Respiratory Mechanics and Outcomes in Immunocompromised Patients With ARDS A Secondary Analysis of the EFRAIM Study

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Respiratory Mechanics and Outcomes in Immunocompromised Patients With ARDS

A Secondary Analysis of the EFRAIM Study

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BACKGROUND: In view of the high mortality rate of immunocompromised patients with 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 [ΔPrs]).

STUDY DESIGN AND METHODS: This study consisted of a predefined secondary analysis of the EFRAIM data. Overall, 789 of 1,611 patients met the Berlin criteria for ARDS, and Pplat,rs, ΔPrs, 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 ARDS of undetermined etiology (OR, 1.66; 95% CI, 1.01-2.72), need for vasopressors (OR, 1.91; 95% CI, 1.27-2.88), and need for renal replacement therapy (OR, 2.02; 95% CI, 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 ΔPrs, 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: ΔPrs (OR, 1.08; 95% CI, 1.05-1.12), Pplat,rs (OR, 1.07; 95% CI, 1.04-1.11), and Crs (OR, 0.97; 95% CI, 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. CHEST 2020; 158(5):1947-1957

KEY WORDS: acute respiratory failure; ARDS; diagnosis; driving pressure; immunocompromised; outcome; plateau pressure

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ABBREVIATIONS: Crs = respiratory system compliance; ΔPrs = respiratory system driving pressure; PEEP = positive end-expiratory pressure; Pplat,rs = end-inspiratory respiratory system plateau pressure; V_T = tidal volume

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Acute hypoxemic respiratory failure is the leading cause of ICU admission in immunocompromised patients.[1,2] In this population, 35% to 75% of patients develop 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 noninfectious lung injury mimicking ARDS (ie, drug-related pulmonary toxicity) or lung involvement by underlying diseases.[4] Finally, patients with neutropenia are at higher risk of ICU-acquired infections and deterioration during recovery of neutropenia.[5]

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 patients with ARDS, 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 (V_T). In addition, a better understanding of the relevance of respiratory system driving pressure (ΔPrs) is needed, especially because this variable has been described as one of the strongest predictors of mortality in patients with ARDS.[8]

The primary goal of this 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, Crs, and ΔPrs. We hypothesized that (1) immunocompromised patients with ARDS present specific risk factors for death that are not observed in immunocompetent patients; and (2) Plat,rs, Crs, and ΔPrs 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 acute hypoxemic respiratory failure in immunocompromised patients.[9] This initiative from the Caring for Critically Ill Immuno-compromised Patients Multinational Network (Nine-I) included patients from 68 ICUs in 16 countries. Participating physicians and teams have

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extensive experience in the management of various groups of critically ill immunocompromised patients. The full description of this cohort has been published elsewhere.[9] Participating centers and collaborators are listed in e-Table 1. The study was approved by each institutional review board according to local ethical regulations (e-Table 1).

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 mm Hg or pulse oxygen saturation < 90% on room air, or tachypnea > 30/min, or labored breathing or respiratory distress or dyspnea at rest or cyanosis), need for > 6 L/min oxygen, respiratory symptoms lasting < 72 h and non-AIDS-related immune deficiency defined as hematologic malignancy or solid tumor (active or in remission for < 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/d methylprednisolone) corticosteroids, or any immunosuppressive drug for < 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 h 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, France.

The following demographic data and medical history were collected: age, sex, Sequential Organ Failure Assessment score,[11] cause of immunosuppression, neutropenia within 24 h after admission, BMI, and performance status. The cause of ARDS was recorded after being reviewed by two study investigators (E. A. and V. L.) for consistency with established definitions. The pulmonary characteristics recorded on the first day of ARDS were as follows Pao_2 to Fio_2 ratio, respiratory rate, V_T expressed as absolute value and expressed in relation to ideal predicted body weight, positive end-expiratory pressure (PEEP), Pplat,rs, ΔPrs defined as Pplat,rs − PEEP, and Crs defined as ΔPrs/V_T. 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) and were compared between groups using the nonparametric Wilcoxon rank sum test. Qualitative variables are expressed as

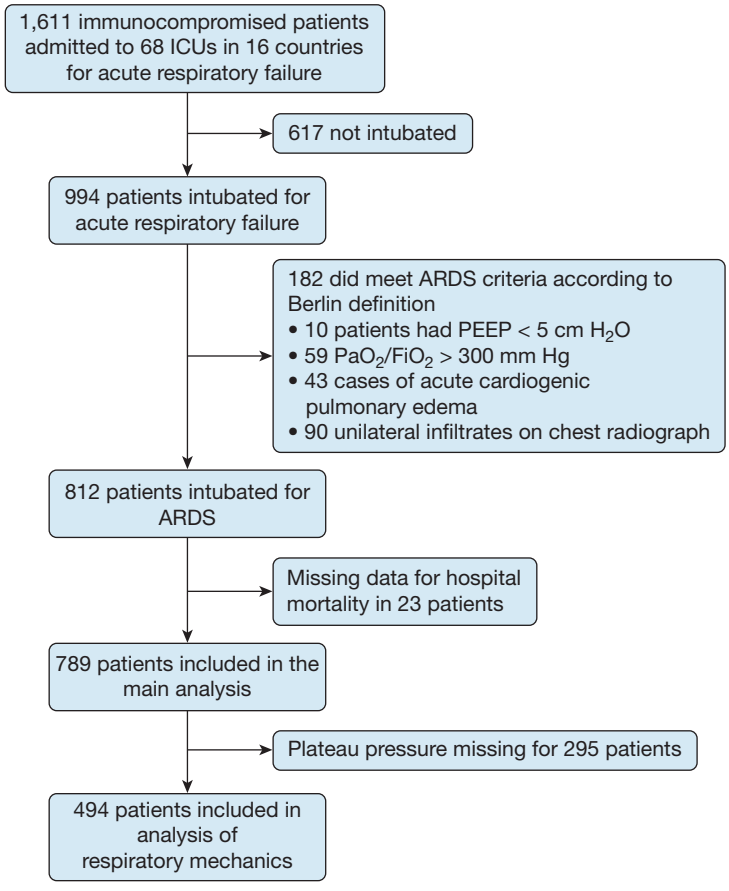

Figure 1 – *Study flowchart. PEEP = positive end-expiratory pressure.*

TABLE 1] Characteristics According to Status at Hospital Discharge

Characteristics	All (N = 789)	Nonsurvivors (n = 444)	Survivors (n = 345)	*P* Value
Patient characteristics				
Female sex	321/782 (41)	172/439 (39)	149/343 (43)	.229
Age, y	63 (55-71)	64 (56-72)	63 (53-70)	.088
Poor performance status, ECOG = 3	136/664 (20)	94/381 (25)	42/283 (15)	.002
BMI, kg/m^2	25 (22-29)	25 (22-29)	25 (23-30)	.395
Underlying condition				
Solid tumor	274 (35)	159 (36)	115 (33)	.468
Hematologic malignancy	409 (52)	239 (52)	170 (49)	.204
Connective tissue diseases	152 (19)	73 (16)	79 (23)	.023
Solid organ transplant	69 (10)	34 (9)	35 (11)	.260
Drug-related immunosuppression	9 (1)	3 (1)	6 (2)	.163
Allogeneic HSCT	54 (7)	35 (8)	19 (6)	.190
Autologous HSCT	80 (10)	46 (10)	34 (10)	.816
Neutropenia	165 (21)	104 (23)	61 (18)	.049
SOFA score on day 1	8 (5-11)	9 (6-12)	8 (5-11)	.001
Cause of ARDS				
Bacterial infection	252 (32)	145 (33)	107 (31)	.623
Viral infection	151 (19)	84 (19)	67 (19)	.859
Septic shock from extrathoracic source	88 (11)	47 (11)	41 (12)	.565
All invasive fungal infections	152 (19)	94 (21)	58 (17)	.123
Pneumocystis pneumonia	43 (5)	28 (6)	15 (4)	.229
Invasive pulmonary aspergillosis	45 (6)	27 (6)	18 (5)	.604
Candidemia	27 (3)	16 (4)	11 (3)	.750
Aspiration	35 (4)	18 (4)	17 (5)	.554
Airway-related disorders	32 (4)	12 (3)	20 (6)	.029
Drug-related pulmonary toxicity	25 (3)	12 (3)	13 (4)	.397
Disease-related infiltrates	78 (10)	48 (11)	30 (9)	.323
Undetermined	100 (13)	65 (15)	35 (10)	.060
ARDS characteristics				
Berlin category				.468
Mild	165 (21)	86 (19)	79 (23)	.227
Moderate	372 (47)	212 (48)	160 (46)	.702
Severe	252 (32)	146 (33)	106 (31)	.519
Pao_2/Fio_2 on day 1, mm Hg	132 (92-192)	130 (90-187)	135 (94-195)	.139
Respiratory rate on day 1, min^{-1}	28 (23-34)	28 (23-34)	27 (23-33)	.932
Tidal volume on day 1,[a] mL	440 (390-480)	430 (380-480)	450 (400-485)	.127
Tidal volume on day 1,[a] mL/PBW kg	6.8 (6.1-7.8)	6.8 (6.0-7.6)	6.9 (6.2-7.9)	.070
PEEP on day 1, cm H_2O	10 (7-12)	10 (7-12)	8 (7-12)	.221
Plateau pressure on day 1,[b] cm H_2O	24 (20-28)	25 (20-29)	23 (19-27)	< .001
Driving pressure on day 1,[b] cm H_2O	14 (11-18)	15 (12-19)	13 (10-16)	< .001
Tidal compliance on day 1,[c] mL/cm H_2O	30 (23-41)	28 (21-38)	42 (26-45)	< .001
Adjunctive therapies during ICU stay				
Neuromuscular blocking agent	192 (24)	89 (20)	103 (30)	.512
Nitric oxide	167 (21)	92 (21)	75 (22)	.646
Prone positioning	72 (9)	46 (10)	26 (8)	.172

(Continued)

TABLE 1] *(Continued)*

Characteristics	All (N = 789)	Nonsurvivors (n = 444)	Survivors (n = 345)	*P* Value
Extracorporeal lung support	10 (1)	6 (1)	4 (1)	.837
Organ support during ICU stay				
Vasopressors	625 (79)	370 (83)	255 (74)	.001
Renal replacement therapy	197 (25)	133 (30)	64 (19)	< .001
Treatment limitation decision	45 (6)	30 (7)	15 (4)	.148

Quantitative variables are described as median (interquartile range) and were compared between groups using the nonparametric Wilcoxon rank sum test. Qualitative variables are described as No. (%) or No./total No. (%). ECOG = Eastern Oncology Study Group; HSCT = hematopoietic stem cell transplantation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment.
[a]Available for 543 patients.
[b]Available for 494 patients.
[c]Available for 417 patients.

frequency (%) and were compared between groups using the Fisher 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 .20 as the critical *P* value for entry into the model, and .10 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 interquartile range. 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 ORs of variables present in the final model are presented with their 95% CIs. We did not perform imputation for missing data.

In view of the high rate of missing data and the strong correlation between ΔPrs, Crs, and Pplat,rs, 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 ΔPrs, Pplat,rs, and Crs on mortality was plotted, reporting mortality per quintile for each variable. Comparisons across quintiles were performed using Wilcoxon test.

$P < .05$ was considered significant. Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (IBM SPSS Inc) and with R statistical software, version 3.4.3 (available at http://www.r-project.org/) and Survival, lme4, and lmerTest packages.

Results

Study Population

Figure 1 displays the study flowchart. 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 definition,[10] 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. Because Pplat,rs was missing in 295 of these patients, respiratory mechanics indexes were not included in the main analysis. An analysis restricted to the 494 patients with available Pplat,rs was then performed.

Underlying conditions were as follows: hematologic malignancies (n = 409, 52%), solid tumors (n = 274, 35%), connective tissue diseases (n = 152, 19%), solid organ transplants (n = 69, 10%), and drug-related immunosuppression (n = 9, 1%). Fifty-four patients (7%) had undergone allogeneic stem cell transplantation, 80 patients (10%) had undergone autologous stem cell transplantation, and 165 patients (21%) had neutropenia. Median Sequential Organ Failure Assessment 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 nonsurvivors at hospital discharge (Table 1). After adjustment for confounders and clustering effect, variables independently associated with hospital mortality were ARDS of undetermined etiology (OR, 1.66; 95% CI, 1.01-2.72; $P = .045$), need for vasopressors (OR, 1.91; 95% CI, 1.27-2.88; $P = .002$), and need for

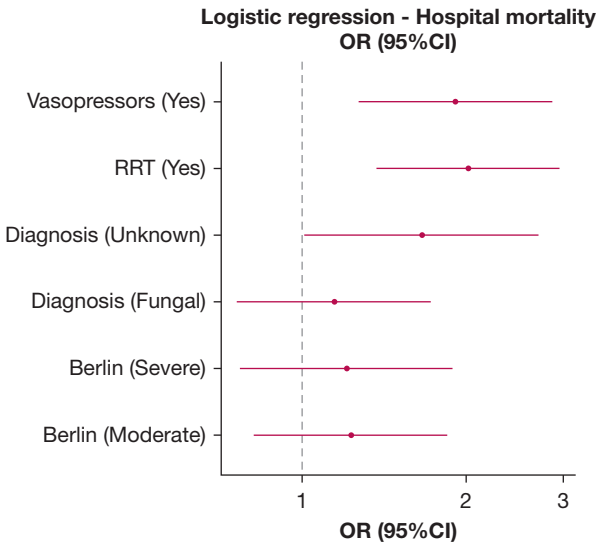

Figure 2 – *Hierarchical model assessing variables independently associated with hospital mortality. Center was included in the model as random effect. Plots report variables independently associated with hospital mortality in the final model, with their 95% CIs. Model C-stat is 0.65 (95% CI, 0.61-0.69), Hosmer-Lemeshow goodness of fit P = .098. RRT = renal replacement therapy.*

renal replacement therapy (OR, 2.02; 95% CI, 1.37-2.97; $P < .001$) (Fig 2).

Pulmonary severity according to the Berlin definition of ARDS was not significantly associated with mortality before or after adjustment (e-Table 2; Figs 2, 3). When forced in the final model, neutropenia was neither selected for (OR, 1.37; 95% CI, 0.92-1.37; $P = .13$) nor changed the final model. Similarly, the influence of underlying hematologic malignancy was assessed in a post hoc analysis, but this variable was not selected for (OR, 1.01; 95% CI, 0.95-1.08; $P = .75$) and did not change the final model.

Impact of Respiratory System Mechanics Indexes in the 494 Patients for Whom Pplat,rs Was Available

Among the 494 patients with available Pplat,rs, there were 226 (45.7%) survivors and 268 (54.3%) nonsurvivors at hospital discharge. Figure 4 displays Pplat,rs, ΔPrs, PEEP, and V_T in survivors and nonsurvivors (e-Table 3).

Before adjustment, higher Pplat,rs, higher ΔPrs (four with missing data), and lower Crs (64 with missing data) were associated with higher mortality (Fig 5). ΔPrs > 14 cm H_2O and Pplat,rs > 24 cm H_2O were associated with higher mortality.

There was a significant correlation between Pplat,rs, ΔPrs, and Crs (e-Fig 1). When included separately in the final hierarchical model taking into account the influence of BMI, ΔPrs (OR, 1.08 per cm H_2O; 95% CI, 1.05-1.12) (Fig 6), Pplat,rs (OR, 1.07 per cm H_2O; 95% CI, 1.04-1.11) (e-Fig 2), and Crs (OR, 0.97 per cm H_2O; 95% CI, 0.95-0.98) (e-Fig 3) were independently associated with hospital mortality.

Discussion

This large preplanned secondary analysis of a multicenter multinational prospective study challenges

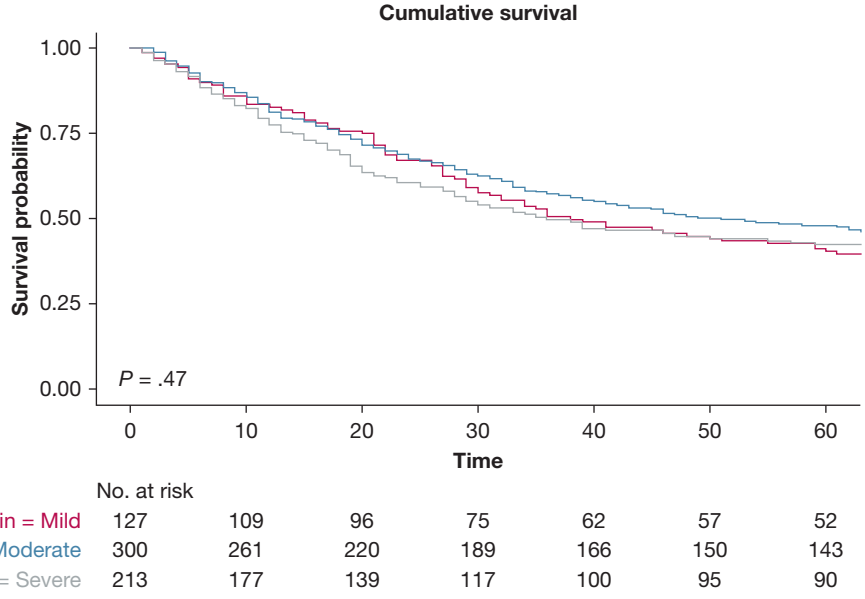

Figure 3 – *Cumulative survival according to the Berlin ARDS severity category. The red line indicates mild ARDS, the blue line indicates moderate ARDS, and the gray line indicates severe ARDS. The three groups were compared using the log-rank test (P = .47).*

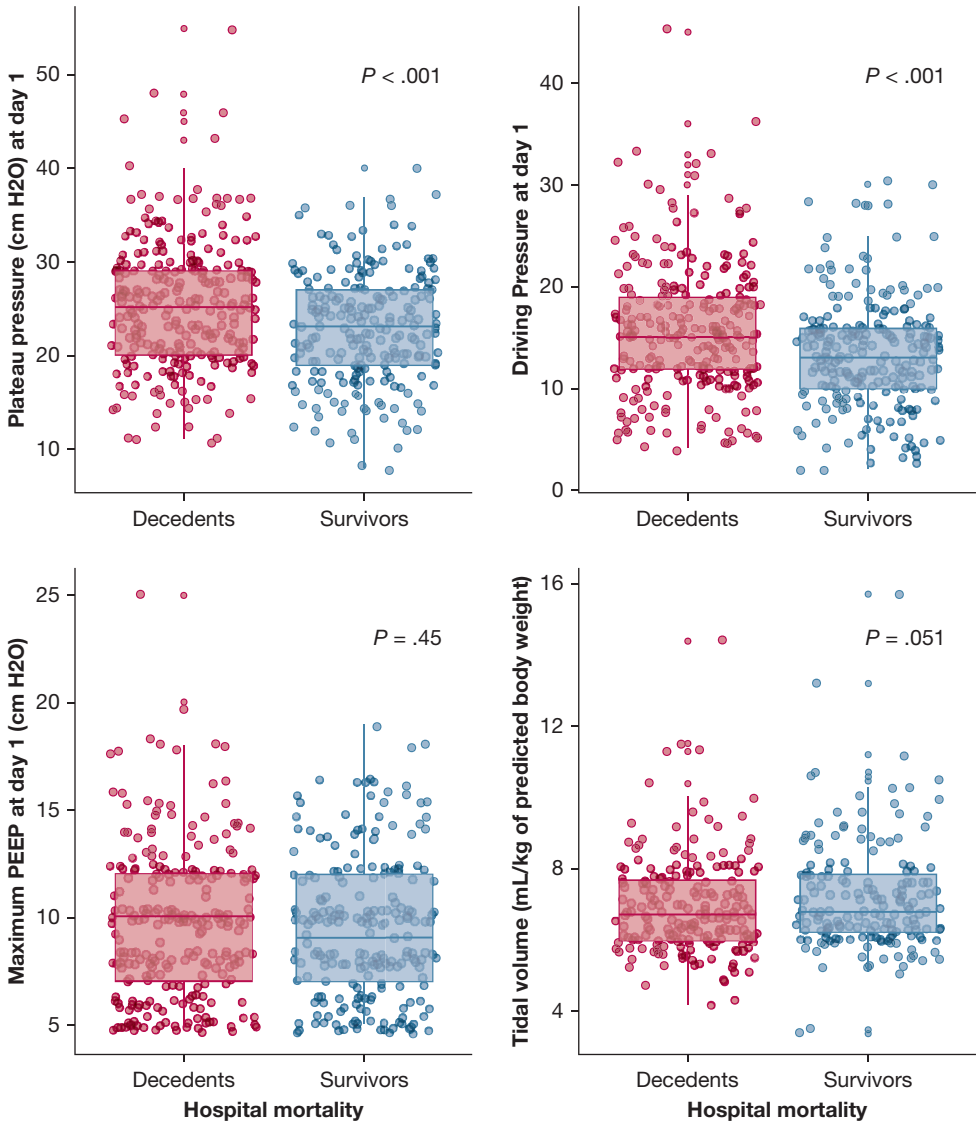

Figure 4 – *Respiratory system plateau pressure and driving pressure, maximum positive end-expiratory pressure, and tidal volume expressed in relation to predicted body weight at day 1 in hospital survivors and nonsurvivors among the 494 patients with available plateau pressure.*

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 nonimmunocompromised 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 with that reported in the 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. ORs were similar to those observed in one study conducted in 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 patients with ARDS.

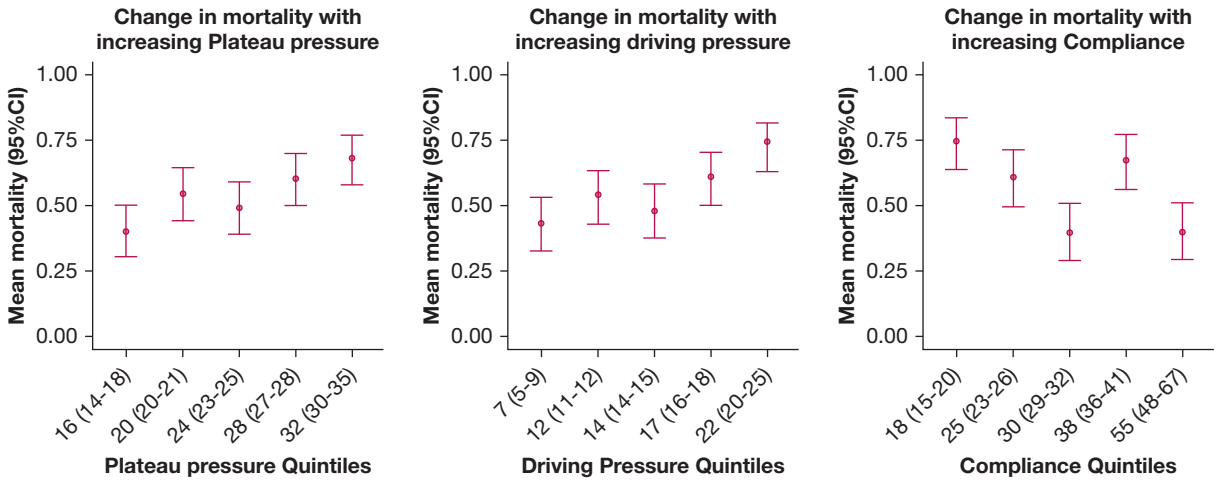

Figure 5 – *Unadjusted hospital mortality across quintiles of plateau pressure, driving pressure, and respiratory system compliance. Dots represents mean mortality and bars represent the 95% CI. The numbers below the x axis are median (interquartile range) of respiratory system characteristics across each quintile (P < .001 across quintiles).*

In contrast with previous reports, we did not find a clear superiority of ΔPrs over Pplat,rs for prediction of patient outcome.[8] Inversely, ΔPrs and Pplat,rs were both independently associated with mortality and were strongly correlated,[14] which could be explained by the relatively low VT, because the superiority of ΔPrs over Pplat,rs to predict mortality is mostly observed in the context of a wide dispersion of VT.[8] Inversely, the superiority of ΔPrs to Pplat,rs to predict mortality was no longer observed when VT was close to 6 mL/kg, as in the patients in this study.[14] The low VT 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 patients. Given the benefit of this therapy in moderate to severe ARDS, this may have influence on 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.

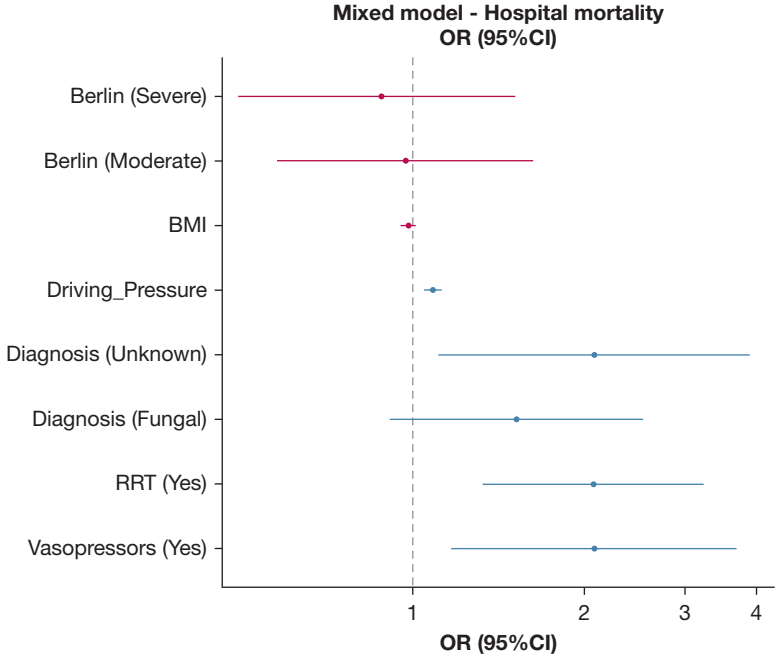

Figure 6 – *Influence of driving pressure in the final hierarchical model assessing variables associated with hospital mortality. Center was included in the model as random effect. Only the 494 patients with available driving pressure measurement were included. Plots report variables independently associated with hospital mortality in the final model, with their 95% CIs. Model C-stat 0.63 (95% CI, 0.59-0.68), Hosmer-Lemeshow goodness of fit: P = .711. See Figure 6 legend for expansion of abbreviation.*

Finally, it is noteworthy that ARDS severity according to the Berlin definition was not associated with mortality. In this cohort, ΔPrs, 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 large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE) study, with less mild ARDS and more severe ARDS.[6] We also cannot exclude the possibility that, because of their specific ARDS causes, immunocompromised patients do not have the same severity criteria as immunocompetent patients. Furthermore, 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 h after intubation did not have any impact on outcome, in contrast with a 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 h after admission. The duration and severity of neutropenia prior to ICU admission and during the ICU stay were therefore not analyzed.

The 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.

This study has several limitations. First, the observational design precludes any causal conclusions. Second, 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. Third, indexes of respiratory system mechanics were not available in all patients, and analyses involving Pplat,rs, ΔPrs, and Crs could not be performed in the whole population. Finally, we focused on patients who were intubated and subsequently excluded patients with ARDS managed by standard oxygen, noninvasive ventilation, or high-flow oxygen because respiratory mechanics indexes cannot be measured in these patients.

Conclusions

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, ΔPrs, Pplat,rs, and Crs 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.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Azoulay E, Pène F, Darmon M, et al. Managing critically Ill hematology patients: time to think differently. *Blood Rev*. 2015;29(6):359-367.
2. Azoulay E, Mokart D, Kouatchet A, Demoule A, Lemiale V. Acute respiratory failure in immunocompromised adults. *Lancet Respir Med*. 2019;7(2):173-186.
3. Azoulay E, Lemiale V, Mokart D, et al. Acute respiratory distress syndrome in patients with malignancies. *Intensive Care Med*. 2014;40(8):1106-1114.
4. Azoulay E, Fieux F, Moreau D, et al. Acute monocytic leukemia presenting as acute respiratory failure. *Am J Respir Crit Care Med*. 2003;167(10):1329-1333.
5. Mokart D, van Craenenbroeck T, Lambert J, et al. Prognosis of acute respiratory distress syndrome in neutropenic cancer patients. *Eur Respir J*. 2012;40(1):169-176.
6. Cortegiani A, Madotto F, Gregoretti C, et al. Immunocompromised patients with acute respiratory distress syndrome: secondary analysis of the LUNG SAFE database. *Crit Care*. 2018;22(1):157.
7. Azoulay E, Lemiale V, Mourvillier B, et al. Management and outcomes of acute respiratory distress syndrome patients with and without comorbid conditions. *Intensive Care Med*. 2018;44(7):1050-1060.
8. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-755.

9. Azoulay E, Pickkers P, Soares M, et al. Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. *Intensive Care Med*. 2017;43(12):1808-1819.

10. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526-2533.

11. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.

12. de Prost N, Pham T, Carteaux G, et al. Etiologies, diagnostic work-up and outcomes of acute respiratory distress syndrome with no common risk factor: a prospective multicenter study. *Ann Intensive Care*. 2017;7(1):69.

13. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800.

14. Guérin C, Papazian L, Reignier J, et al. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. *Crit Care*. 2016;20(1):384.

15. SRLF Trial Group. Hypoxemia in the ICU: prevalence, treatment, and outcome. *Ann Intensive Care*. 2018;8(1):82.

16. Georges Q, Azoulay E, Mokart D, et al. Influence of neutropenia on mortality of critically ill cancer patients: results of a meta-analysis on individual data. *Crit Care*. 2018;22(1):326.

17. Bouteloup M, Perinel S, Bourmaud A, et al. Outcomes in adult critically ill cancer patients with and without neutropenia: a systematic review and meta-analysis of the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH). *Oncotarget*. 2017;8(1):1860-1870.

18. Till GO, Johnson KJ, Kunkel R, Ward PA. Intravascular activation of complement and acute lung injury. Dependency on neutrophils and toxic oxygen metabolites. *J Clin Invest*. 1982;69(5):1126-1135.

19. Looney MR, Su X, Van Ziffle JA, Lowell CA, Matthay MA. Neutrophils and their Fc gamma receptors are essential in a mouse model of transfusion-related acute lung injury. *J Clin Invest*. 2006;116(6):1615-1623.