



Article

Early Prediction of ICU Mortality in Patients with Acute Hypoxemic Respiratory Failure Using Machine Learning: The MEMORIAL Study

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Abstract: Background: Early prediction of ICU death in acute hypoxemic respiratory failure (AHRF) could inform clinicians for targeting therapies to reduce harm and increase survival. We sought to determine clinical modifiable and non-modifiable features during the first 24 h of AHRF associated with ICU death. **Methods:** This is a development, testing, and validation study using data from a prospective, multicenter, nation-based, observational

cohort of 1241 patients with AHRF (defined as $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg on mechanical ventilation [MV] with positive end-expiratory pressure [PEEP] ≥ 5 cmH₂O and $\text{FiO}_2 \geq 0.3$) from any etiology. Using relevant features captured at AHRF diagnosis and within 24 h, we developed a logistic regression model following variable selection by genetic algorithm and machine learning (ML) approaches. **Results:** We analyzed 1193 patients, after excluding 48 patients with no data at 24 h after AHRF diagnosis. Using repeated random sampling, we selected 75% ($n = 900$) for model development and testing, and 25% ($n = 293$) for final validation. Risk modeling identified six major predictors of ICU death, including patient's age, and values at 24 h of PEEP, FiO_2 , plateau pressure, tidal volume, and number of extrapulmonary organ failures. Performance with ML methods was similar to logistic regression and achieved a high area under the receiver operating characteristic curve (AUROC) of 0.88, 95%CI 0.86–0.90. Validation confirmed adequate model performance (AUROC 0.83, 95%CI 0.78–0.88). **Conclusions:** ML and traditional methods led to an encouraging model to predict ICU death in ventilated AHRF as early as 24 h after diagnosis. More research is needed to identify modifiable factors to prevent ICU deaths.

Keywords: acute hypoxemic respiratory failure; ICU mortality; clinical trials; lung-protective ventilation; machine learning; mortality prediction; observational studies

1. Introduction

Acute hypoxemic respiratory failure (AHRF), as defined by $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg on positive end-expiratory pressure (PEEP) ≥ 5 cmH₂O and $\text{FiO}_2 \geq 0.3$ under mechanical ventilation (MV), is a frequent and heterogeneous clinical syndrome in the intensive care unit (ICU) with a reported mortality ranging between 35% and 55% [1–6]. There is a wide variability in the definition and description of the baseline characteristics of this syndrome [1,5–7]. With a wide range of etiologies and manifestations (coma, acute heart failure, stroke, sepsis, pneumonia, trauma, etc.), it usually requires endotracheal intubation and MV. It is estimated that worldwide, 1 million patients develop AHRF every year [8]. Conversely, hypoxemia is common in patients on MV, although there is conflicting information regarding prevalence and outcome [1–9].

ICU patients have a broad range of baseline clinical characteristics that will progress for benefit or harm, despite the implementation of best management guidelines [10,11]. In general, critical care physicians have a limited ability to predict the death of AHRF patients in ICU very early, despite existing prediction models combining multiple variables driving prognosis [12,13]. Commonly used general risk prediction scores such as SAPS-II and APACHE-2 have shown to be unreliable [14]. A more accurate and clinically relevant estimation for assessment of ICU outcome might be beneficial for targeting therapeutic interventions in AHRF patients to avoid iatrogenic harm and to enhance organ dysfunction recovery. AHRF outcome is usually influenced by a wide spectrum of clinical features dependent and independent of pulmonary function [1,2,10,11,15,16]. Identifying modifiable clinical variables that could be associated with death in ICU within 24 h of therapy could suggest treatment alternatives to increase survival. The modern use of machine learning (ML), a healthcare innovation that identifies a recognizable problem with a likely solvable solution, could capture a complex interaction among variables [17,18] associated with AHRF outcome.

Few studies have investigated the prediction of ICU mortality in AHRF in the era of lung-protective MV. Predicting AHRF outcome could inform clinicians' decision making by targeting specific therapeutic interventions to facilitate organ recovery, reduce harm,

and decrease mortality. Therefore, in this study we aimed to assess the value of machine learning approaches in the development of a multivariable model for an early prediction of ICU death in patients with AHRF.

2. Methods

This is a secondary analysis of an observational, non-interventional, multicenter study, approved by the Ethics Committees of Hospital Universitario Dr. Negrín (Las Palmas de Gran Canaria, Spain, #2021-321-1), with preexisting ethical approval/exemptions allowing retrospective analysis [1]. The need for informed consent was waived based on Spanish legislation for biomedical research, due to the retrospective nature of analysis, anonymization/dissociation of data, and no potential harm or benefit to patients (Supplemental File). The study was conducted following the principles for medical research of the Declaration of Helsinki [19] and the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines for prediction models [20].

We used a large dataset of AHRF patients representing the full diversity of AHRF patients seen in ICUs and treated with lung-protective MV [1]. We excluded patients who died or were extubated during the first day of AHRF diagnosis. All our patients were treated from admission into ICU. For prediction of ICU death, we followed three steps: (i) a methodology to report the model's prediction, (ii) to present the performance of the prediction, and (iii) to explain the model's reasoning.

2.1. Sites, Patient Populations and Study Design

We performed a comprehensive secondary analysis, termed the MEMORIAL (Machine learning Model to predict ICU Outcome in patients with acute hypoxemic Respiratory fAiLure) Study, of an unrestricted dataset derived from 1241 adult (≥ 18 years) patients with AHRF [1] from any etiology, treated with lung-protective MV, conducted at 22 ICUs from 14 geographical areas of Spain, and enrolled during three periods covering several seasons (Supplemental File). Based on previous work [21], we focused our analysis on variables collected within the first 24 h of AHRF diagnosis to estimate early probability of ICU death, independent of any underlying disease or cause of death (Figure S1). We analyzed a total of 1193 patients (Tables 1 and S1), after excluding 48 patients with no data at 24 h. Patients were excluded if they were extubated or died during the first day of AHRF diagnosis (Table S2). The unit of observation was having data collected at AHRF diagnosis (T0) and at 24 h (T24) (Tables 1, S1 and S2).

We used harmonized data from 22 hospitals across Spain (Supplemental File). We used variables (Tables S3 and S4) including demographics, comorbidities, cause of AHRF (or reason for MV), acute physiology and chronic health evaluation II (APACHE II) score [22] during the first 24 h of AHRF diagnosis, and data from ventilator settings and lung mechanics [tidal volume (VT), respiratory rate (RR), positive end-expiratory pressure (PEEP), plateau pressure (Pplat)], and gas exchange [(PaO₂, PaCO₂, FiO₂, PaO₂/FiO₂, pH)] at T0 and T24. We recorded the sequential organ failure assessment (SOFA) score [23] and occurrence of extrapulmonary organ system failures (OFs) included in the SOFA scale at diagnosis of AHRF and 24 h later. Sepsis was defined by Sepsis-3 criteria [24]. We recorded the date and status (alive or dead) of patients at ICU and hospital discharge. Primary outcome was all-cause ICU mortality (defined as death while admitted into ICU).

Table 1. Baseline characteristics and outcome data of 1241 ventilated patients with acute hypoxemic respiratory failure (AHRF) and 1193 patients with data at 24 h after AHRF diagnosis.

Variables	N = 1241 T0	N = 1193 T0	p-Value
Age, years, median (IQR)	65 (54–74)	65 (54–74)	
Age, years, mean ± SD	62.8 ± 14.3	62.7 ± 14.4	0.864
Sex	n (%: 95%CI)	n (%:95%CI)	
Male	834 (67.2: 64.6 to 69.8)	806 (67.6: 64.9 to 70.2)	0.888
Female	407 (32.8: 30.2 to 35.4)	387 (32.4: 29.8 to 35.1)	0.888
Etiology (reasons for invasive MV), n (%: 95%CI)			
Post-surgery	208 (16.8: 14.7 to 18.8)	190 (15.9: 13.9 to 18.0)	0.617
Stroke or coma	191 (15.4: 13.4 to 17.4)	189 (15.8: 13.8 to 17.9)	0.806
Pneumonia	169 (13.6: 11.7 to 15.5)	167 (14.0: 12.0 to 16.0)	0.823
Sepsis/Acute pancreatitis	152 (12.3;10.4 to 14.1)	146 (12.2: 10.4 to 14.1)	1
Trauma	151 (12.2: 10.4 to 14.0)	150 (12.6: 10.7 to 14.5)	0.806
Cardiac arrest	117 (9.4: 7.8 to 11.1)	108 (9.1: 7.4 to 10.7)	0.807
Cardiac failure/fluid overload	62 (5.0: 3.8 to 6.2)	59 (5.0: 3.7 to 6.2)	1
Aspiration/Inhalation	49 (4.0: 2.9 to 5.0)	47 (3.9: 2.8 to 5.0)	0.920
Others	137 (11.0: 9.3 to 12.8)	132(11.1: 9.3 to 12.8)	1
Unknown etiology	5 (0.4: 0 to 0.1)	5 (0.4: 0.0 to 0.1)	1
APACHE II score, mean ± SD	21.0 ± 8.0 [§]	21.0 ± 7.8 [§]	1.0
SOFA score, mean ± SD	8.95 ± 3.47	8.94 ± 3.39	0.943
FiO ₂ , mean ± SD	0.63 ± 0.22	0.63 ± 0.21	1.0
PaO ₂ , mmHg, mean ± SD	98.9 ± 34.6	98.8 ± 34.4	0.943
PaO ₂ /FiO ₂ , mmHg, mean ± SD	170.5 ± 64.1	170.9 ± 64.0	0.878
PaCO ₂ , mmHg, mean ± SD	46.1 ± 12.4	45.9 ± 12.0	0.686
pH, mean ± SD	7.32 ± 0.11	7.32 ± 0.11	1.0
VT, mL/kg PBW, mean ± SD	6.88 ± 1.07	6.89 ± 1.06	0.817
Respiratory rate, ventilator cycles/min, mean ± SD	19.7 ± 4.4	19.7 ± 4.4	1.0
Minute ventilation, L/min, mean ± SD	8.6 ± 2.1	8.6 ± 2.1	1.0
PEEP, cmH ₂ O, mean ± SD	7.8 ± 2.8	7.8 ± 2.8	1.0
Plateau pressure, cmH ₂ O, mean ± SD	22.3 ± 5.5	22.3 ± 5.4	1.0
Driving pressure, cmH ₂ O, mean ± SD	14.5 ± 4.9	14.4 ± 4.8	0.611
No. extrapulmonary OFs, mean ± SD	1.72 ± 1.05	1.71 ± 1.03	0.813
Length of ICU stay, d, median (IQR)	10 (4–21)	11 (5–21)	0.449
Days from last day MV to ICU discharge, median (IQR)	2 (0–5)	2 (0–5)	0.734
All-cause ICU mortality, n (%: 95%CI)	438 (35.3: 32.6 to 38.0)	416 (34.9: 32.2 to 37.7)	0.862
All-cause hospital mortality, n (%: 95%CI)	514 (41.4: 38.7 to 44.2)	489 (41.0: 38.2 to 43.8)	0.862

APACHE: acute physiology and chronic health evaluation; AHRF: acute hypoxemic respiratory failure; CI: confidence intervals; d: days; FiO₂: fraction of inspired oxygen concentration; ICU: intensive care unit; IQR: interquartile range; MV: mechanical ventilation; OF: organ failure; PBW: predicted body weight; PEEP: positive end-expiratory pressure; SD: standard deviation; SOFA: sequential organ failure assessment scale; T0: at AHRF diagnosis; VT: tidal volume. [§] APACHE II was not reported at baseline in 40 patients from the entire 1241 cohort, and in 39 from the 1193 patients.

2.2. Predefined Rules, Variable Selection, and Statistical Analysis

The study was conducted in three steps (Figure S2). For the first step (model training and testing) and third step (validation) we used random sampling for selecting 75.4% (n = 900) and 24.6% (n = 293), respectively (Supplemental File). We searched in the data

for model specification since the model was not pre-specified. Once risk features were identified by univariate logistic regression analysis (Table S5), we performed a multivariable logistic regression analysis. In the second step, and since prediction models often perform poorly when assessed in validation studies, we performed internal–external validation by leaving out patients enrolled in each of the three periods (phases) once [1,25,26]. The strength for assessing internal–external validation increases when studies include patients from different hospitals, as in our patient population. We revalidated the model by testing it on 293 unseen patients.

Although we collected 246 variables in each patient during their ICU stay, variable selection has vital importance in developing an actionable and interpretable prediction model in clinical practice. Our goal for variable selection was to include clinically relevant features, avoiding redundant variables. We analyzed the following variables as potential predictors of ICU death: age at ICU admission, gender, comorbidities (only those with a prevalence $\geq 5\%$) (Tables S3 and S4), number of extrapulmonary OFs, SOFA score, PaO₂, PaO₂/FiO₂, FiO₂, PaCO₂, pH, VT, RR, PEEP, Pplat, driving pressure (calculated as Pplat minus PEEP), and minute ventilation at T0 and T24 (Tables S6 and S7). No information on medication or special procedures was used in our prediction model. We defined and specified the statistical analysis plan before the final statistical analyses were conducted (Supplemental File).

We first performed descriptive statistical analyses. We performed a univariate analysis to predict ICU outcome and identified variables that could be included in the potential prediction model based on predefined rules and area under the receiver operating characteristic curves (AUCROC). Because the inclusion of all available variables in ML can lead to complex models, we screened the collected variables using a genetic algorithm (GA) variable selection method [27] to achieve parsimony with a small subset of variables while excluding redundant variables [28]. We applied GA to optimize the selected variables by minimizing the Akaike and the Bayesian information criteria (AIC, BIC) [29]. We report the variance inflation factor as a measure of multicollinearity in regression logistic analysis. A two-sided *p*-value < 0.005 was considered for identification of prognostic variables to keep the false discovery rate below 5% [30].

We constructed the MEMORIAL prediction model by considering the minimum number of features selected by GA that provided a similar performance as an all-variables prediction model. We used a five-fold cross-validation to randomly split the 900-patient cohort into 720 patients for training and 180 for testing (see Supplemental File). We evaluated this minimum number features model using logistic regression and three supervised ML methods: multilayer perceptron (MLP), random forest (RF), and support vector machine (SVM) [31,32] (Supplement File), to assess the performance using AUROC of each ML. Calculations were conducted using R Core Team software 2024 (R version 4.4.2 (<https://www.r-project.org>) (R Foundation for Statistical Computing, Vienna, Austria). We assessed calibration and discrimination in a validation cohort of 293 unseen random patients for validation [33,34] (Supplemental File).

Figures 1 and S2 summarize the study design.

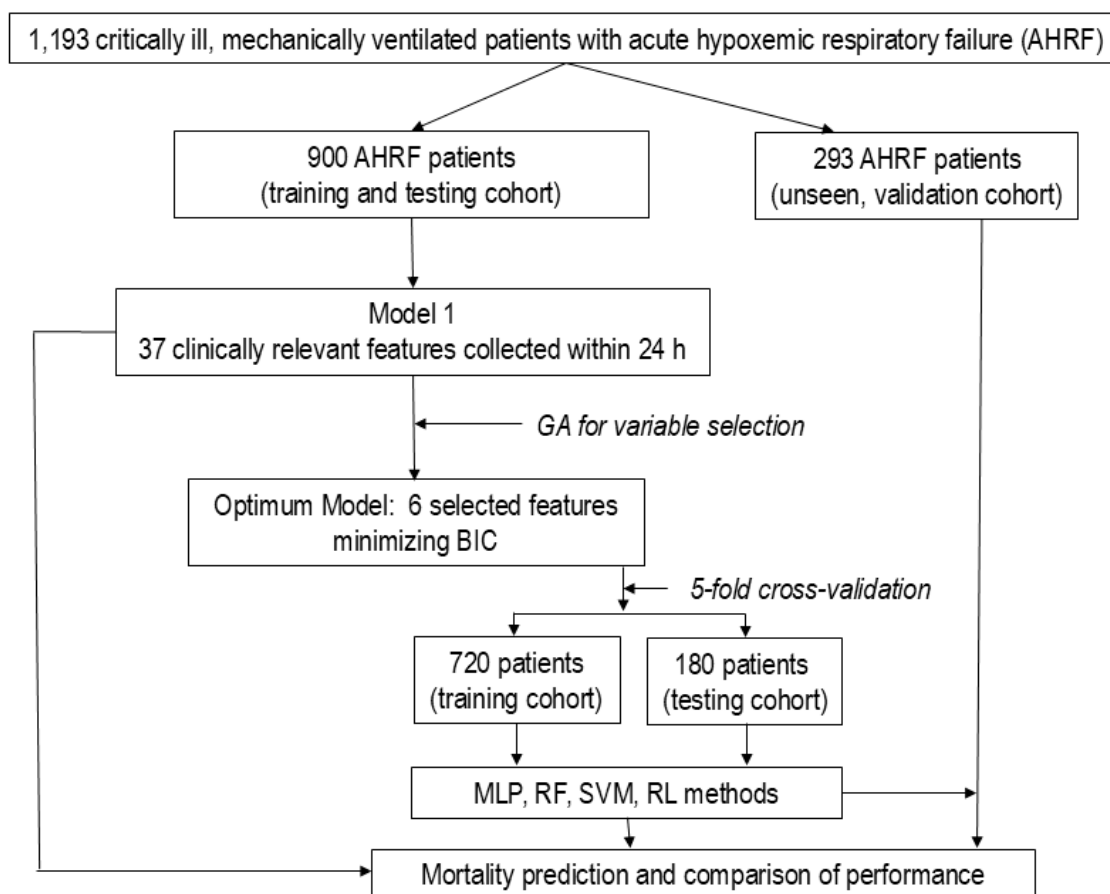


Figure 1. Diagram representing the study design. The flowchart illustrates the scheme for the database of 1193 patients with acute hypoxemic respiratory failure (AHRF), selection of variables for final analysis, machine learning approaches, and comparisons among prediction models. Once the most relevant variables were selected by a genetic algorithm (GA) in the dataset of 900 patients, this dataset was divided into five folders to perform five-fold randomized cross-validation, repeated 100 times using machine learning. AIC: Akaike information criterion, BIB: Bayesian information criterion, MLP: multilayer perceptron, RF: random forest, RL: logistic regression; SVM: support vector machine.

3. Results

After removing 48 patients with no data at 24 h (Table S2), we included 1193 patients in our analysis (Table 1). ICU mortality was 35% ($n = 416$), with no differences in mortality ($p = 0.686$) among the parent ($n = 1241$), study ($n = 1193$), training/testing ($n = 900$), and validation cohorts ($n = 293$), respectively (Tables 1 and 2). We observed a broad range of changes between values at baseline and after 24 h of routine ICU management. No patients were discharged and subsequently readmitted to the ICU during the study period. The median age at the time of AHRF was 65 years, with fewer women (32.4%) than men (67.6%). The patients' race was not available in our datasets.

Only comorbidities with a >5% prevalence were considered in the model (Tables S3 and S4). In the univariate analysis, 16 variables had a prognostic relation with ICU death and 12 variables had an AUROC ≥ 0.60 (Table S5). In the multivariable logistic regression analysis, fewer features became predictors of ICU death (Tables S6–S10). The performance of the model with 37 variables had an AUCROC of 0.89 (95%CI 0.88–0.91), but most variables were correlated (Figures S3 and S4). After applying GA for variable selection using optimization of BIC, the AUCROC with six variables was 0.88 (95%CI 0.86–0.90) (Table 3) without strong multicollinearity (Table S10). Those six variables with

strong relation to ICU death were age and values at T24 of PEEP, Pplat, FiO₂, number of extrapulmonary OFs, and VT (Figure S5). The order of importance of those variables was: PEEP at T24, Pplat at T24, patient's age at ICU admission, FiO₂ at T24, number of extrapulmonary OFs at T24, and VT at T24. Of note, PEEP and VT at T24 had an OR < 1 and, therefore, were protective (greater values associated with lower mortality). A sensitivity analysis sustained these findings (Table S11). A data-driven stratification based on thresholds for those variables had a distinctive ICU mortality, mostly at T24.

Table 2. Baseline and outcome data of 1193 ventilated patients with acute hypoxemic respiratory failure, randomly sampled into training/testing cohort (n = 900) and validation cohort (n = 293).

Variables	N = 900 T0	N = 293 T0	p-Value
Age, years, median (IQR)	65 (54–74)	65 (55–74)	
Age, years, mean ± SD	62.5 ± 14.5	63.2 ± 13.9	0.469
Sex	n (%: 95%CI)	n (%:95%CI)	
Male	607 (67.4: 64.4 to 70.5)	199 (67.9: 62.6 to 73.3)	0.920
Female	293 (32.6: 29.5 to 35.6)	94 (32.1: 26.7 to 37.4)	0.920
Etiology (reasons for invasive MV), n (%: 95%CI)			
Post-surgery	136 (15.1: 12.8 to 17.5)	54 (18.4: 14.0 to 22.9)	0.209
Stroke or coma	140 (15.6: 13.2 to 17.9)	49 (16.7: 12.5 to 21.0)	0.699
Pneumonia	133 (14.8: 12.5 to 17.1)	34 (11.6: 7.9 to 15.3)	0.206
Sepsis/Acute pancreatitis	113 (12.6: 10.4 to 14.7)	33 (11.3: 7.6 to 14.9)	0.632
Trauma	114 (12.7: 10.4 to 14.0)	36 (12.3: 8.5 to 16.1)	1.0
Cardiac arrest	79 (8.8: 6.9 to 10.6)	29 (9.9: 6.5 to 13.3)	0.647
Cardiac failure/fluid overload	44 (4.9: 3.5 to 6.3)	15 (5.1: 2.6 to 7.6)	1.0
Aspiration/Inhalation	37 (4.1: 2.8 to 5.4)	10 (3.4: 1.3 to 5.5)	0.718
Others	99 (11.0: 9.0 to 13.0)	33 (11.3: 7.6 to 14.9)	1.0
Unknown etiology	5 (0.6: 0 to 1)	0 (0: 0 to 0)	-
APACHE II score, mean ± SD	20.9 ± 7.9 [§]	21.2 ± 7.7 [§]	0.570
SOFA score, mean ± SD	8.9 ± 3.3	9.0 ± 3.5	0.657
FiO ₂ , mean ± SD	0.63 ± 0.22	0.62 ± 0.21	0.495
PaO ₂ , mmHg, mean ± SD	99.3 ± 35.6	97.5 ± 30.7	0.438
PaO ₂ /FiO ₂ , mmHg, mean ± SD	170.9 ± 63.8	170.8 ± 64.4	0.982
PaCO ₂ , mmHg, mean ± SD	45.7 ± 12.0	46.7 ± 12.1	0.217
pH, mean ± SD	7.32 ± 0.11	7.31 ± 0.11	0.177
VT, mL/kg PBW, mean ± SD	6.9 ± 1.0	6.8 ± 1.1	0.147
Respiratory rate, ventilator cycles/min, mean ± SD	20 ± 4	20 ± 5	1.0
Minute ventilation, L/min, mean ± SD	8.6 ± 2.1	8.7 ± 2.1	0.479
PEEP, cmH ₂ O, mean ± SD	8 ± 3	8 ± 3	1.0
Plateau pressure, cmH ₂ O, mean ± SD	22 ± 5	22 ± 5	1.0
Driving pressure, cmH ₂ O, mean ± SD	14 ± 5	14 ± 5	1.0
No. extrapulmonary OFs, mean ± SD	1.7 ± 1.0	1.8 ± 1.0	0.137
Length of ICU stay, d, median (IQR)	10 (7.22–21)	12 (5–21)	0.944
Days from last day MV to ICU discharge, median (IQR)	2 (0–5)	2 (0–6)	0.825
All-cause ICU mortality, n (%: 95%CI)	312 (34.7: 31.6 to 37.8)	104 (35.5: 30.0 to 41.0)	0.841
All-cause hospital mortality, n (%: 95%CI)	369 (41.0: 37.8 to 44.2)	120 (41.0: 35.3 to 46.6)	1.0

APACHE: acute physiology and chronic health evaluation; CI: confidence intervals; d: days; FiO₂: fraction of inspired oxygen concentration; ICU: intensive care unit; IQR: interquartile range; MV: mechanical ventilation; OF: organ failure; PBW: predicted body weight; PEEP: positive end-expiratory pressure; SD: standard deviation; SOFA: sequential organ failure assessment scale; VT: tidal volume. [§] APACHE II was not reported at baseline in 30 patients from the entire 900 cohort, and in 9 from the 293 patients.

Table 3. Performance of a parsimonious model for predicting ICU mortality (6-variable model) within 24 h of diagnosis of AHRF using the genetic algorithm variable selection method, logistic regression analysis, and minimizing the Bayesian information criterion (BIC) in 900 patients. This model reduced the number of variables from 37 to 6. Data are expressed as mean values of logistic coefficients.

Variable	b	SE	OR	95% CI	p-Value
Intercept	−8.19	0.98	0	0–0	<0.001
Age	0.05	0.01	1.05	1.04–1.07	<0.001
VT at T24	−0.25	0.09	0.78	0.64–0.93	0.007
FiO ₂ at T24	1.78	0.64	5.92	1.71–20.79	0.005
PEEP at T24	−0.24	0.04	0.79	0.73–0.85	<0.001
Plateau pressure at T24	0.26	0.02	1.29	1.24–1.35	<0.001
No. extrapulmonary OFs at T24	0.87	0.1	2.38	1.97–2.89	<0.001
AIC	741.88				
BIC	775.4986				
AUC ROC	0.881 (0.860–0.903)				

AHRF: acute hypoxemic respiratory failure, AIC: Akaike information criterion, AUC ROC: area under the receiving operating characteristic curve, BIC: Bayesian information criterion, CI: confidence intervals, OF: extrapulmonary organ failures included in the sequential organ failure assessment scale, OR: odds ratio, SE: standard error, T24: at 24 h of diagnosis of AHRF, VT: tidal volume.

Before implementing the ML model, we checked that patients and ICU deaths were similarly distributed in the three phases of the study (Tables S12–S14). Internal validation of the 6-variable model provided a high performance (AUCROC 0.88, 95%CI 0.84–0.93), using MLP or conventional logistic regression (Table S15). Internal–external validation by leaving each of the three phases out once provided an average AUCROC of 0.88 (95%CI 0.85–0.93) by MLP and 0.87 (95%CI 0.85–0.92) by logistic regression (Table S16). The validation cohort, using as few as 293 unseen patients, demonstrated a good performance of the model (AUCROC 0.83, 95%CI 0.78–0.88) (Table S17). Calibration and discrimination suggested good reliability of predictions, with logistic regression being as good as multiplayer perceptron ML (Figure S6).

4. Discussion

The main findings of this study are that prediction models of ICU mortality among patients with AHRF provided adequate performance whether developed by ML techniques or conventional regression analysis. Six clinical features (patient’s age, and values at T24 of PEEP, Pplat, FiO₂, number of extrapulmonary OFs, and VT) contained the most prognostic information on ICU death within the first 24 h after diagnosis of AHRF. At the time that the epidemiological study was designed [1], the focus of lung-protective MV was to target VT, although recent data suggest that targeting driving pressure or mechanical power could be more effective in ventilated patients [35,36]. In our study, most patients with AHRF were ventilated according to the ARDS network and international societies’ criteria [37,38], whereas most patients in other studies did not receive proven or recommended approaches to lung-protective MV [2,9]. Clinical determinants of ICU death in AHRF are multifactorial. Apart from patient age, the rest of the five variables that were used to predict ICU mortality changed over 24 h with routine ICU management and treatment for each specific condition, although it is unknown whether combining precision medicine modalities for each predictor is synergistic. We are unaware of any complex interactions between the variables and treatment [11]. Even when complex interactions and treatment are identified among subgroups, a prediction model may unravel heterogeneity in treatment responses [10].

Previous observational studies in patients with acute respiratory failure had large variability in the definitions and description of baseline features, and had a lack of clinically relevant information on management and complications [2–4,7,39–44]. In our study, baseline characteristics were useless for predicting ICU outcome, and $\text{PaO}_2/\text{FiO}_2$ did not stratify patients by risk of death at baseline, but it worked at 24 h of AHRF diagnosis, independent of the use of Berlin criteria [45] or the 150-mmHg threshold [46]. Other studies have required the presence of parenchymal abnormalities, whereas our study did not mandate radiographic findings for diagnosis of AHRF. On the other hand, much of the information on differences in staffing, expertise, and practice surrounding managing AHRF with MV at individual hospitals may not be captured in the available clinical data [16]. Although there are a broad range of features that may modify the risk of ICU death, little is known about the true drivers of heterogeneity in treatment effects in AHRF (including patients and relative preferences, hospital load, and organization) [14,16]. We recognize that clinicians are often mostly interested in actionable and modifiable variables for improving expected outcomes [10].

Little is known about how many hospitals may actually be needed for robust training. Multicenter training allows the model to see more data and a more varied pattern of care, which may improve generalizability [47]. As data from more hospitals become available for training, models may become increasingly generalizable. Training and testing on data from several hospitals likely performs better compared with data trained only at a single hospital [48]. On the other hand, our sensitivity analysis assessed the robustness of our ML findings. We acknowledge that fundamental differences between hospitals or healthcare systems may affect the models' ability to generalize to a given dataset, but we believe that our data adequately represent the range of clinical context encountered in ventilated AHRF patients. Changing a treating hospital may not always be an actionable intervention, although detailing current MV guidelines represents an important initial step for conducting further studies.

Based on our sensitivity analysis, it seems that most of the prognostic information in the first 24 h for predicting ICU death was due to the greatest changes occurring with adjustments of acute physiology, as suggested before [16]. One predictor is static (patient age) and the other five variables are modifiable, time-varying, from T0 (diagnosis of AHRF) to T24: applying PEEP, inspiratory Pplat, level of FiO_2 , treating extrapulmonary organ failure, and setting appropriate VT. It has been known that ICU outcome is worse with higher age [49], patients with severe hypoxemia requiring higher FiO_2 , and PEEP [13,46]. There is a direct relationship between Pplat and mortality [50], and the greater the number of extrapulmonary OFs, the higher the mortality [51]. To date, the best strategies to achieve improvement in AHRF have not been elucidated and should be subject to further research. Of note, PEEP at T24 and VT at T24 had an OR < 1 and, therefore, were protective (greater values were associated with lower mortality in AHRF). Predictors of ICU death were most relevant if collected close to 24 h, suggesting that ventilator, gas-exchange, and organ failure parameters at baseline are unhelpful for predicting outcome at the time of diagnosis of AHRF. We have previously shown that restricting AHRF severity to the hypoxemia level at baseline could lead to discrepancies in outcome prediction since hypoxemia is impacted by clinician-set ventilatory strategies [46].

The strengths of our study include the broad inclusion and limited exclusion criteria. Hence, our dataset represents the full diversity of AHRF patients seen in critical care units in most ICUs in the developed world. Second, the model identified six simple variables predicting ICU death that are routinely recorded and collected at the bedside of AHRF ventilated patients. Also, in our analysis, we were able to identify different subpopulations of AHRF patients with distinct mortality. Although one variable was static (patient age),

the others changed with time, and contributed to high accuracy. Third, despite a similar protocol for this study, working very differently at participating hospitals, we assessed multicenter training and validation in the three phases and in the unseen cohort using tests across resampling folds. Fourth, we identified common variables that ICU clinicians have used in the management of AHRF across the world. Fifth, we think that a major finding of this study is that baseline features did not explain the individual's likelihood of ICU outcome, suggesting that, in general, ICU treatment influences the potential outcome of AHRF patients.

We also acknowledge that this study has some limitations. First, the model does not include any information on medication, special procedures, or the socioeconomic status of patient population. Second, the model does not include information of staffing, hospital quality level, and individual and relative preferences, which are the main modifiable factors in recent publications [16]. Third, the study was conducted in a European country following international guidelines for the management of patients with AHRF [10,11,16,38]. Fourth, no patients with COVID-19 were enrolled, since the study was conducted in the pre-COVID era [1]. Finally, external validation of the proposed model in another clinical setting is needed to confirm performance before clinical implementation can be considered [25]. Any further validation of our model, including comparison to other general ICU risk predictions models, should be carried out in a new, prospectively collected dataset, preferably in a more diverse patient population.

In conclusion, six common variables are important to predict ICU mortality in ventilated patients with AHRF. Adherence to risk-precision-based management strategies may reduce the ICU mortality in AHRF patients. If the prediction model is further validated, clinicians, scientists, and health care administrators may impact the medical treatment that could improve the outcome of patients with AHRF.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jcm14051711/s1>. References [52–68] are cited in Supplementary Materials.

Author Contributions: J.V., J.M.G.-M., E.W.S. and T.S. contributed to the initial study concept and design. C.F. (Cristina Fernández) provided important methodological input to the analysis. All authors contributed to the final study design, or participated in its coordination, or in drafting the first manuscript. J.M.A., C.F. (Carlos Ferrando), J.M.M.-O., D.M., F.M., A.A., L.F., I.M., A.V., D.P., M.A.R., R.M., A.M.D.-B. and J.A.S. enrolled patients into the study and participated in the data collection and data analysis. J.V., C.F. (Cristina Fernández), E.G.-B., J.M.G.-M., E.W.S. and T.S. are responsible for data analysis and/or interpretation of data. J.V., C.F. (Cristina Fernández), E.G.-B. and J.M.G.-M. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.V., J.M.G.-M., C.F. (Cristina Fernández), C.F. (Carlos Ferrando), J.M.A., E.W.S. and T.S. participated in the final version of this manuscript. J.V., J.M.G.-M., E.W.S. and T.S. contributed to the final revised article. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Approval of this study was given by the Ethics Committee of Hospital Universitario Dr. Negrín (Las Palmas de Gran Canaria, Spain, #2021-321-1, date of approval: 30 July 2021). This was a comprehensive analysis using unrestricted data from our previously published study in patients with acute hypoxemic respiratory failure (AHRF) that were approved by the referral Ethics Committees of Hospital Universitario Dr. Negrín (Las Palmas de Gran Canaria, Spain), Ethics Committees of Hospital Universitario La Paz, Madrid (#PI-2694, date of approval: 2021), and Hospital Clínico Universitario de Valladolid (#PI17-594, date of approval: 2021), Spain, and adopted by all participating centers. This study was conducted in accordance with the fundamental principles established in the Declaration of Helsinki, the Convention of the European Council related to human rights and biomedicine, the Ethical Guidelines for Health-related Research Involving Humans by the Council for International Organization of medical Sciences of the World Health Organization (WHO), and within the requirements established by the Spanish legislation for biomedical research, the protection of personal data, and bioethics.

Informed Consent Statement: The requirement for informed consent was waived (Ref. CEI/CEIm 2021-321-1) under the Royal Decrees 1090/2015 and 957/2020 based on the Spanish legislation for biomedical research due to the retrospective nature of the secondary analysis, the anonymization/dissociation of data, and no harm or benefit for managing patients.

Data Availability Statement: All data needed to evaluate the conclusions in this article are presented and tabulated in the main text or the Supplemental File. Data are available from the corresponding author on reasonable request.

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