) | 0.06 | 0.55 |

ARDS: acute respiratory distress syndrome, AUC: area under the receiver operating characteristic curve, b: beta, CI: confidence intervals, OF: organ failures, OR: odds ratio, PEEP: positive end-expiratory pressure, SE: standard error, SOFA: sequential organ failure assessment, T0: at the time of moderate/severe ARDS diagnosis, T24: at 24 hr after moderate/severe ARDS diagnosis, T72: at 72 hr after moderate/severe ARDS diagnosis, VT: tidal volume.

**Table S2. Baseline demographics, etiology, degree of severity, and outcome data of 1,173 patients with moderate/severe ARDS.**

| Variables | Development cohort n = 920 | Testing cohort n = 253 | p-value |
|---|---|---|---|
| Age, yr, mean ± SD | 56.5 ± 16.0 | 57.2 ± 14.7 | 0.531* |
| Sex, n (%) | | | 0.043¶ |
| Male | 624 (67.8) | 189 (74.7) | |
| Female | 296 (32.2) | 64 (25.3) | |
| Etiology, n (%) | | | |
| Pneumonia | 458 (49.8) | 92 (36.4) | <0.001¶ |
| Sepsis | 246 (26.7) | 60 (23.7) | 0.374¶ |
| Aspiration | 90 (9.8) | 45 (17.8) | <0.001¶ |
| Trauma | 72 (7.8) | 35 (13.8) | 0.005¶ |
| Acute pancreatitis | 23 (2.5) | 8 (3.2) | 0.718¶ |
| Multiple transfusions | 9 (1.0) | 3 (1.2) | 0.729¶ |
| Others | 22 (2.4) | 10 (4.0) | 0.258¶ |
| Degree of severity, n (%) | | | 0.134¶ |
| Severe | 370 (40.2) | 88 (34.8) | |
| Moderate | 550 (59.8) | 165 (65.2) | |
| APACHE II, mean ± SD | 20.4 ± 6.4 | 20.6 ± 7.7 | 0.688* |
| Days on MV, mean ± SD | 19.6 ± 17.8 | 16.0 ± 15.8 | 0.004* |
| All-cause ICU mortality, n (%) | 307 (33.4) | 77 (30.4) | 0.420¶ |
| All-cause hospital mortality, n (%) | 347 (37.7) | 87 (34.4) | 0.368¶ |

*APACHE: acute physiology and chronic health evaluation, ARDS: acute respiratory distress syndrome, ICU: intensive care unit, IQR: interquartile range, MV: mechanical ventilation.*

*(\*) Student's t-test; (¶) Fisher's exact test*

**Table S3. Distribution and outcome of patients with moderate/severe ARDS in relation to duration of mechanical ventilation.** ARDS: acute respiratory distress syndrome, CI: confidence intervals, ICU: intensive care unit, MV: mechanical ventilation, OR: odds ratio, T0: time of diagnosis of moderate/severe ARDS.

| Duration of MV | Derivation cohort (N=920) | | Validation cohort (N=253) | | Difference (95%CI) in ICU mortality (derivation vs. validation) OR (95%CI) | p-value |
|---|---|---|---|---|---|---|
| | n | ICU deaths | n | ICU deaths | | |
| 3-14 days from T0 | 479 | 155 (32.4%) | 153 | 52 (34.0%) | 1.6% (-6.7 to 10.4) 0.93 (0.63 to 1.37) | 0.714 0.767 |
| >14 days from T0 | 441 | 152 (34.5%) | 100 | 25 (25.0%) | 9.5% (-0.7 to 18.2) 1.58 (0.96 to 2.58) | 0.068 0.077 |
| Difference (95%CI) ICU deaths (3-14 vs. >14 days) OR (95%CI) | 2.1% (-4.0 to 8.2) 0.91 (0.69 to 1.20) | | 9.0% (-2.7 to 19.8) 1.54 (0.88 to 2.71) | | - - | - - |
| p-value | 0.500 0.529 | | 0.129 0.162 | | - | - |

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**Table S4. Performance of a model predicting duration of MV>14 days considering clinically relevant variables (n=16) collected at diagnosis (T0) in 920 patients with moderate/severe ARDS using logistic regression analysis.** $PaO_2$, $FiO_2$, driving pressure, and SOFA (sequential organ failure assessment) score are not included due to multicollinearity (see text for details). Data are expressed as mean values of logistic coefficients.

| Variables | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -14.66 | 6.47 | 0 (0 - 0.13) | 0.024 | |
| Age | 0.01 | 0 | 1.01 (1 - 1.02) | 0.093 | 1.17 |
| Sex (male) | 0.34 | 0.15 | 1.41 (1.05 - 1.89) | 0.021 | 1.06 |
| Cardiac disease | -0.51 | 0.27 | 0.6 (0.35 - 1.02) | 0.062 | 1.08 |
| Diabetes | -0.06 | 0.20 | 0.94 (0.64 – 1.39) | 0.773 | 1.06 |
| Immunosuppressed | 0.32 | 0.24 | 1.37 (0.86 – 2.2) | 0.184 | 1.09 |
| Obesity | 0.37 | 0.24 | 1.45 (0.9 – 2.35) | 0.128 | 1.08 |
| Liver disease | -0,19 | 0.31 | 0.83 (0.45 – 1.52) | 0.547 | 1.09 |
| Neoplastic disease | -0.05 | 0.18 | 0.96 (0.67 – 1.36) | 0.798 | 1.08 |
| VT | 0.12 | 0.07 | 1.12 (0.97 – 1.3) | 0.117 | 1.30 |
| Respiratory rate | 0.02 | 0.02 | 1.02 (0.99 – 1.05) | 0.153 | 1.18 |
| PEEP | 0.03 | 0.02 | 1.03 (0.98 – 1.08) | 0.220 | 1.27 |
| Plateau pressure | 0.01 | 0.02 | 1.01 (0.98 – 1.04) | 0.687 | 1.18 |
| $PaO_2/FiO_2$ | 0 | 0 | 1 (0.99 – 1.0) | 0.052 | 1.08 |
| $PaCO_2$ | 0.01 | 0.01 | 1.01 (1 – 1.03) | 0.043 | 1.73 |
| pH | 1.59 | 0.85 | 4.89 (0.93 – 26.24) | 0.062 | 1.78 |
| No. extrapulmonary OF | 0.16 | 0.07 | 1.17 (1.02 – 1.35) | 0.021 | 1.17 |
| AIC | | | | | 1273.26 |
| BIC | | | | | 1355.28 |
| AUC | | | | | 0.6125 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, PEEP: positive end-expiratory pressure, SE: standard error, VIF: variance inflation factor, VT: tidal volume.

**Table S5. Performance of a model predicting duration of MV>14 days considering clinically relevant variables (n=16) collected at 24 hours of diagnosis (T24) of 920 patients with moderate/severe ARDS using logistic regression analysis.** $PaO_2$, $FiO_2$, driving pressure, and SOFA (sequential organ failure assessment) score are not included due to multicollinearity (see text for details). Data are expressed as mean values of logistic coefficients.

| Variables | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -6.7 | 7.93 | 0 (0 – 6778) | 0.398 | |
| Age | 0.01 | 0 | 1.01 (1 - 1.02) | 0.078 | 1.16 |
| Sex (male) | 0.3 | 015 | 1.34 (1.01 – 1.8) | 0.046 | 1.05 |
| Cardiac disease | -0.48 | 0.28 | 0.62 (0.36 – 1.05) | 0.080 | 1.07 |
| Diabetes | -0.06 | 0.2 | 0.94 (0.64 – 1.39) | 0.757 | 1.07 |
| Immunosuppressed | 0.3 | 0.24 | 1.35 (0.85 – 2.17) | 0.202 | 1.08 |
| Obesity | 0.38 | 0.24 | 1.47 (0.91 – 2.38) | 0.118 | 1.08 |
| Liver disease | -0.22 | 0.31 | 0.8 (0.43 – 1.48) | 0.481 | 1.08 |
| Neoplastic disease | -0.08 | 0.18 | 0.92 (0.65 – 1.32) | 0.665 | 1.09 |
| VT | 0.05 | 0.08 | 1.05 (0.89 – 1.24) | 0.549 | 1.20 |
| Respiratory rate | 0.02 | 0.01 | 1.02 (0.99 – 1.05) | 0.247 | 1.21 |
| PEEP | 0.02 | 0.03 | 1.02 (0.97 – 1.07) | 0.375 | 1.21 |
| Plateau pressure | 0.01 | 0.02 | 1.01 (0.97 – 1.04) | 0.737 | 1.32 |
| $PaO_2/FiO_2$ | 0 | 0 | 1 (1 – 1) | 0.235 | 1.14 |
| $PaCO_2$ | 0.02 | 0.01 | 1.02 (1 – 1.04) | 0.029 | 1.65 |
| pH | 0.53 | 1.03 | 1.71 (0.23 – 12.95) | 0.604 | 1.59 |
| No. extrapulmonary OF | 0.13 | 0.07 | 1.14 (1 – 1.31) | 0.046 | 1.20 |
| AIC | | | | | 1273.40 |
| BIC | | | | | 1355.46 |
| AUC | | | | | 0.6119 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, PEEP: positive end-expiratory pressure, SE: standard error, VIF: variance inflation factor, VT: tidal volume.

**Table S6. Performance of a model predicting duration of MV>14 days considering clinically relevant variables (n=16) collected at 72 hours of diagnosis (T72) of 920 patients with moderate/severe ARDS using logistic regression analysis.** $PaO_2$, $FiO_2$, driving pressure, and SOFA (sequential organ failure assessment) score are not included due to multicollinearity (see text for details). Data are expressed as mean values of logistic coefficients.

| Variables | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -34.07 | 8.1 | 0 (0 - 0) | <0.001 | |
| Age | 0.01 | 0 | 1.01 (1 – 1.02) | 0.071 | 1.16 |
| Sex (male) | 0.38 | 0.15 | 1.46 (1.09 – 1.97) | 0.012 | 1.05 |
| Cardiac disease | -0.52 | 0.28 | 0.59 (0.34 – 1.03) | 0.066 | 1.07 |
| Diabetes | 0.01 | 0.2 | 1.01 (0.68 – 1.51) | 0.948 | 1.07 |
| Immunosuppressed | 0.39 | 0.24 | 1.48 (0.92 – 2.4) | 0.109 | 1.08 |
| Obesity | 0.32 | 0.25 | 1.38 (0.85 – 2.26) | 0.198 | 1.08 |
| Liver disease | -0.22 | 0.31 | 0.8 (0.43 – 1.47) | 0.475 | 1.06 |
| Neoplastic disease | 0 | 01.8 | 1 (0.69 – 1.44) | 0.996 | 1.10 |
| VT | 0.1 | 0.07 | 1.1 (0.96 – 1.27) | 0.168 | 1.19 |
| Respiratory rate | 0.03 | 0.01 | 1.03 (1 – 1.06) | 0.036 | 1.21 |
| PEEP | 0.05 | 0.02 | 1.05 (1.01 – 1.1) | 0.029 | 1.28 |
| Plateau pressure | 0.01 | 0.02 | 1.01 (0.98 – 1.05) | 0.410 | 1.33 |
| $PaO_2/FiO_2$ | 0 | 0 | 1 (0.99 – 1) | <0.001 | 1.17 |
| $PaCO_2$ | 0.03 | 0.01 | 1.03 (1.01 – 1.05) | 0.002 | 1.38 |
| pH | 4.06 | 1.07 | 57.81 (7.22 - 483.9) | <0.001 | 1.48 |
| No. extrapulmonary OF | 0.13 | 0.07 | 1.14 (1.01 – 1.3) | 0.040 | 1.23 |
| AIC | | | | | 1232.5 |
| BIC | | | | | 1314.47 |
| AUC | | | | | 0.6600 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, PEEP: positive end-expiratory pressure, SE: standard error, VIF: variance inflation factor, VT: tidal volume.

**Table S7. Performance of a model of predicting MV duration >14 days at the time of diagnosis (T0) of 920 patients with moderate/severe ARDS, using logistic regression analysis and minimizing the Akaike information criterion.** The model reduced the number of selected variables from 16 to 9.

| Variable | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -13.33 | 6.4 | 0 (0 – 0.42) | 0.037 | |
| Age | 0.01 | 0 | 1.01 (1 – 1.02) | 0.129 | 1.07 |
| Sex (male) | 0.3 | 0.15 | 1.36 (1.02 – 1.81) | 0.038 | 1.03 |
| Cardiac Disease | -0.53 | 0.27 | 0.59 (0.34 – 1) | 0.052 | 1.07 |
| Obesity | 0.39 | 0.24 | 1.48 (0.93 – 2.37) | 0.098 | 1.02 |
| Respiratory rate | 0.02 | 0.01 | 1.02 (0.99 – 1.05) | 0.056 | 1.05 |
| $PaO_2/FiO_2$ | 0 | 0 | 1 (0.99 – 1) | 0.023 | 1.03 |
| $PaCO_2$ | 0.01 | 0.01 | 1.01 (1 – 1.03) | 0.052 | 1.64 |
| pH | 1.61 | 0.84 | 5.01 (0.97 – 26.46) | 0.056 | 1.76 |
| No. extrapulmonary OF | 0.16 | 0.07 | 1.17 (1.03 – 1.34) | 0.018 | 1.1 |
| AIC | | | | | 1265.36 |
| BIC | | | | | 1313.61 |
| AUC | | | | | 0.6055 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, SE: standard error, VIF: variance inflation factor.

**Table S8. Performance of a model of predicting MV duration >14 days at 24 hours (T24) after the diagnosis of 920 patients with moderate/severe ARDS, using logistic regression analysis and minimizing the Akaike information criterion.** The model reduced the number of selected variables from 16 to 6.

| Variable | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -1.86 | 0.43 | 0.16 (0.07 – 0.36) | <0.001 | |
| Age | 0.01 | 0 | 1.01 (1 – 1.02) | 0.136 | 1.06 |
| Sex (male) | 0.27 | 0.15 | 1.31 (0.99 – 1.75 | 0.061 | 1.02 |
| Cardiac Disease | -0.48 | 0.27 | 0.62 (0.36 – 1.06) | 0.082 | 1.06 |
| Obesity | 0.42 | 0.24 | 1.53 (0.96 – 2.44) | 0.073 | 1.02 |
| $PaCO_2$ | 0.02 | 0.01 | 1.02 (1.01 – 1.04) | 0.002 | 1.01 |
| No. extrapulmonary OF | 014 | 0.06 | 1.15 (1.02 – 1.3) | 0.019 | 1.01 |
| AIC | | | | | 1260.70 |
| BIC | | | | | 1294.52 |
| AUC | | | | | 0.5974 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, SE: standard error, VIF: variance inflation factor.

**Table S9. Performance of a model of predicting MV duration >14 days at 72 hours (T72) after the diagnosis of 920 patients with moderate/severe ARDS, using logistic regression analysis and minimizing the Akaike information criterion.** The model reduced the number of selected variables from 16 to 11.

| Variable | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -33.36 | 8.13 | 0 (0 - 0) | <0.001 | |
| Age | 0.01 | 0 | 1.01 (1 – 1.02) | 0.071 | 1.10 |
| Sex (male) | 0.36 | 0.15 | 1.43 (1.07 – 1.92) | 0.018 | 1.04 |
| Cardiac disease | -0.5 | 0.28 | 0.60 (0.34 -1.04) | 0.074 | 1.07 |
| Immunosuppressed | 0.36 | 0.24 | 1.43 (0.9 – 2.29) | 0.135 | 1.04 |
| VT | 0.1 | 0.07 | 1.11 (0.96 – 1.27) | 0.152 | 1.19 |
| Respiratory rate | 0.03 | 0.01 | 1.03 (1.0 – 1.06) | 0.027 | 1.19 |
| PEEP | 0.06 | 0.02 | 1.07 (1.02 – 1.11) | 0.004 | 1.11 |
| $PaO_2/FiO_2$ | 0 | 0 | 1.0 (0.99 – 1.0) | <0.001 | 1.11 |
| $PaCO_2$ | 0.03 | 0.01 | 1.03 (1.01 – 1.05) | 0.001 | 1.36 |
| pH | 3.99 | 1.06 | 54.21 (6.88 – 446) | <0.001 | 1.46 |
| No. extrapulmonary OF | 0.12 | 0.06 | 1.13 (1.0 – 1.28) | 0.055 | 1.16 |
| AIC | | | | | 1225.30 |
| BIC | | | | | 1283.23 |
| AUC | | | | | 0.6582 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, PEEP: positive end-expiratory pressure, SE: standard error, VIF: variance inflation factor.

**Table S10. Performance of a model of predicting MV duration >14 days at 72 hours (T72) after the diagnosis of 920 patients with moderate/severe ARDS, using logistic regression analysis and minimizing the Bayesian information criterion (BIC).** The model reduced the number of variables from 16 to 4.

| Variable | b | SE | OR (95%CI) | p-value | VIF |
|---|---|---|---|---|---|
| Intercept | -21.64 | 7.36 | 0 (0 – 0) | 0.003 | |
| PEEP | 0.06 | 0.02 | 1.06 (1.02 – 1.11) | 0.004 | 1.07 |
| $PaO_2/FiO_2$ | 0 | 0 | 1 (0.99 – 1) | <0.001 | 1.10 |
| $PaCO_2$ | 0.03 | 0.01 | 1.03 (1.01 – 1.04) | 0.001 | 1.24 |
| pH | 2.75 | 0.98 | 15.59 (2.32 – 108.02) | 0.005 | 1.26 |
| AIC | | | | | 1232.50 |
| BIC | | | | | 1256.67 |
| AUC | | | | | 0.6313 |

ARDS: acute respiratory distress syndrome, AIC: Akaike information criterion, AUC: area under the receiver operating characteristic curve, b: beta, BIC: Bayesian information criterion, CI: confidence intervals, OF: organ failures, OR: odds ratio, PEEP: positive end-expiratory pressure, SE: standard error, VIF: variance inflation factor.

**Table S11. External validation of the 11 and 4-variable model at T72 in an independent cohort of 253 patients with moderate/severe ARDS.** NOTE: We used the 920-patient population as the training cohort and the new 253 patients as the testing cohort.

| Time | Methods | Model | AUC (95%CI) | Sensitivity | Specificity | Accuracy | PPV | NPV |
|------|---------|-------|-------------|-------------|-------------|----------|-----|-----|
| T72 | Multilayer Perceptron | 11-variable | 0.51 (0.44-0.58) | 0.41 | 0.58 | 0.51 | 0.39 | 0.60 |
| | Random Forest | 11-variable | 0.51 (0.44-0.58) | 0.38 | 0.61 | 0.52 | 0.39 | 0.60 |
| | Support Vector Machine | 11-variable | 0.45 (0.38-0.53) | 0.19 | 0.80 | 0.56 | 0.38 | 0.60 |
| | Logistic regression | 11-variable | 0.50 (0.42-0.57) | 0.63 | 0.44 | 0.52 | 0.43 | 0.65 |
| T72 | Multilayer Perceptron | 4-variable | 0.57 (0.50-0.64) | 0.21 | 0.82 | 0.58 | 0.43 | 0.61 |
| | Random Forest | 4-variable | 0.54 (0.46-0.61) | 0.45 | 0.59 | 0.54 | 0.42 | 0.62 |
| | Support Vector Machine | 4-variable | 0.56 (0.48-0.63) | 0.19 | 0.80 | 0.56 | 0.38 | 0.60 |
| | Logistic regression | 4-variable | 0.52 (0.44-0.59) | 0.48 | 0.59 | 0.55 | 0.44 | 0.64 |

*AUC: area under the receiver operating characteristic curve, CI: confidence intervals, NPV: negative predictive value, PPV: positive predictive value.*

**Figure S1. Time line for the early prediction model on duration of mechanical ventilation (MV) >14 days.** In many cases, the duration of MV finalized at the time of ICU death. The duration of MV was predicted using the data at the time of moderate/severe ARDS diagnosis, at 24 h, and at 72 hours later.
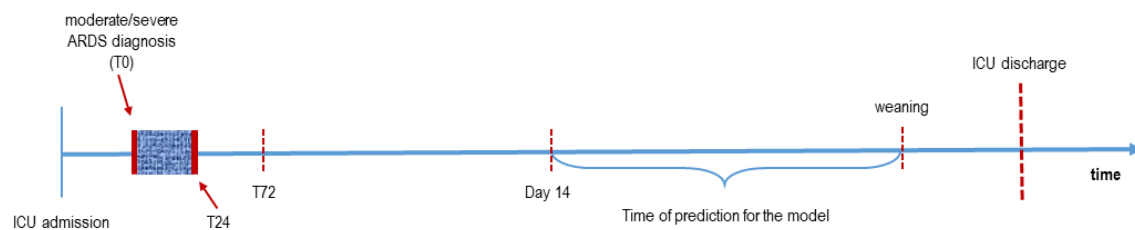
**Figure S2. Analysis flowchart.** *AIC: Akaike information criterion; ARDS: acute respiratory distress syndrome; BIC: Bayesian information criterion (see text for details).*
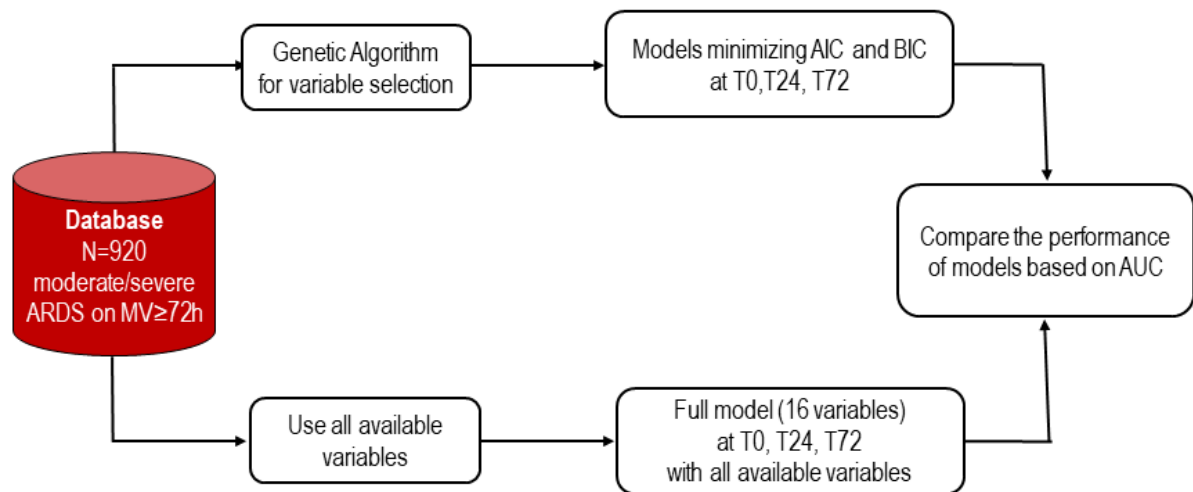
**Figure S3: Correlation matrices at T0, T24 and T72 of 12 variables associated with MV duration.**

Blue represents positive correlation, and red represents negative correlation. The area of the pie chart represents the specific value of correlation coefficients.
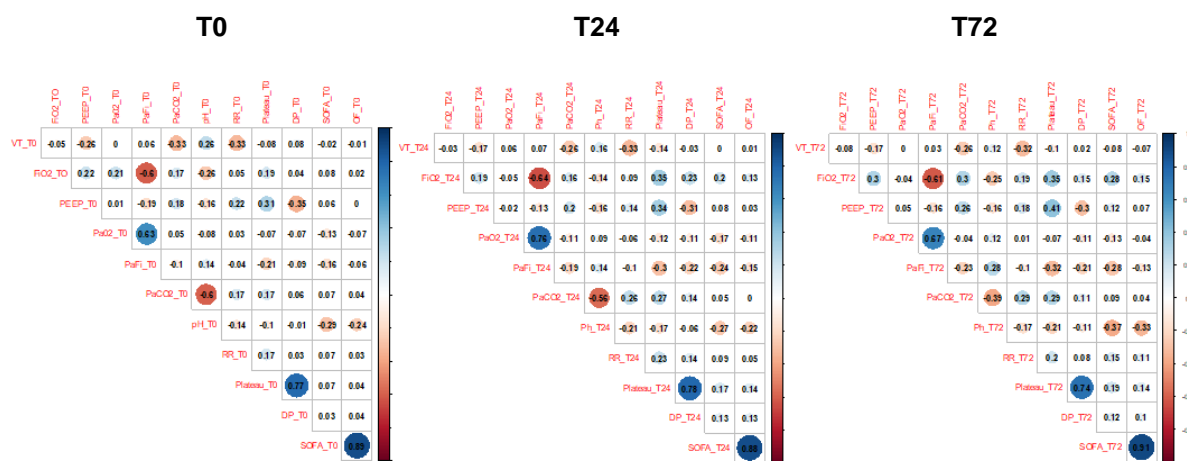
**Figure S4. Principal component analysis (PCA) of predictors of MV duration in ARDS patients**
(Cluster of patients on MV>14 days is marked in blue and cluster of patients on MV ≤14days in red).
Although there is overlapping between the clusters, the two clusters differed more at T72 (Dim1 + Dim2
= 43.7 + 21.8 = 65.5) than at any other study time.
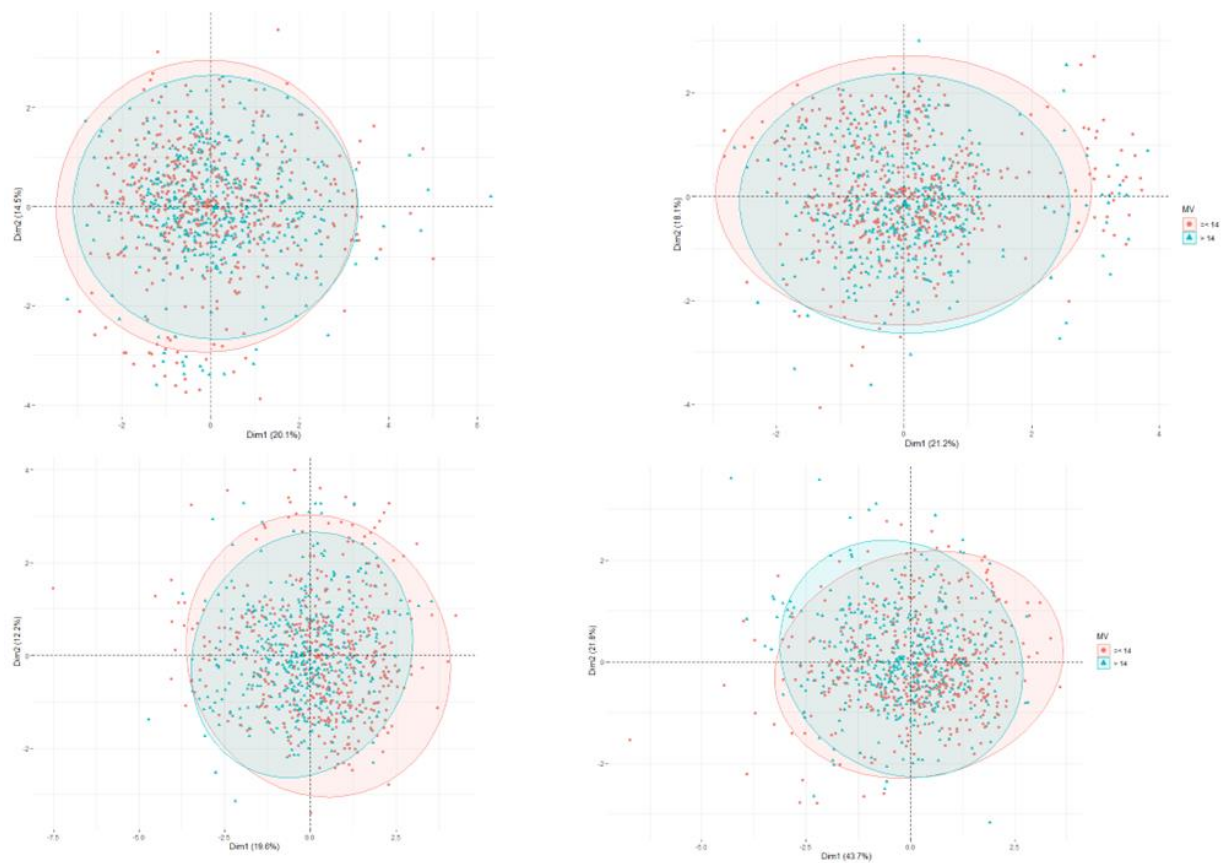
**Figure S5. Variable importance of variables at T0, T24 and T72 of 9, 6, 11 and 4 variable models for prediction of duration of MV>14 days in terms of mean decrease in Gini using Random Forest classification.** The mean decrease in GINI coefficient is a measure on how each variable contributes to the homogeneity in the resulting ML algorithm. The higher the value of mean decrease accuracy or mean decrease Gini score, the higher the importance of the variable in the model.
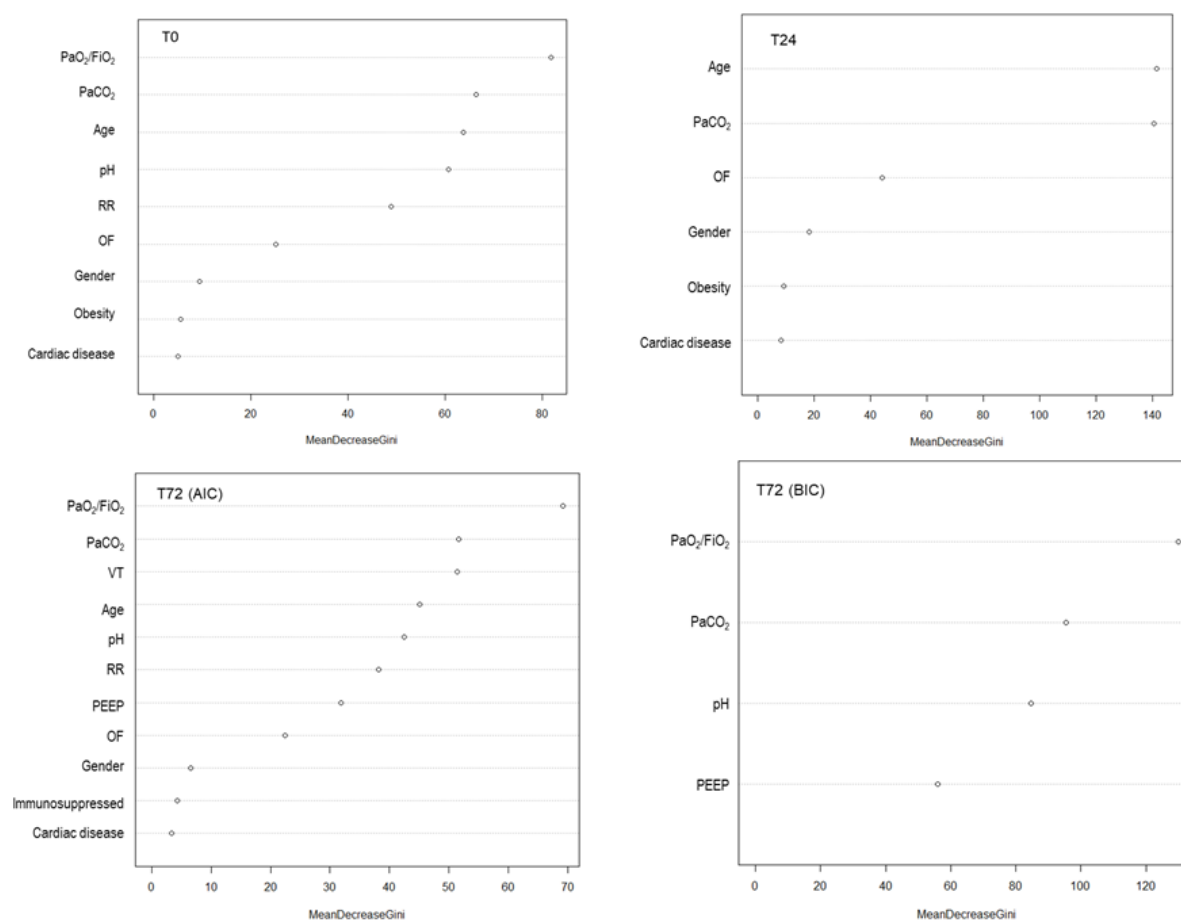
**Figure S6. Calibration plots of the Multilayer Perceptron-based (A,B), Random Forest-based (C,D), Support Vector Machine-based (E,F), and logistic regression-based (G,H) MV >14 days prediction model at T72 for the 11- and 4-variable model, respectively.** The intercept relates to calibration-in-the-large, which compares mean observed with mean predicted risks. The calibration slope reflects the coefficient of the calibration plot. The c-statistic indicates the discriminative ability.
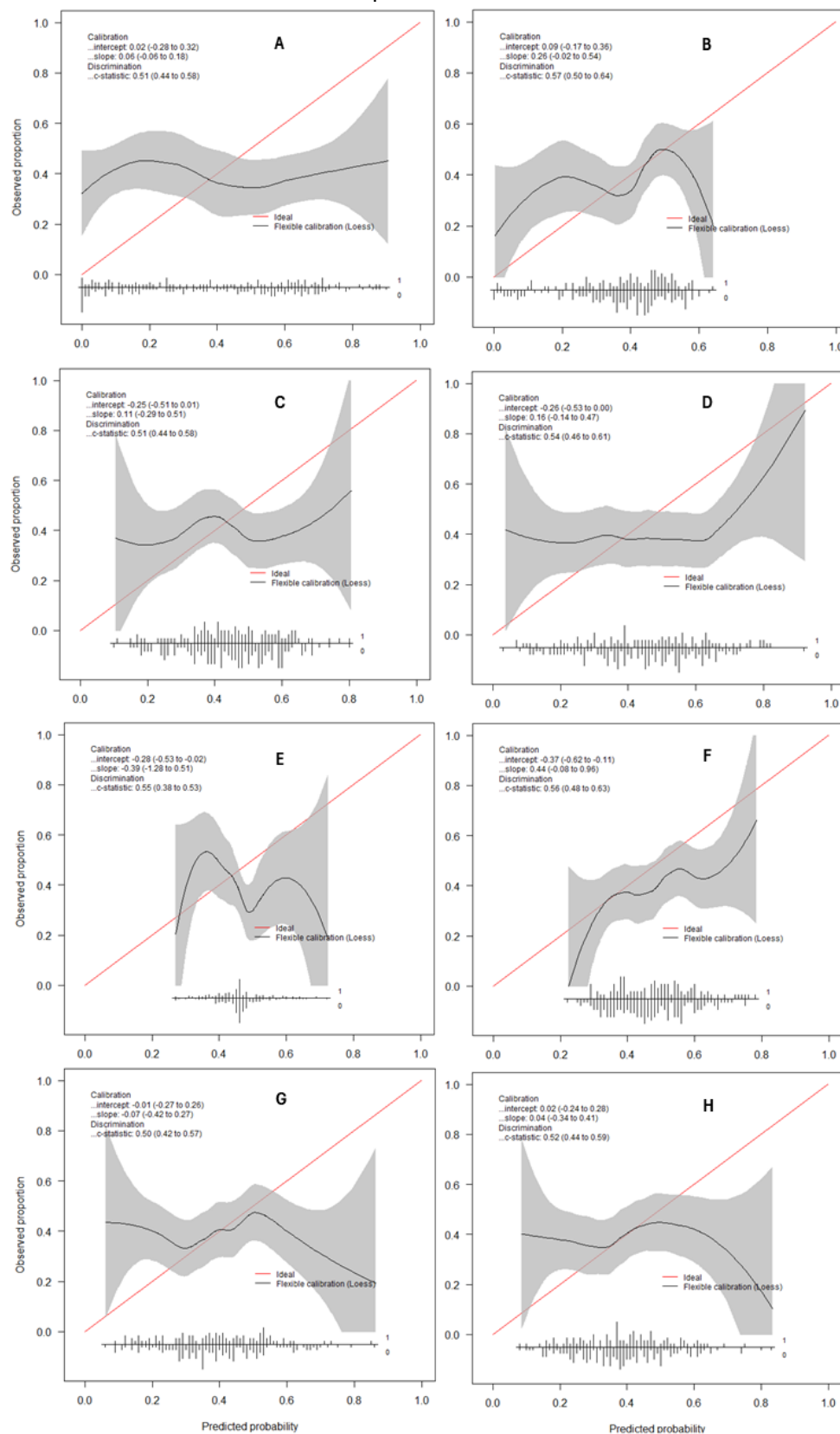
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