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Respiratory Mechanics and Outcomes in Immunocompromised patients with ARDS – A secondary analysis of the EFRAIM study

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This study was performed on behalf of the Caring for Critically Ill Immuno-compromised Patients Multinational Network (Nine-I). This group includes critical care specialists from 16 countries in Europe, the USA, Canada and South America. The primary aim of this group is to improve and standardize practices in the management of critically ill immunocompromised patients.

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Abbreviation list:

- ARF: acute hypoxemic respiratory failure
- ICU: intensive care unit
- Crs: respiratory system compliance
- Pplat,rs: end-inspiratory respiratory system plateau pressure
- VT: tidal volume
- Δ Prs: respiratory system driving pressure
- PaO₂: partial pressure of oxygen
- FiO₂: inspired oxygen fraction
- SpO₂: pulse oxygen saturation
- SOFA: Sequential Organ Failure Assessment score
- PEEP: positive end-expiratory pressure
- OR: adjusted odds ratios

Abstract

Background. In view of the high mortality rate of immunocompromised patients with acute respiratory distress syndrome (ARDS), it is important to identify targets for improvement.

Research question. This study investigated factors associated with mortality in this specific ARDS population, including factors related to respiratory mechanics (plateau pressure [Pplat,rs], compliance [Crs] and driving pressure [Δ Prs]).

Study design and methods. This study consisted of a predefined secondary analysis of the Efrain data. Overall, 789/1611 patients met the Berlin criteria for ARDS, and Pplat,rs, Δ Prs and Crs were available for 494 patients. A hierarchical model was used to assess factors at ARDS onset independently associated with hospital mortality.

Results. Hospital mortality was 56.3%. After adjustment, variables independently associated with hospital mortality included (odds ratio [95% confidence interval]) ARDS of undetermined etiology (1.66 [1.01-2.72]), need for vasopressors (1.91 [1.27-2.88]) and need for renal replacement therapy (2.02 [1.37-2.97]). ARDS severity according to the Berlin definition, neutropenia on admission and the type of underlying disease were not significantly associated with mortality. Before adjustment, higher Pplat,rs, higher Δ Prs and lower Crs were associated with higher mortality. Addition of each of these individual variables to the final hierarchical model revealed a significant association with mortality: Δ Prs (1.08 [1.05-1.12]), Pplat,rs (1.07 [1.04-1.11]), and Crs (0.97 [0.95-0.98]). Tidal volume was not associated with mortality.

Interpretation. In immunocompromised patients with ARDS, respiratory mechanics provide additional prognostic information to predictors of hospital mortality. Studies designed to define lung-protective ventilation guided by these physiological variables may be warranted in this specific population.

INTRODUCTION

Acute hypoxemic respiratory failure (ARF) is the leading cause of intensive care unit (ICU) admission in immunocompromised patients ^{1,2}. In this population, 35%-75% of patients develop acute respiratory distress syndrome (ARDS) ³. ARDS in immunocompromised patients is characterized by various specific features. Infectious causes differ from those reported in immunocompetent patients, with a high proportion of opportunistic infections and superinfections ³. Extrapulmonary ARDS commonly complicates septic shock, and may be caused by fungal pathogens ³. Moreover, a proportion of patients exhibit non-infectious lung injury mimicking ARDS (i.e., drug-related pulmonary toxicity) or lung involvement by underlying diseases ⁴. Finally, neutropenic patients are at higher risk of ICU-acquired infections and deterioration during recovery of neutropenia ⁵.

Over recent years, cohort studies focusing on ARDS in immunocompromised patients have suggested that case fatality has decreased over the last decade, but it nevertheless remains much higher than that observed in immunocompetent patients ^{3,6,7}. These studies have also defined factors associated with mortality in this population. However, important variables, such as invasive fungal infection, ARDS of undetermined etiology and neutropenia have not been adequately investigated ⁶.

Importantly, none of these studies on ARDS patients, characterized by stiff lungs with a marked reduction of respiratory system compliance (Crs), investigated the prognostic impact of lung-protective ventilation, limiting end-inspiratory respiratory system plateau pressure (Pplat,rs) and tidal volume (VT). In addition, a better understanding of the relevance of respiratory system driving pressure (ΔP_{rs}) is needed, especially as this variable has recently been described as one of the strongest predictors of mortality in patients with ARDS ⁸.

The primary goal of the present study was to investigate the factors associated with mortality in immunocompromised, invasively mechanically ventilated adults with ARDS.

More specifically, this study investigated respiratory mechanics by analyzing $Plat_{rs}$, Cr_s and ΔPr_s . We hypothesized that 1) immunocompromised ARDS patients present specific risk factors for death that are not observed in immunocompetent patients, 2) $Plat_{rs}$, Cr_s and ΔPr_s are independently associated with mortality in this population, suggesting that they could constitute targets to improve survival in this high-risk population.

PATIENTS AND METHODS

This was a predefined secondary analysis from the EFRAIM multinational, observational prospective cohort study on ARF in immunocompromised patients⁹. This initiative from the Nine-I (Caring for critically ill immunocompromised patients) study group included patients from 68 ICUs in 16 countries. Participating physicians and teams have extensive experience in the management of various groups of critically ill immunocompromised patients. The full description of this cohort has been published elsewhere⁹. Participating centers and collaborators are listed in the online supplement. The study was approved by each institutional review board according to local ethical regulations (see e-Table 1 in the Online Supplement).

Study population

After Institutional Review Board approval, each participating ICU prospectively included patients between November 2015 and July 2016. Inclusion criteria were age (≥ 18 years), acute hypoxemic respiratory failure ($PaO_2 < 60$ mmHg or $SpO_2 < 90\%$ on room air, or tachypnea > 30 /min, or labored breathing or respiratory distress or dyspnea at rest or cyanosis), need for more than 6 L/min oxygen, respiratory symptoms lasting less than 72 hours and non-AIDS-related immune deficiency defined as hematologic malignancy or solid tumor (active or in remission for less than 5 years, including autologous or allogeneic hematopoietic stem cell transplantation recipients), solid organ transplant with long-term ($>$

30 days) or high-dose (> 1 mg/kg/day methylprednisolone) corticosteroids, or any immunosuppressive drug for more than 30 days. Patients with postoperative acute respiratory failure (within 6 days of surgery), those admitted after cardiac arrest, patients admitted only to perform bronchoscopy, and patients/surrogates who declined study participation were not included.

For the purposes of this predefined ancillary study, only intubated patients who met the Berlin criteria for ARDS ¹⁰ within 48 hours of intubation were included. Patients for whom hospital mortality was unknown were excluded.

Data collection

Patients were followed at given time-points in the ICU, at hospital discharge and 90 days after ICU discharge. At each time-point, study investigators completed a standardized paper case report form that was subsequently sent to the coordinating center in Paris.

The following demographic data and medical history were collected: age, gender, Sequential Organ Failure Assessment score (SOFA) ¹¹, cause of immunosuppression, neutropenia within 24 hours following admission, body mass index and performance status. The cause of ARDS was recorded after being reviewed by two study investigators (EA and VL) for consistency with established definitions. The pulmonary characteristics recorded on the first day of ARDS were: PaO₂-to-FiO₂ ratio, respiratory rate, tidal volume (VT) expressed as absolute value and expressed in relation to ideal predicted body weight, positive end-expiratory pressure (PEEP), P_{plat,rs}, ΔPr_s defined as P_{plat,rs} - PEEP, and Cr_s defined as ΔPr_s/VT. Adjuvant and rescue therapies, such as prone positioning, neuromuscular blocking agents, extracorporeal lung support and inhaled nitric oxide, were also collected together with organ supports, such as vasopressors and renal replacement therapy. Finally, hospital mortality and patient's goals of care on ICU admission (full code or treatment limitation decisions) were also recorded.

Statistical analysis

Quantitative variables are expressed as median (interquartile range [IQR]) and were compared between groups using the non-parametric Wilcoxon rank-sum test. Qualitative variables are expressed as frequency (percentages) and were compared between groups using Fisher's exact test.

Hierarchical models were used to assess factors independently associated with mortality. First, logistic regression was performed for variable selection. We used conditional stepwise regression with 0.2 as the critical P-value for entry into the model, and 0.1 as the P-value for removal. It was planned *a priori* to force the Berlin classification of ARDS in the final model and to test the influence of neutropenia, should these variables not be selected. Interactions and correlations between explanatory variables were carefully checked. Continuous variables for which log-linearity was not confirmed were transformed into categorical variables according to median or IQR. The final models were assessed by calibration, discrimination and relevancy. Residuals were plotted, and the distributions were inspected. A hierarchical model was then performed using variables previously selected together with center as random effect on the intercept. This model, adjusting for the clustering effect, was planned *a priori* to be the main result of the analysis. Adjusted odds ratios (OR) of variables present in the final model are presented with their 95% confidence intervals. We did not perform imputation for missing data.

In view of the high rate of missing data and the strong correlation between Δ Prs, Crs, and Pplat, the influence of these variables in the final model was assessed by including each variable individually.

Kaplan-Meier graphs were used to express the probability of death from the time of inclusion until hospital discharge, censored at day 60 and were compared across groups by the log rank test. The influence of Δ Prs, Pplat,rs and Crs on mortality was plotted, reporting

mortality per quintile for each variable. Comparisons across quintiles were performed using Wilcoxon's test.

A p value <0.05 was considered significant. Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (IBM SPSS Inc., Chicago, IL, USA) and with R statistical software, version 3.4.3 (available online at <http://www.r-project.org/>) and 'Survival', 'lme4', and 'lmerTest' packages.

RESULTS

Study population

Figure 1 displays the study flow chart. During the study period, 1,611 immunocompromised patients were admitted for acute respiratory failure and 994 (62%) of them were intubated. Of the 994 intubated patients, 182 did not meet criteria for ARDS according to the Berlin definition¹⁰ and hospital mortality data were missing for 23 patients. A total of 789 patients were included in the main analysis for factors associated with mortality. As Pplat,rs was missing in 295 of these patients, respiratory mechanics indices were not included in the main analysis. An analysis restricted to the 494 patients with available Pplat,rs was then performed.

Underlying conditions were: hematological malignancies (409 patients, 52%), solid tumors (274 patients, 35%), connective tissue diseases (152 patients, 19%), solid organ transplants 69 patients, 10%) and drug-related immunosuppression (9 patients, 1%). Fifty-four patients (7%) had undergone allogeneic stem cell transplantation, 80 patients (10%) had undergone autologous stem cell transplantation and 165 (21%) patients were neutropenic. Median SOFA score was 8 (interquartile range: 5-11).

Causes of ARDS were bacterial infections in 252 patients (32%), viral infections in 151 (19%), invasive fungal infections in 152 (19%), septic shock from extrathoracic sources in 88

(11%) and disease-related infiltrates in 78 (10%). The etiology of ARDS was undetermined in 100 patients (13%).

Main analysis in the 789 patients

In this population of 789 patients, 345 (44%) were survivors and 444 (56%) were non-survivors at hospital discharge (Table 1). After adjustment for confounders and clustering effect, variables independently associated with hospital mortality were ARDS of undetermined etiology (odds ratio [OR] 1.66; 95% confidence interval [CI] 1.01-2.72, $P=0.045$), need for vasopressors (OR 1.91, 95%CI 1.27 - 2.88, $P=0.002$) and need for renal replacement therapy (OR 2.02, 95%CI 1.37 - 2.97, $P<0.001$) (Figure 2).

Pulmonary severity according to the Berlin definition of ARDS was not significantly associated with mortality before or after adjustment (Figure 2 and 3, see also e-Table 2 in the Online Supplement). When forced in the final model, neutropenia was neither selected for (OR 1.37, 95%CI 0.92-1.37; $P=0.13$) nor changed the final model. Similarly, the influence of underlying hematological malignancy was assessed in a *post hoc* analysis, but this variable was not selected for (OR 1.01, 95%CI 0.95-1.08; $P=0.75$) and did not change the final model.

Impact of respiratory system mechanics indices in the 494 patients for whom $P_{plat,rs}$ was available

Among the 494 patients with available $P_{plat,rs}$, there were 226 (45.7%) survivors and 268 (54.3%) non-survivors at hospital discharge. Figure 4 displays $P_{plat,rs}$, ΔP_{rs} , PEEP and V_T in survivors and non-survivors (see also e-Table 3 in the Online Supplement).

Before adjustment, higher $P_{plat,rs}$, ΔP_{rs} (4 missing data), as well as lower C_{rs} (64 missing data) were associated with higher mortality (Figure 5). $\Delta P_{rs} > 14$ cmH₂O and $P_{plat,rs} > 24$ cmH₂O were associated with higher mortality.

There was a significant correlation between $P_{plat,rs}$, ΔP_{rs} and C_{rs} (see e-Figure 1 in the Online Supplement). When included separately in the final hierarchical model taking into

account the influence of body mass index, Δ Prs (OR 1.08 per cmH₂O; 95%CI 1.05-1.12, Figure 6), Pplat,rs (OR 1.07 per cmH₂O; 95%CI 1.04-1.11; see e-Figure 2 in the Online Supplement), and Crs (OR 0.97 per cmH₂O; 95%CI 0.95-0.98; see e-Figure 3 in the Online Supplement) were independently associated with hospital mortality.

DISCUSSION

This large preplanned secondary analysis of a multicenter multinational prospective study challenges existing knowledge on ARDS in immunocompromised patients. Survival in this critically ill population was substantial and the underlying conditions were not associated with mortality. Most importantly, this study revealed that, as with non-immunocompromised patients, respiratory mechanics variables were associated with mortality, suggesting that ventilation strategies tailored to the severity of lung injury may translate into improved survival.

Data on ARDS in immunocompromised patients are scarce and to our knowledge, our study is the largest study on this topic to date ^{3,6,7}. Our prospective data collection allowed assessment of variables such as ARDS etiology and respiratory mechanics. It is noteworthy that mortality was comparable to that reported in the most recent studies ^{6,7}, but still substantial ³ and much higher than that observed in immunocompetent patients ^{7,12,13}.

Markers of lung mechanics and appropriate lung-protective ventilation were independent predictors of mortality in our study. Odds ratios were similar to those observed in one study conducted immunocompetent patients ¹⁴, but lower than those observed in another study ⁸, which may indicate that lung mechanics play a less significant role in immunocompromised ARDS patients.

In contrast with previous reports, we did not find a clear superiority of Δ Prs over Pplat,rs for prediction of patient outcome ⁸. Inversely, Δ Prs and Pplat,rs were both

independently associated with mortality and were strongly correlated ¹⁴, which could be explained by the relatively low tidal volume, as the superiority of Δ Prs over Pplat,rs to predict mortality is mostly observed in the context of a wide dispersion of tidal volume ⁸. Inversely, the superiority of Δ Prs to Pplat,rs to predict mortality was no longer observed when tidal volume was close to 6 ml/kg, as in our patients ¹⁴. The low tidal volume observed in this study suggests that physicians must be aware of the marked benefit of lung-protective ventilation, even in immunocompromised patients ^{13,15}. However, it is of notice that prone positioning was performed in a small proportion of patient. Given the benefit of this therapy in moderate to severe ARDS, this may have influence the outcome. Despite the fact that ARDS in immunocompromised patients exhibits various specific features (opportunistic infections, drug-related lung injury, acute lung infiltration by malignant cells, bone marrow transplant-related lung injury) and frequently occurs in a context of neutropenia, lung-protective ventilation should remain the golden rule.

Finally, it is noteworthy that ARDS severity according to the Berlin definition was not associated with mortality. In our cohort, Δ Prs, Pplat,rs and Crs were more reliable predictors of mortality than the severity of hypoxemia. Although some studies have observed an association between mortality and ARDS severity according to the Berlin definition in immunocompromised patients ^{3,6}, others have not ¹⁴, but no obvious explanation for this disparity can be proposed. In our study, hypoxemia was more severe than that observed in immunocompromised patients of the LUNG SAFE study, with less mild ARDS and more severe ARDS ⁶. We also cannot exclude the possibility that, due to their specific ARDS causes, immunocompromised patients do not have the same severity criteria as immunocompetent patients. Further, our sample size may have been too small to detect any impact of ARDS severity according to the Berlin definition on mortality.

The major impact of an unknown diagnosis and invasive fungal infections observed in this study has been extensively discussed in a previous report from this cohort ⁹. It is noteworthy that neutropenia during the first 48 hours after intubation did not have any impact on outcome, in contrast with a recent meta-analysis suggesting that neutropenia is a factor for poor prognosis ¹⁶. However, this association between neutropenia and outcome remains controversial ¹⁷, especially when the presence of neutrophil depletion did not prevent patients from developing severe ARDS ^{18,19}. Note that, in this study, neutropenia was defined as at least one episode of neutropenia within 24 hours following admission. The duration and severity of neutropenia prior to ICU admission and during the ICU stay were therefore not analyzed.

Strengths of our study include the multinational, multicenter, prospective design, which ensures a good external validity of our results. This study is the most comprehensive study on this subject in terms of the large number of patients and the variety of data collected. The profile of infectious diseases indicates severe immunologic impairment.

The present study has several limitations. Firstly, the observational design precludes any causal conclusions. Secondly, management strategies were not standardized across centers. However, the center effect did not have any impact on our findings and a cluster effect was taken into account in the final results. Thirdly, indices of respiratory system mechanics were not available in all patients and analyses involving P_{plat,rs}, ΔP_{rs} and C_{rs} could not be performed in the whole population. Fourthly, we focused on intubated patients and subsequently excluded ARDS patients managed by standard oxygen, non-invasive ventilation or high-flow oxygen, as respiratory mechanics indices cannot be measured in these patients.

CONCLUSION

In immunocompromised patients with ARDS, mortality is influenced by specific features, highlighting the critical importance of diagnostic strategies. Future research should investigate both the diagnostic yield of innovative laboratory tests and the benefits of empirical therapeutic strategies. In addition, in immunocompromised patients with ARDS, ΔP_{rs} , $P_{plat,rs}$ and C_{rs} remain independently associated with mortality. This study reinforces the fundamental importance of lung-protective ventilation, including in immunocompromised patients. This study suggests that easily available bedside physiologic variables could help stratify patients at high risk of death and could be used to develop advanced lung protective ventilation strategies and early rescue strategies, regardless of oxygenation status.

Guarantor: A Demoule, M Darmon and E Azoulay takes responsibility for the content of the manuscript, including the data and analysis.

Author contributions: AD, EA and MD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. All the authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Tables

Table 1. Characteristics according to status at hospital discharge

	All n=789	Non-survivors n=444	Survivors n=345	p
Patient characteristics				
Female gender, <i>n (%)</i>	321/782 (41)	172/439 (39)	149/343 (43)	0.229
Age, years	63 (55 – 71)	64 (56 – 72)	63 (53 – 70)	0.088
Poor performance status, ECOG = 3, <i>n (%)</i>	136/664 (20)	94/381 (25)	42/283 (15)	0.002
BMI, <i>kg/m²</i>	25 (22 – 29)	25 (22 – 29)	25 (23 – 30)	0.395
Underlying condition, <i>n (%)</i>				
Solid tumor, <i>n (%)</i>	274 (35)	159 (36)	115 (33)	0.468
Hematological malignancy, <i>n (%)</i>	409 (52)	239 (52)	170 (49)	0.204
Connective tissue diseases, <i>n (%)</i>	152 (19)	73 (16)	79 (23)	0.023
Solid organ transplant, <i>n (%)</i>	69 (10)	34 (9)	35 (11)	0.260
Drug-related immunosuppression, <i>n (%)</i>	9 (1)	3 (1)	6 (2)	0.163
Allogeneic HSCT, <i>n (%)</i>	54 (7)	35 (8)	19 (6)	0.190
Autologous HSCT, <i>n (%)</i>	80 (10)	46 (10)	34 (10)	0.816
Neutropenia, <i>n (%)</i>	165 (21)	104 (23)	61 (18)	0.049
SOFA score on day 1	8 (5 – 11)	9 (6 – 12)	8 (5 – 11)	0.001
Cause of ARDS				
Bacterial infection, <i>n (%)</i>	252 (32)	145 (33)	107 (31)	0.623
Viral infection, <i>n (%)</i>	151 (19)	84 (19)	67 (19)	0.859
Septic shock from extrathoracic source, <i>n</i>	88 (11)	47 (11)	41 (12)	0.565
All invasive fungal infections, <i>n (%)</i>	152 (19)	94 (21)	58 (17)	0.123
Pneumocystis pneumonia, <i>n (%)</i>	43 (5)	28 (6)	15 (4)	0.229
Invasive pulmonary aspergillosis, <i>n (%)</i>	45 (6)	27 (6)	18 (5)	0.604
Candidemia, <i>n (%)</i>	27 (3)	16 (4)	11 (3)	0.750
Aspiration, <i>n (%)</i>	35 (4)	18 (4)	17 (5)	0.554
Airway-related disorders, <i>n (%)</i>	32 (4)	12 (3)	20 (6)	0.029
Drug-related pulmonary toxicity, <i>n (%)</i>	25 (3)	12 (3)	13 (4)	0.397
Disease-related infiltrates, <i>n (%)</i>	78 (10)	48 (11)	30 (9)	0.323
Undetermined, <i>n (%)</i>	100 (13)	65 (15)	35 (10)	0.060
ARDS characteristics				
Berlin category				0.468
Mild, <i>n (%)</i>	165 (21)	86 (19)	79 (23)	0.227
Moderate, <i>n (%)</i>	372 (47)	212 (48)	160 (46)	0.702
Severe, <i>n (%)</i>	252 (32)	146 (33)	106 (31)	0.519
PaO ₂ /FiO ₂ on day 1, <i>mmHg</i>	132 (92 – 192)	130 (90 – 187)	135 (94 – 195)	0.139
Respiratory rate on day 1, <i>min⁻¹</i>	28 (23 – 34)	28 (23 – 34)	27 (23 – 33)	0.932
Tidal volume on day 1 ^a , <i>ml</i>	440 (390–480)	430 (380–480)	450 (400–485)	0.127
Tidal volume on day 1 ^a , <i>ml/PBW kg</i>	6.8 (6.1 – 7.8)	6.8 (6.0 – 7.6)	6.9 (6.2 – 7.9)	0.070
PEEP on day 1, <i>cmH₂O</i>	10 (7 – 12)	10 (7 – 12)	8 (7 – 12)	0.221
Plateau pressure on day 1 ^b , <i>cmH₂O</i>	24 (20 – 28)	25 (20 – 29)	23 (19 – 27)	<0.001
Driving pressure on day 1 ^b , <i>cmH₂O</i>	14 (11 – 18)	15 (12 – 19)	13 (10 – 16)	<0.001

Tidal compliance on day 1 ^c , ml/cmH ₂ O	30 (23 – 41)	28 (21 – 38)	42 (26 – 45)	<0.001
Adjunctive therapies during ICU stay				
Neuromuscular blocking agent, n (%)	192 (24)	89 (20)	103 (30)	0.512
Nitric oxide, n (%)	167 (21)	92 (21)	75 (22)	0.646
Prone positioning, n (%)	72 (9)	46 (10)	26 (8)	0.172
Extracorporeal lung support, n (%)	10 (1)	6 (1)	4 (1)	0.837
Organ support during ICU stay				
Vasopressors, n (%)	625 (79)	370 (83)	255 (74)	0.001
Renal replacement therapy, n (%)	197 (25)	133 (30)	64 (19)	<0.001
Treatment limitation decision, n (%)	45 (6)	30 (7)	15 (4)	0.148

Quantitative variables were described as median (interquartile range [IQR]) and were compared between groups using the non-parametric Wilcoxon rank-sum test. Qualitative variables were described as frequency (percentages).

ECOG, Eastern oncology study group; BMI, body mass index; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; NMBA, neuromuscular blocking agent; NO, nitric oxide.

^a Available for 543 patients

^b Available for 494 patients

^c Available for 417 patients

Figure Legends

Figure 1. Study flow chart

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

Figure 2. Hierarchical model assessing variables independently associated with hospital mortality.

Center was included in the model as random effect.

Plots report variables independently associated with hospital mortality in the final model, with their 95% confidence intervals. Model C-stat 0.65 (95%CI 0.61-0.69), Hosmer-Lemeshow goodness of fit P=0.098.

RRT, renal replacement therapy.

Figure 3. Cumulative survival according to the Berlin acute respiratory distress syndrome (ARDS) severity category.

The blue line indicates mild ARDS, the red line indicates moderate ARDS and the green line indicates severe ARDS. The three groups were compared using the log-rank test (p=0.47)

Figure 4. Respiratory system plateau pressure and driving pressure, maximum positive end-expiratory pressure (PEEP) and tidal volume expressed in relation to predicted body weight at day 1 in hospital survivors and non-survivors among the 494 patients with available plateau pressure.

Figure 5. Unadjusted hospital mortality across quintiles of plateau pressure (Pplat,rs), driving pressure (Δ Prs) and respiratory system compliance (Crs).

Dots represents mean mortality and bars the 95% confidence interval. The numbers below the x axis are median (IQR) range of respiratory system characteristics across each quintile (P < 0.001 across quintiles).

Figure 6. Influence of driving pressure in the final hierarchical model assessing variables associated with hospital mortality. Center was included in the model as random effect. Only the 494 patients with available driving pressure measurement were included.

Plots report variables independently associated with hospital mortality in the final model, with their 95% confidence intervals. Model C-stat 0.63 (95%CI 0.59-0.68), Hosmer-Lemeshow goodness of fit: P=0.711.

RRT, renal replacement therapy; BMI, body mass index.

Figure 1

1611 immunocompromised patients
admitted to 68 ICUs in 16 countries
for acute respiratory failure

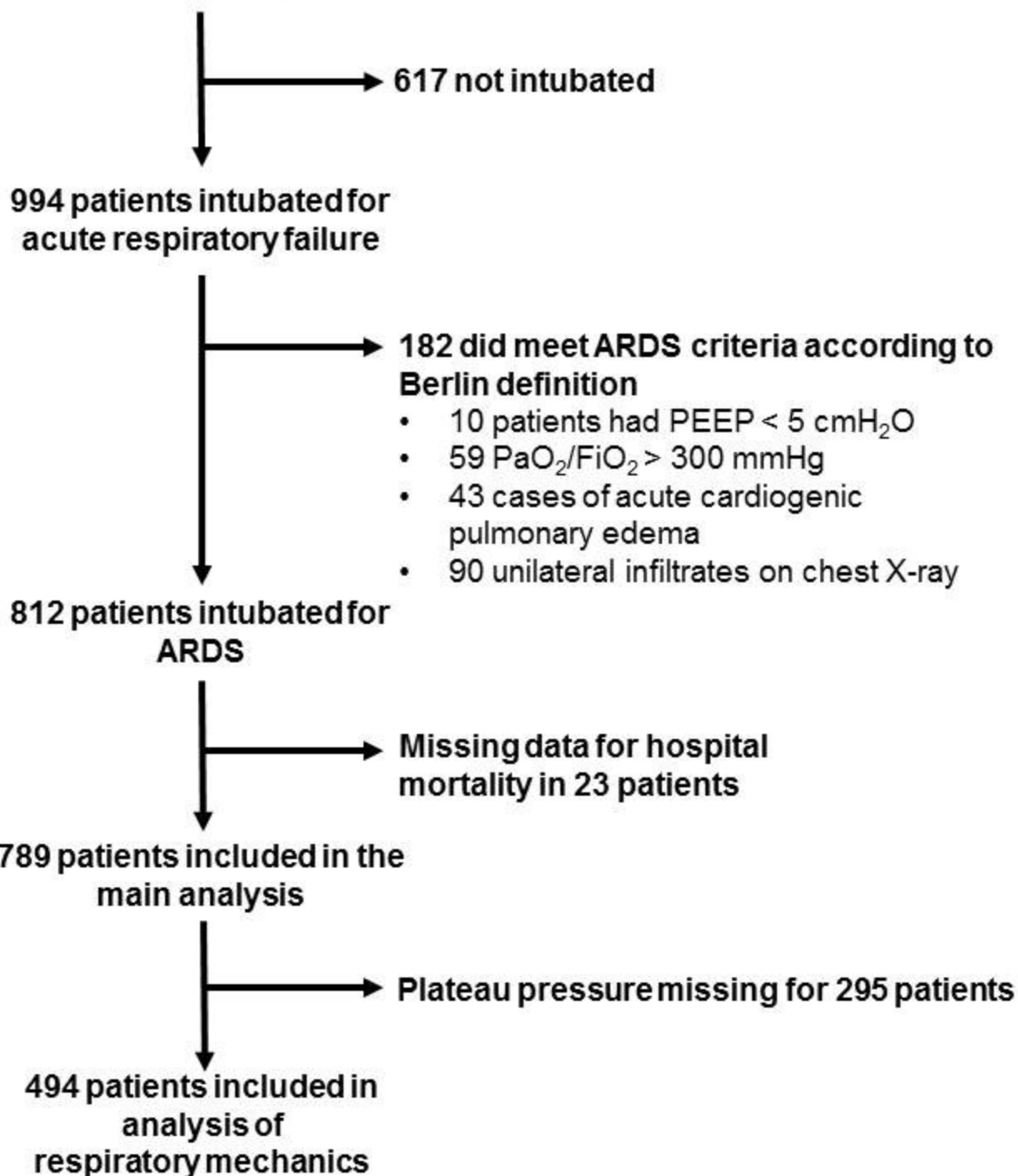


Figure 2

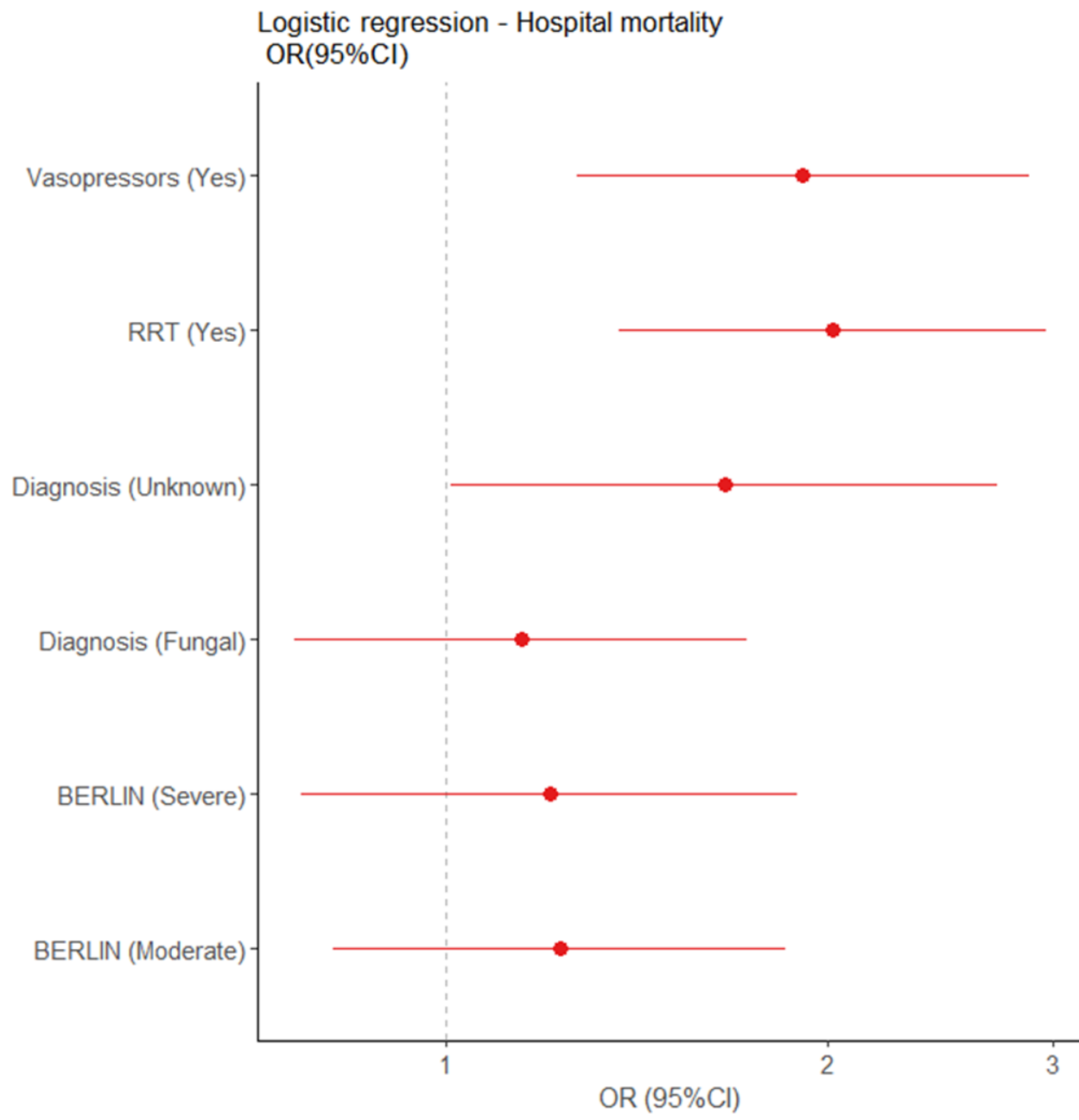
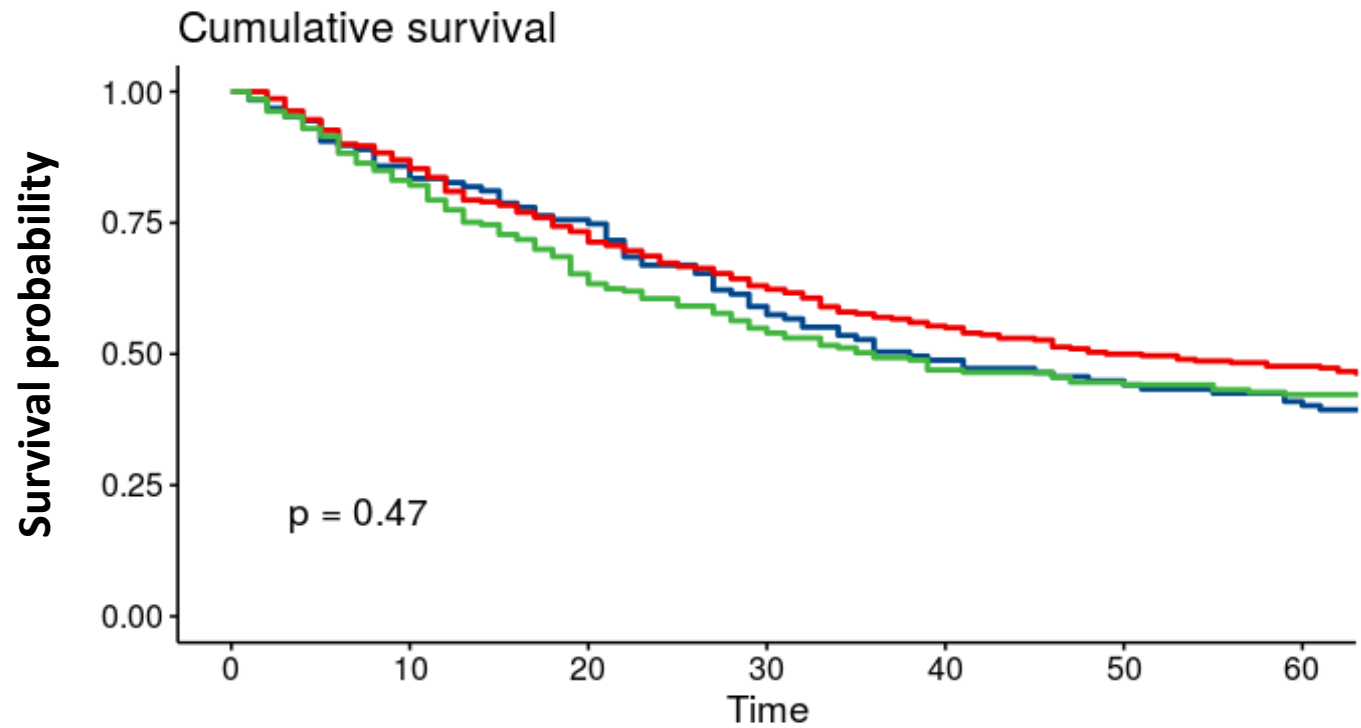


Figure 3



Number at risk

BERLIN=Mild	127	109	96	75	62	57	52
BERLIN=Moderate	300	261	220	189	166	150	143
BERLIN=Severe	213	177	139	117	100	95	90

Figure 4

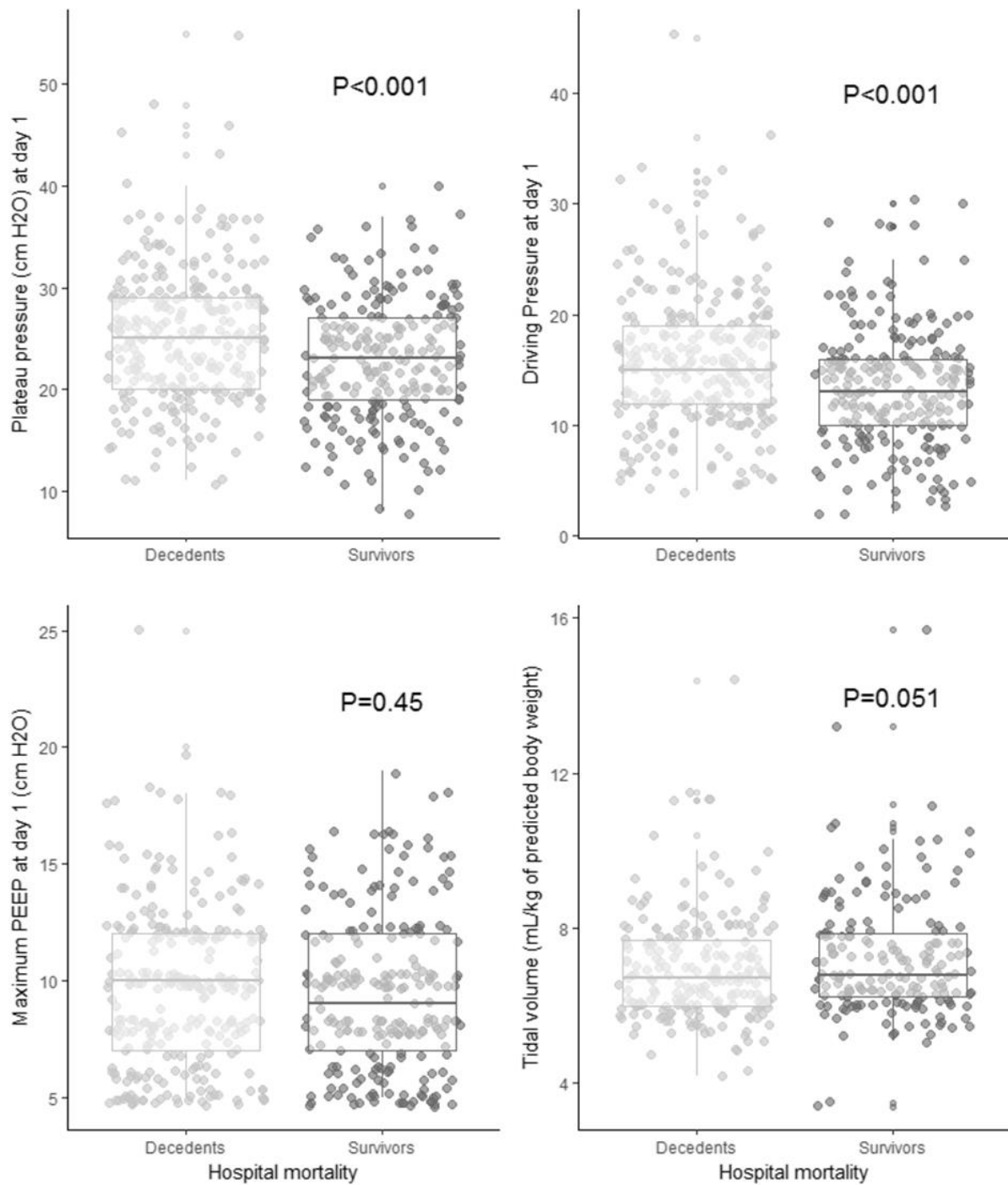


Figure 5

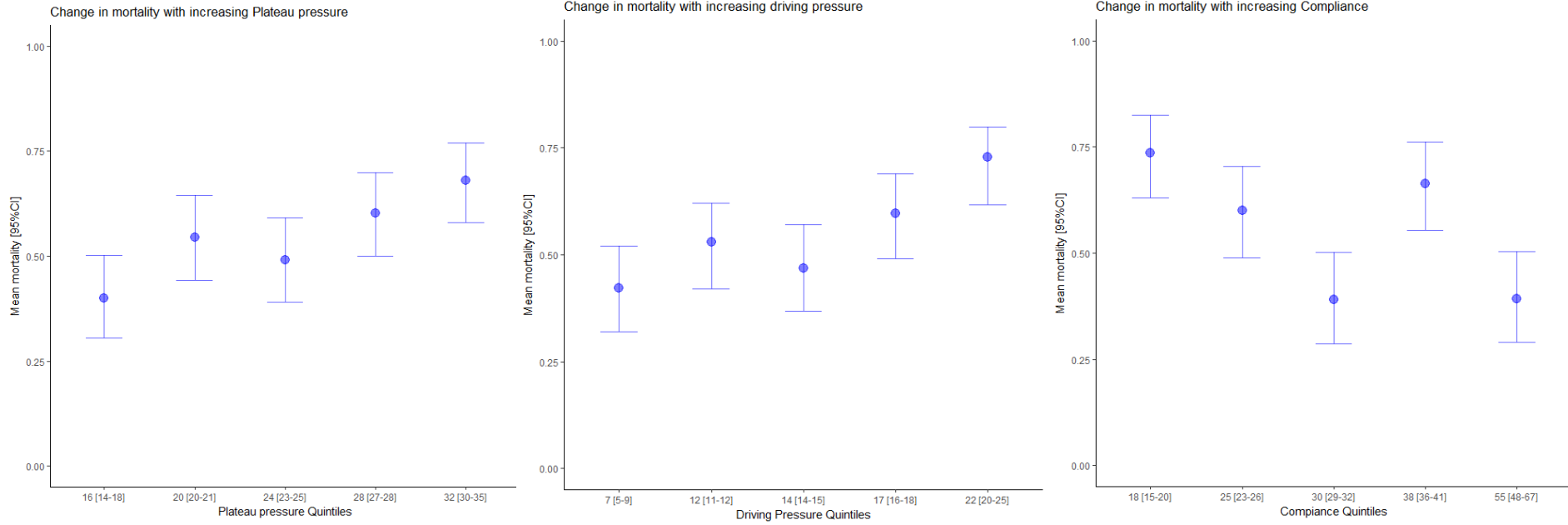


Figure 6

