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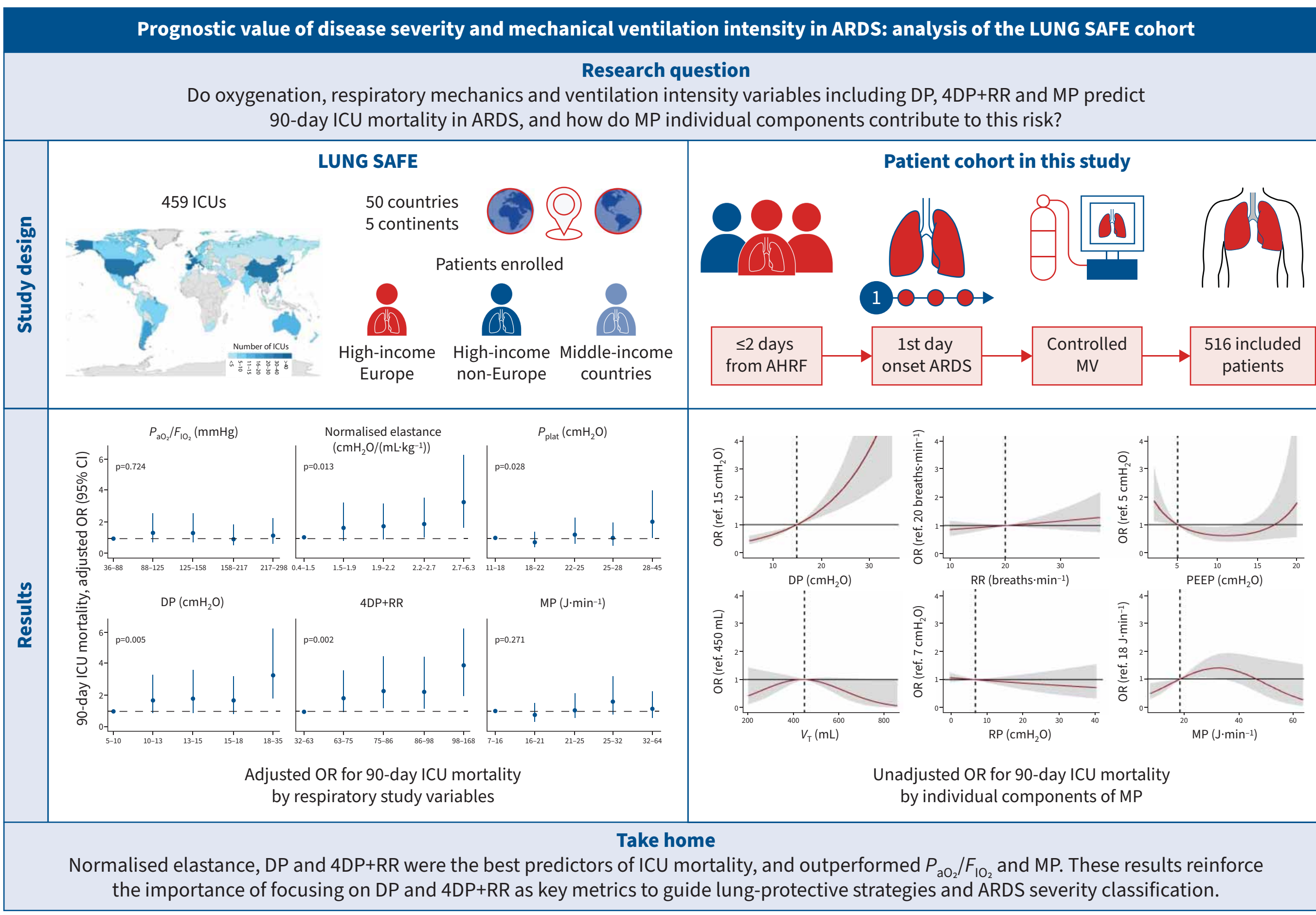

GRAPHICAL ABSTRACT Overview of the study. ARDS: acute respiratory distress syndrome; DP: driving pressure; RR: respiratory rate; MP: mechanical power; ICU: intensive care unit; AHRF: acute hypoxaemic respiratory failure; CMV: controlled mechanical ventilation; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_{plat}: plateau pressure; PEEP: positive end-expiratory pressure; V_T: tidal volume; RP: resistive pressure.

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Prognostic value of disease severity and mechanical ventilation intensity in acute respiratory distress syndrome: analysis of the LUNG SAFE cohort

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In ARDS, normalised static elastance, DP and 4DP+RR were the best predictors of ICU mortality, and outperformed oxygenation and MP. DP performed best in terms of predictive simplicity, should be targeted to limit VILI and used to categorise ARDS severity. https://bit.ly/3IKCgPS

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Abstract

Background We aimed to assess the prognostic performance of different indexes of oxygenation, respiratory mechanics and ventilation intensity in predicting 90-day mortality, and to estimate their independent associations, in a "real-world" observational cohort of acute respiratory distress syndrome (ARDS) patients on intensive care unit (ICU) mortality.

Methods This is a secondary analysis of LUNG SAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE), an international prospective cohort study of patients with severe respiratory failure involving 459 ICUs from 50 countries. We evaluated the prognostic performance of oxygenation (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2})), respiratory mechanics (normalised elastance) and ventilation intensity (plateau pressure (P_{plat}), driving pressure (DP), 4DP+respiratory rate (RR) and mechanical power (MP)) measured on day 1 of controlled mechanical ventilation in ARDS patients, with respect to ICU mortality within 90 days of admission. For each parameter, associations with mortality were assessed using logistic regression models, estimating effect sizes (odds ratios with 95% confidence interval), model discrimination (area under the receiver operating characteristic curve), calibration and overall predictive accuracy.

Results Among 2813 early ARDS patients, 516 (18.3%) met the inclusion criteria: mean±SD age 60±16 years, 61% male. Normalised elastance, P_{plat}, DP and 4DP+RR were significantly associated with

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mortality, with adjusted ORs ranging from 1.02 (95% CI 1.01–1.03) for 4DP+RR to 1.48 (95% CI 1.15–1.95) for normalised elastance. These parameters showed higher predictive accuracy for mortality compared with P_{aO_2}/F_{IO_2} and MP. MP showed a U-shaped relationship with mortality but was not significantly associated with it. Its predictive accuracy decreased after accounting for positive end-expiratory pressure (PEEP) and dynamic resistance, with PEEP also demonstrating a U-shaped association with mortality.

Conclusions Normalised elastance, DP and 4DP+RR, measured at day 1 of ARDS, were the best predictors of ICU mortality, and outperformed oxygenation and MP. DP showed the best balance between predictive accuracy and clinical simplicity. These results reinforce the importance of focusing on DP and 4DP+RR as key metrics to guide lung-protective strategies and ARDS severity classification.

Introduction

Identifying patients at risk for poor outcomes in the earliest stages of acute respiratory distress syndrome (ARDS) can help in tailoring patient management, targeting advanced therapies and reducing complications in patients at greatest risk. There are considerable controversies about the best index to describe the severity of ARDS or the risks of mechanical ventilation, from oxygenation to mechanical power (MP). Currently, the vast majority of clinical trials used oxygenation parameters for stratification of ARDS severity, lacking any enrichment strategy [1, 2]. Furthermore, the intrinsic elastic property of the respiratory system (*i.e.* static elastance) is not used to define the severity of ARDS in the Berlin and "global" ARDS criteria [3, 4] despite its known correlation with the degree of lung injury [5]. Further, normalised elastance was recently suggested as a potential novel respiratory variable to associate on mortality in the era of protective mechanical ventilation [6]. A key issue is optimising mechanical ventilation [7, 8], thereby reducing the risk of ventilator-induced lung injury (VILI) [9] and ventilation intensity [10] in these patients, and MP has been proposed as an integrative way to describe this risk. The risk for VILI is related both to lung injury severity *per se* and to the specific ventilatory settings used to maintain gas exchange.

High tidal volume (V_T) [11] and higher plateau pressure (P_{plat}) [12] have been traditionally associated with VILI in clinical trials, and more recently the role of driving pressure (DP) [13] has received increasing attention [14]. The role of respiratory rate (RR) [15] and the total energy delivered by mechanical ventilation have also been taken into account by the MP or energy delivered by mechanical ventilation over time [16], as a way to capture the contribution of multiple ventilatory components to the development of VILI. MP also includes the resistive component dissipated on the airways, RR and positive end-expiratory pressure (PEEP), both of which have been debated [17–19]. Finally, recently, Costa *et al.* [20] proposed a simpler index combining DP and RR (*i.e.* 4DP+RR) that was strongly associated with mortality.

With regard to both the clinical utility at the bedside and the enrichment capacity for clinical trials, the respective performance of these indexes remains to be fully elucidated. Given these issues, we wished to evaluate their utility in the LUNG SAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE) database of patients with ARDS undergoing controlled mechanical ventilation (CMV) [21]. We evaluated the predictive capacity for intensive care unit (ICU) mortality within 90 days of admission of oxygenation, respiratory mechanics and ventilation intensity including P_{plat}, DP, 4DP+RR and MP measured on day 1 of CMV. We also estimated the independent associations of these parameters with mortality after adjustment for relevant confounders. Further, we explored the contribution of individual elements of MP, particularly PEEP, and whether the recently proposed index combining DP with respiratory frequency (*i.e.* 4DP+RR) would enhance the predictive capacity of DP.

Methods

Patients, study design and data collection, and definitions

LUNG SAFE was a prospective, observational, international multicentre cohort study with a 4-week enrolment window in the winter season in both hemispheres and it enrolled patients with acute hypoxaemic respiratory failure (AHRF) admitted to the ICU who underwent non-invasive or invasive mechanical ventilation. LUNG SAFE methods are detailed elsewhere [21]. National coordinators and site investigators (supplementary appendix) were responsible for obtaining ethics committee approval and patient consent (where required), and for ensuring data integrity and validity.

For the purpose of this analysis, we selected patients with ARDS who underwent CMV within 2 days from AHRF onset (supplementary figure E1). A patient was included if they met at least one of the following conditions: ARDS onset and CMV at the first day of AHRF or confirmed ARDS and CMV at the second day of AHRF [22].

CMV was identified by confirming total RR matched the set RR.

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ARDS was defined according the Berlin definition [3]. CMV included both volume- and pressure-controlled ventilatory modes.

We calculated respiratory mechanics variables from the following variables: V_T, PEEP, P_{plat}, peak inspiratory pressure, RR and predicted body weight.

Composite variables, the analysis of the single components of MP using the simplified equations and further methodological information are reported in the Methods section of the supplementary material.

Mortality was defined as death occurring in the ICU within 90 days of ICU admission. Patients discharged alive from the ICU before day 90 were considered survivors and retained as non-mortality cases in all analyses.

Statistical analysis

Continuous variables were reported as mean with standard deviation and categorical variables as count with percentage. Group comparisons between survivors and non-survivors were performed using Chi-squared tests for categorical data, t-tests for continuous variables with normal distributions and Wilcoxon rank-sum tests for non-normally distributed variables. For each respiratory parameter of interest, both linear and quadratic associations with 90-day ICU mortality were assessed using likelihood ratio testing (LRT), to identify potential non-linear effects.

Prognostic performance was evaluated by univariate and multivariable logistic regression models adjusted for predefined clinical confounders: age, sex, body mass index, arterial pH, presence of comorbidities [23], pulmonary ARDS risk factors [15], non-respiratory Sequential Organ Failure Assessment score, ARDS severity by number of quadrants involved by infiltrates [24] and geo-economic region [21].

Discrimination capacity (reflecting how effectively each variable distinguished between survivors and non-survivors) was assessed using the area under the receiver operating characteristic curve (AUROC or C-statistic), with 95% confidence intervals estimated *via* DeLong's method. AUROC values range from 0.5 (no discrimination) to 1 (perfect discrimination).

Calibration was evaluated using the Hosmer–Lemeshow test, with $p \geqslant 0.05$ considered indicative of adequate model fit across risk strata.

Prediction accuracy was quantified by the Brier score, calculated as the mean squared error between predicted and observed outcomes; scores <0.25 were considered acceptable for binary outcome models.

Pairwise AUROC comparisons were conducted using a non-parametric bootstrap approach (50 000 resamples) to generate robust statistical estimates accounting for possible curve shape and directionality differences. To quantify the magnitude of association, odds ratios with 95% confidence intervals were estimated from logistic models. For parameters with identified non-linear effects, quadratic terms were incorporated and average marginal effects derived *via* non-parametric bootstrapping (50 000 replicates) to estimate odds ratios. Additionally, all respiratory variables were analysed across quintiles to better show the shape of their relationship with mortality.

To examine time to death patterns within 90 days of ICU admission, empirical cumulative distribution functions were plotted for mortality, stratified by optimal thresholds based on Youden's index. Bootstrap-derived 95% confidence intervals (2000 resamples) were reported for each curve and subgroup differences were tested using the Kolmogorov–Smirnov test.

All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. Analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), Stata/MP 14.2 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 2813 patients that fulfilled ARDS criteria in the LUNG SAFE cohort, 516 patients with a full dataset and having ARDS requiring CMV within 2 days from AHRF onset formed the study population (supplementary figure E1). 212 of these (41.1%) died in the ICU within 90-day follow up. A detailed description of baseline demographics, clinical and geo-economic characteristics of the study population is summarised in supplementary table E1. Differences between the study population and patients excluded because of missing ventilatory parameters are reported in supplementary table E2.

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Oxygenation, respiratory mechanics and ventilation intensity stratified by survival

Differences among survivors and non-survivors in respiratory parameters are reported in table 1. Among the explored variables, only MP was not significantly different between survivors and non-survivors. By exploring linear *versus* quadratic effects of these parameters, we observed a quadratic effect of MP on 90-day ICU mortality (LRT, p=0.038) (supplementary figure E2).

A comprehensive description of other ventilatory variables stratified by ICU mortality is reported in supplementary table E3.

Predictive values of ICU mortality

We show the prognostic performance among the three categories of parameters (oxygenation, respiratory mechanics and ventilation intensity) to predict mortality in table 2. Unadjusted AUROCs ranged from 0.544 (95% CI 0.493–0.594) for MP to 0.626 (95% CI 0.577–0.674) for normalised elastance. P_{aO_2}/F_{IO_2} and MP showed a non-significant discrimination performance. When MP was explored as a quadratic effect, it resulted in a significant AUROC (0.567, 95% CI 0.516–0.617). After adjustment for potential confounders, discrimination of all respiratory parameters increased with an AUROC reaching the highest adjusted discrimination with DP and 4DP+RR (table 2). A graphical representation of the discriminative performance by the AUROCs of all respiratory parameters in the overall cohort, and after stratification by geo-economic area, is presented in figure 1. Pairwise comparisons of AUROCs for 90-day ICU mortality showed higher AUROC for normalised elastance, DP and 4DP+RR compared with P_{aO_2}/F_{IO_2} and MP (supplementary table E4).

All models demonstrated adequate calibration, as indicated by non-significant Hosmer–Lemeshow tests ($p \geqslant 0.05$).

Furthermore, among all parameters examined, acceptable accuracy (based on Brier scores) was observed exclusively for normalised elastance, P_{plat}, DP and 4DP+RR (table 2).

Consistently, after evaluating the strength of association between respiratory study variables and mortality, we observed that only these variables (*i.e.* normalised elastance and ventilation intensity, excluding MP) showed a statistically significant positive odds ratio which was confirmed after adjustment for confounders (table 2). Full estimates for all covariates included in the multivariable models are presented in supplementary table E5. No significant interaction between DP and RR was observed (p=0.3918).

To better characterise the non-linear association between respiratory parameters and 90-day ICU mortality, particularly those showing quadratic patterns, we examined mortality rates across quintile categories. Crude mortality rates differed across categories for normalised elastance, P_{plat} and ventilation intensity indexes with the exclusion of MP (figure 2). For each parameter, adjusted odds ratios were estimated using the lowest quintile as the reference and are reported in supplementary table E6 and supplementary figure E3.

Optimal cut-off values of respiratory parameters for predicting 90-day ICU mortality

We identified optimal cut-off points and evaluated their diagnostic utility in clinical decision making, complementing the overall discrimination assessed by the AUROCs. $P_{aO_2}/F_{IO_2} \leqslant 114$ mmHg showed low

TABLE 1 Early oxygenation, respiratory mechanics and ventilation intensity indexes stratified according to vital status at 90-day intensive care unit (ICU) discharge

	Total (n=516)	90-day ICU survivors (n=304)	90-day ICU non-survivors (n=212)	p-value
Oxygenation parameters				
P_{aO_2}/F_{IO_2} (mmHg)	151±66	156±67	143±63	0.034
Respiratory mechanics				
Normalised elastance ($cmH_2O/(mL \cdot kg^{-1})$)	2.1±0.8	2.0±0.8	2.3±0.9	<0.001
Ventilation intensity				
P_{plat} (cmH_2O)	23.8±5.7	23.0±5.4	25.0±5.9	<0.001
DP (cmH_2O)	15.2±5.2	14.3±4.9	16.5±5.2	<0.001
4DP+RR (unit)	82±22	78.2±20.8	87.5±21.7	<0.001
MP ($J \cdot min^{-1}$)	24.9±9.8	24.5±10.2	25.4±9.1	0.092

Data are presented as mean±SD, unless otherwise stated. P_{aO_2}: arterial oxygen partial tension; F_{IO_2}: inspiratory oxygen fraction; P_{plat}: plateau pressure; DP: driving pressure; RR: respiratory rate; MP: mechanical power.

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TABLE 2 Logistic regression results for respiratory variables with model fit and discrimination statistics

	OR (95% CI)	LRT, p-value	C-statistic (95% CI)	Hosmer–Lemeshow test, p-value	Brier score
Oxygenation parameters					
P_{aO_2}/F_{IO_2} (10 mmHg)					
Unadjusted	0.97 (0.94–1.00)	0.028	0.555 (0.505–0.605)	0.090	0.234
Adjusted#	0.99 (0.96–1.03)	0.688	0.739 (0.695–0.783)	0.241	0.201
Respiratory mechanics					
Normalised elastance ($cmH_2O/(mL \cdot kg^{-1})$)					
Unadjusted	1.65 (1.33–2.07)	<0.001	0.626 (0.577–0.674)	0.842	0.232
Adjusted#	1.48 (1.15–1.91)	0.002	0.748 (0.705–0.791)	0.322	0.197
Ventilation intensity					
P_{plat} (cmH_2O)					
Unadjusted	1.06 (1.03–1.10)	<0.001	0.596 (0.546–0.646)	0.766	0.235
Adjusted#	1.05 (1.01–1.09)	0.013	0.746 (0.702–0.789)	0.639	0.198
DP (cmH_2O)					
Unadjusted	1.09 (1.05–1.13)	<0.001	0.620 (0.571–0.669)	0.653	0.231
Adjusted#	1.08 (1.04–1.13)	<0.001	0.754 (0.711–0.796)	0.290	0.195
4DP+RR (unit)					
Unadjusted	1.02 (1.01–1.03)	<0.001	0.624 (0.576–0.673)	0.311	0.231
Adjusted#	1.02 (1.01–1.03)	<0.001	0.754 (0.711–0.796)	0.167	0.195
MP ($J \cdot min^{-1}$)					
Unadjusted	1.01 (0.99–1.03)	0.323	0.544 (0.493–0.594)	0.571	0.242
Adjusted#	1.01 (0.99–1.03)	0.561	0.739 (0.696–0.783)	0.091	0.201
Unadjusted (quadratic)	1.02 (1.02–1.03)¶	0.009	0.567 (0.516–0.617)	0.135	0.239
Adjusted (quadratic)#	1.02 (1.00–1.03)¶	0.127	0.746 (0.702–0.789)	0.199	0.200

LRT: likelihood ratio test; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_{plat}: plateau pressure; DP: driving pressure; RR: respiratory rate; MP: mechanical power. To quantify the strength and precision of the association between each parameter and 90-day ICU mortality, odds ratios with 95% confidence intervals were estimated using logistic regression models. The LRT assesses the statistical significance of each parameter's contribution to the model; a p-value <0.05 suggests a significant association. The area under the receiver operating characteristic curve (or C-statistic) measures the model's discrimination ability (its capacity to distinguish between survived and non-survived); values range from 0.5 (no discrimination) to 1 (perfect discrimination). The Hosmer–Lemeshow test evaluates the goodness-of-fit of the model by comparing observed and predicted probabilities in groups; a p-value >0.05 suggests good calibration. The Brier score quantifies the accuracy of probabilistic predictions, with lower values indicating better prediction accuracy. A possible quadratic association was tested for all parameters using an LRT (ANOVA); only MP showed a statistically significant non-linear effect (p<0.05). #: each association was further adjusted for potential confounders, including age, sex, body mass index, pH, presence of any comorbidities, pulmonary acute respiratory distress syndrome risk factors, adjusted non-respiratory Sequential Organ Failure Assessment score, number of lung quadrants with infiltrates and geo-economic region; ¶: in this case, the reported odds ratios represent average marginal effects derived from the model including the quadratic term, with 95% confidence intervals obtained using a non-parametric bootstrap approach (50 000 replicates).

sensitivity (43%) but moderate specificity (71%), indicating it better identifies survivors than non-survivors at this threshold. Normalised elastance ⩾2.1 $cmH_2O/(mL \cdot kg^{-1})$ had improved sensitivity (58%) and moderate specificity (62%). Among ventilation intensity parameters, P_{plat} ⩾24 cmH_2O and DP ⩾17 cmH_2O showed moderate diagnostic profiles, with sensitivity and specificity values ranging from 50% to 64%. The combined parameter 4DP+RR ⩾76 achieved the highest sensitivity (71%) but lower specificity (48%). MP ⩾22.1 $J \cdot min^{-1}$ had moderate sensitivity and specificity, suggesting weaker predictive ability compared with the other evaluated parameters (table 3).

Figure 3 shows the empirical cumulative distribution of 90-day ICU mortality across subgroups defined by the optimal cut-off for each respiratory parameter. A clear separation in mortality curves was observed for all variables except MP, which showed overlapping distributions between strata (p=0.053).

MP components and their association with 90-day ICU mortality

To better understand the prognostic performance of MP, we analysed the individual respiratory components contributing to this metric in relation to mortality.

Non-linear effects were found for PEEP and V_T, with quadratic associations observed in relation to 90-day ICU mortality (LRT, p<0.05) (supplementary figure E2g and i). Among them, only PEEP exhibited a statistically significant U-shaped relationship, confirmed after adjustment for clinically relevant

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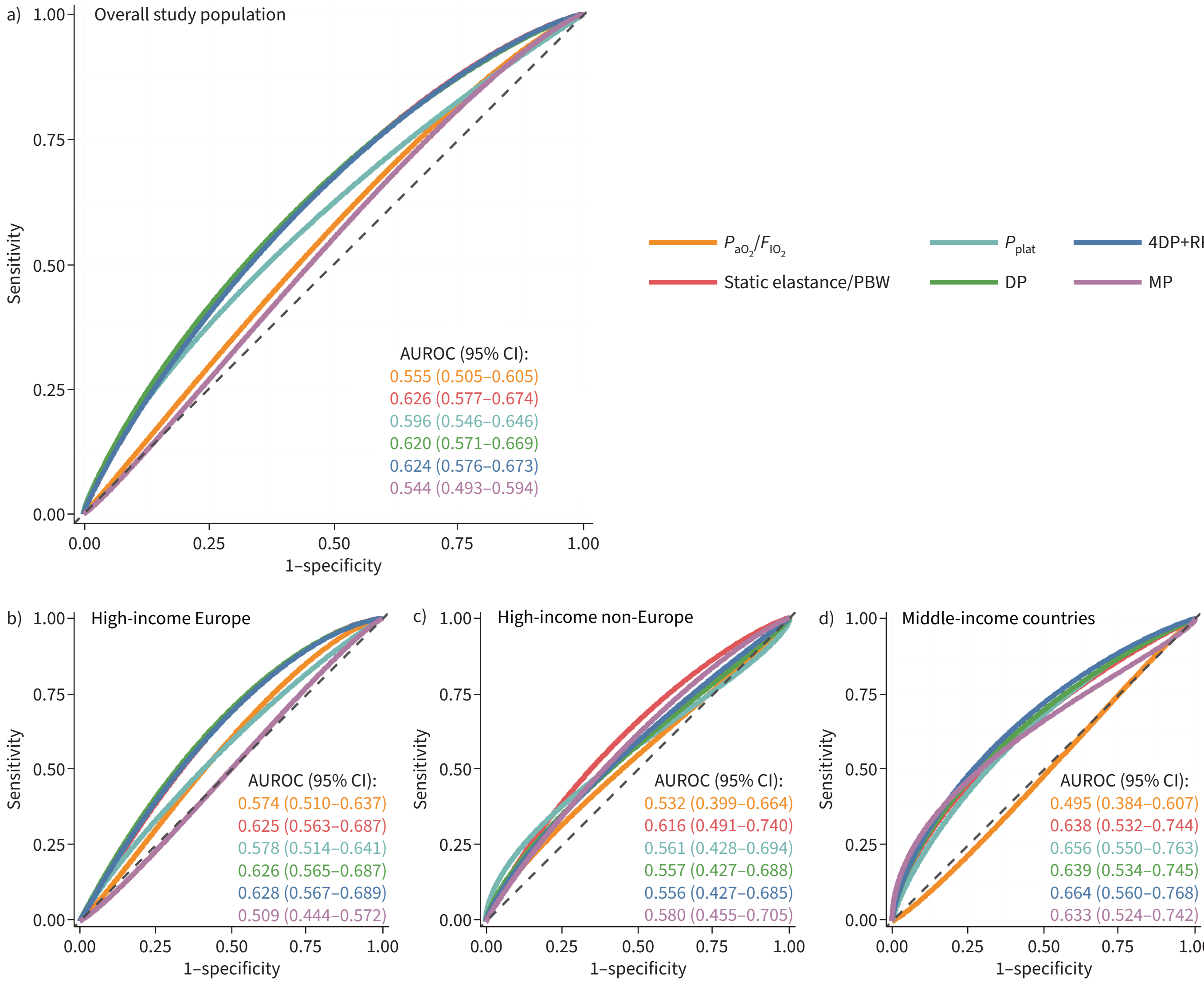

FIGURE 1 Discriminative performance of respiratory parameters for 90-day intensive care unit (ICU) mortality: receiver operating characteristic (ROC) curve analysis. ROC curves for respiratory variables evaluated as predictors of 90-day ICU mortality: arterial oxygen tension (P_{aO_2})/ inspiratory oxygen fraction (F_{IO_2}), normalised elastance (static elastance/predicted body weight (PBW)), plateau pressure (P_{plat}), driving pressure (DP), 4DP+respiratory rate (RR) and mechanical power (MP). ROC curves were smoothed using binormal smoothing. The area under the ROC curve (AUROC) with 95% confidence intervals, estimated using DeLong's method, is reported for each variable and colour-coded to match its corresponding ROC curve. The diagonal dashed line indicates the line of no discrimination (AUROC 0.5). ROC curve analysis was conducted on a) the overall study population and b–d) stratified by geo-economic region: b) high-income European countries, c) high-income countries outside Europe and d) middle-income countries.

confounders (figure 4c and supplementary table E7). Interestingly, PEEP did not show interaction with any of the explored study variables (supplementary table E8).

Excluding PEEP, the static elastic component, from the MP equation improved its discriminative ability, yielding a statistically significant AUROC of 0.562 (95% CI 0.512–0.612) (supplementary table E9, equation 2). Further removal of the resistive component improved its predictive performance (AUROC 0.585, 95% CI 0.536–0.634) (supplementary table E9, equation 5). Among all individual components tested, only the dynamic elastic MP showed adequate discrimination (supplementary table E9, equation 5).

No significant interaction was found between MP and normalised elastance in predicting outcome (supplementary table E10). Similarly, flow profile (decelerating *versus* constant) did not modify the relationship between MP, or its dynamic components such as DP and resistive pressure, and mortality (supplementary table E11).

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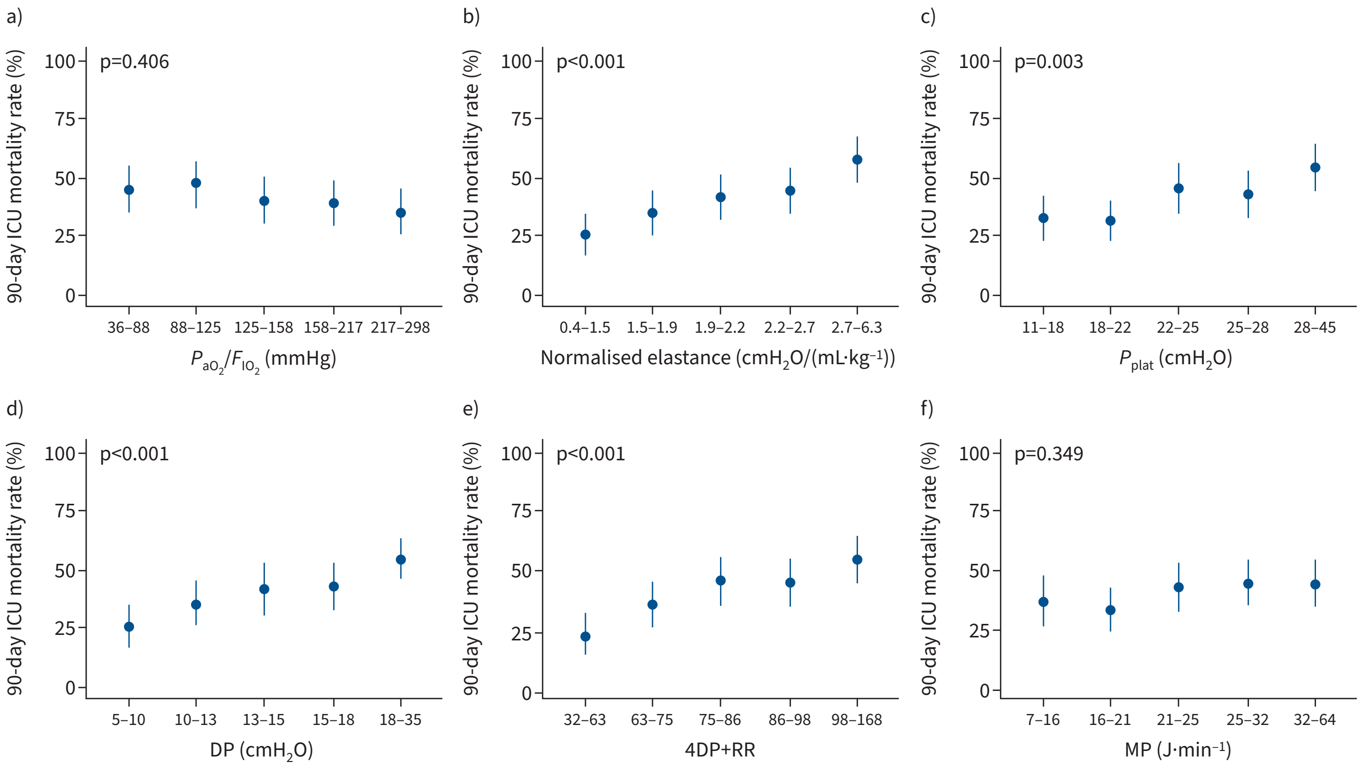

FIGURE 2 90-day intensive care unit (ICU) mortality rate across quintiles of respiratory study variables. Proportion of patients who died within 90 days of ICU admission, stratified by quintiles of respiratory variables. a) Oxygenation was assessed by arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}), b) respiratory mechanics by normalised static elastance, and c–f) ventilation intensity by c) plateau pressure (P_{plat}), d) driving pressure (DP), e) 4DP+respiratory rate (RR) and f) mechanical power (MP). In each panel, p-values refer to the statistical comparison of mortality proportions across quintiles using the Chi-squared test.

Discussion

This analysis of the predictive capacity for mortality of early indices of oxygenation, respiratory mechanics and ventilation intensity in a prospective observational global patient cohort of mechanically ventilated patients with ARDS unveiled a number of clinically relevant findings.

TABLE 3 Optimal cut-off values of respiratory parameters for predicting 90-day intensive care unit (ICU) mortality

	Cut-off to predict 90-day ICU mortality	Youden's index	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Oxygenation parameters						
P_{aO_2}/F_{IO_2} (mmHg)	⩽114	0.137	0.43 (0.36–0.50)	0.71 (0.65–0.76)	0.51 (0.43–0.58)	0.64 (0.59–0.69)
Respiratory mechanics						
Normalised elastance ($cmH_2O/(mL \cdot kg^{-1})$)	⩾2.1	0.200	0.58 (0.51–0.64)	0.62 (0.57–0.68)	0.52 (0.45–0.58)	0.68 (0.62–0.73)
Ventilation intensity						
P_{plat} (cmH_2O)	⩾24	0.180	0.64 (0.57–0.70)	0.54 (0.48–0.60)	0.49 (0.43–0.55)	0.68 (0.62–0.74)
DP (cmH_2O)	⩾17	0.183	0.49 (0.42–0.56)	0.70 (0.64–0.75)	0.53 (0.46–0.60)	0.66 (0.61–0.71)
4DP+RR (unit)	⩾76	0.191	0.71 (0.64–0.77)	0.48 (0.43–0.54)	0.49 (0.43–0.55)	0.70 (0.64–0.76)
MP ($J \cdot min^{-1}$)	⩾22.1	0.122	0.63 (0.56–0.70)	0.49 (0.43–0.55)	0.46 (0.41–0.52)	0.66 (0.59–0.72)

PPV: positive predictive value; NPV: negative predictive value; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_{plat}: plateau pressure; DP: driving pressure; RR: respiratory rate; MP: mechanical power. Cut-off values were determined by maximising Youden's index from receiver operating characteristic curve analyses because Youden's index reflects the best balance between sensitivity and specificity. Sensitivity, specificity, PPV and NPV were estimated with their 95% confidence intervals using the exact (Clopper–Pearson) method.

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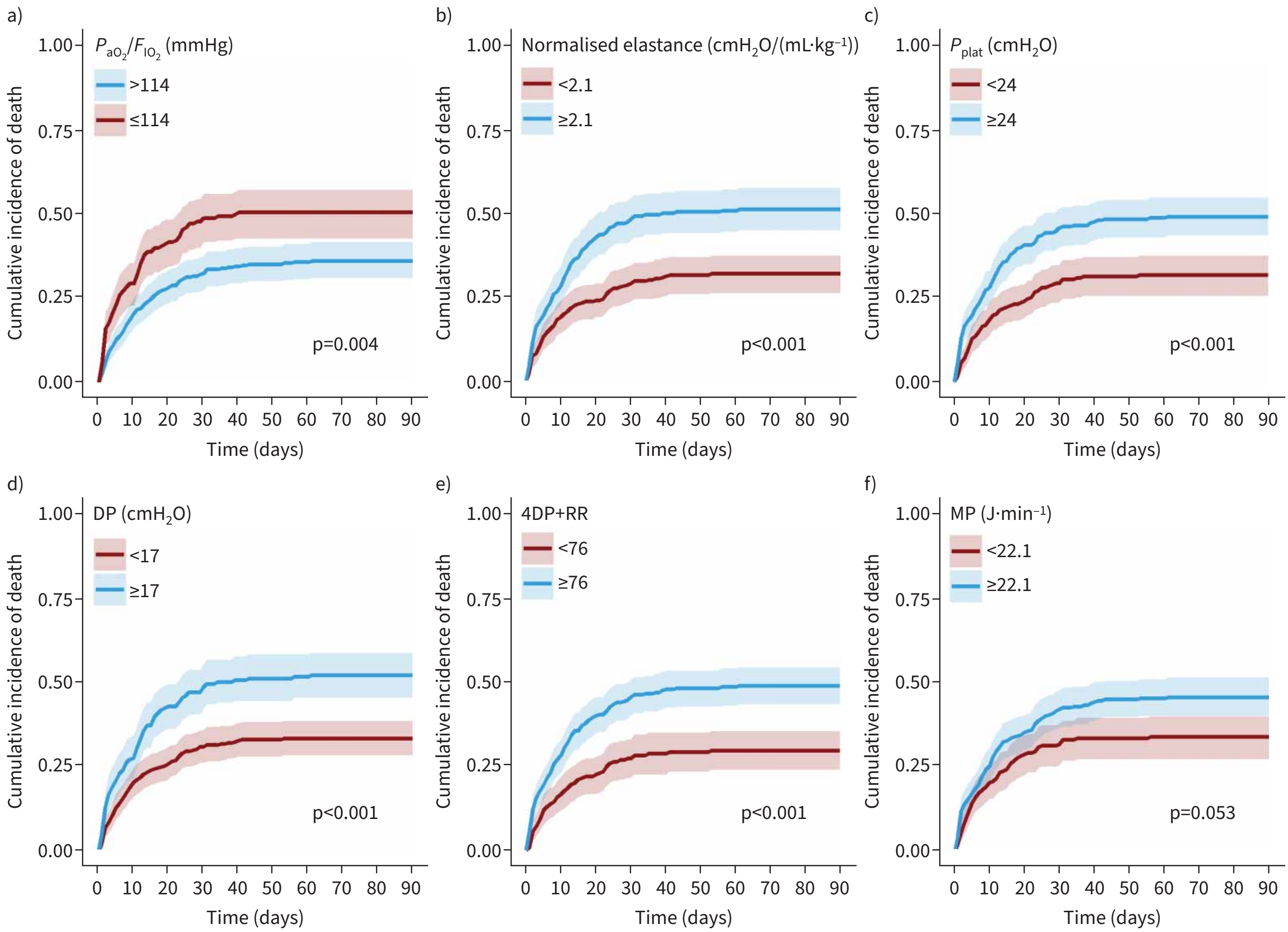

FIGURE 3 Cumulative probability of 90-day intensive care unit (ICU) mortality in the study population, stratified by the optimal threshold for each respiratory parameter: a) arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}), b) normalised elastance, c) plateau pressure (P_{plat}), d) driving pressure (DP), e) 4DP+respiratory rate (RR) and f) mechanical power (MP). Curves represent empirical cumulative distribution functions of time to ICU death. Shaded areas indicate 95% confidence intervals estimated *via* bootstrap (2000 replications). Respiratory study parameters were dichotomised using thresholds identified by Youden's index to optimise discriminative ability. Statistical differences between groups were evaluated using the Kolmogorov–Smirnov test.

First, oxygenation was not significantly associated with ICU mortality in either univariable and multivariable analyses. Further, it showed poor discrimination, suboptimal accuracy and no relevant improvement in calibration, underscoring its limited prognostic utility.

Second, respiratory mechanics (*i.e.* normalised elastance) together with some ventilation intensity parameters (*i.e.* P_{plat}, DP and 4DP+RR) showed a significant association with 90-day ICU mortality after adjustment for clinically meaningful confounders. It is important to note that although none of the explored ventilatory parameters alone achieved high discrimination for 90-day ICU mortality, normalised elastance, DP and 4DP+RR provide better predictive performance than P_{aO_2}/F_{IO_2} and MP at selected cut-offs determined using ROC curve analysis.

Last, MP showed a non-linear (quadratic) relationship with mortality, but did not demonstrate significant prognostic discrimination. A comprehensive analysis of the individual components of MP suggested that its dynamic resistive contribution and PEEP reduced its predictive performance. However, only PEEP was associated with 90-day ICU mortality, even after adjustment for major confounders, with a U-shape.

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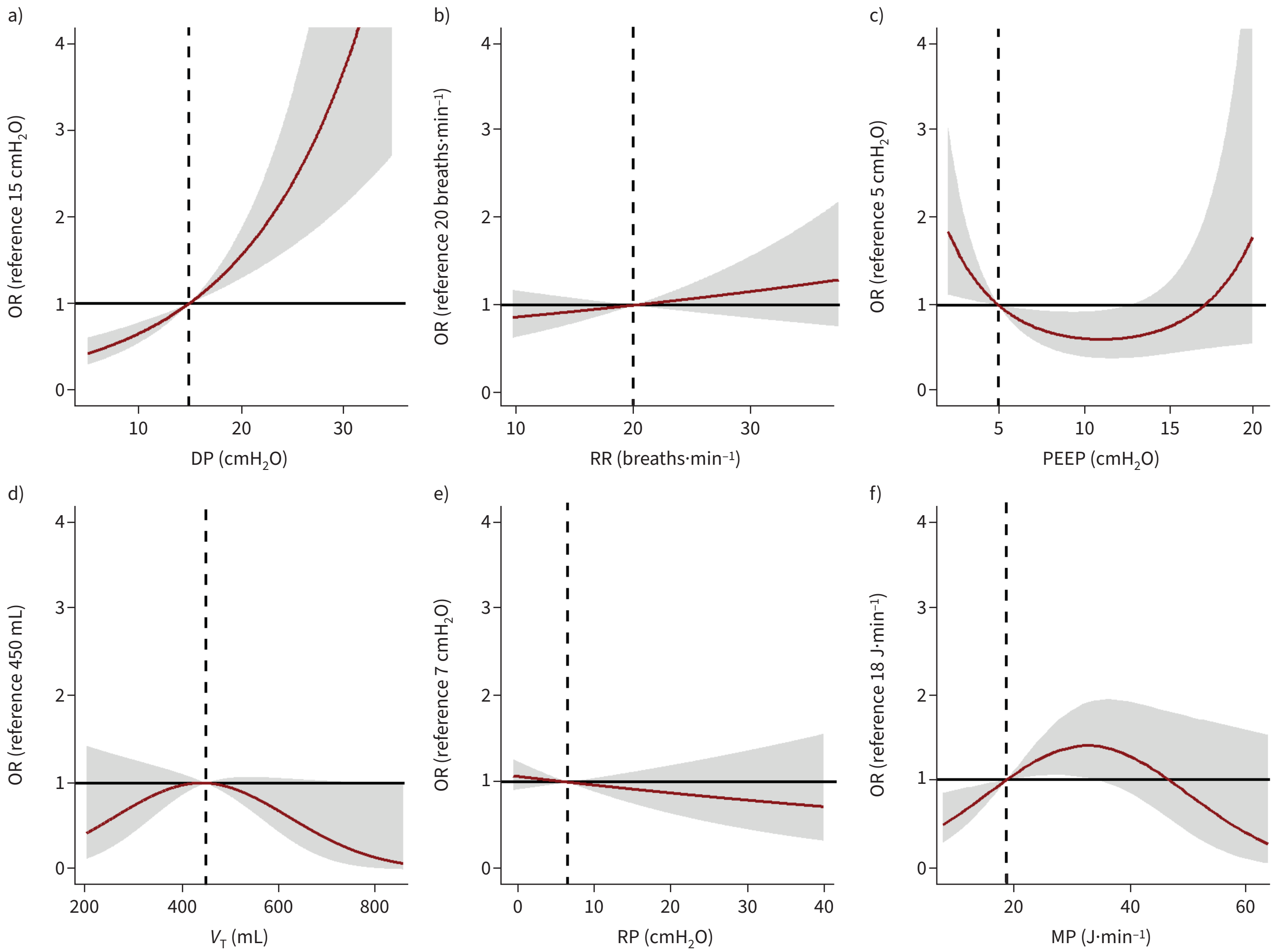

FIGURE 4 Unadjusted odds ratios for 90-day intensive care unit (ICU) mortality according to individual ventilatory components involved in mechanical power (MP) calculation. Odds ratios are expressed relative to the following reference values: a) driving pressure (DP): 15 cmH_2O [13], b) respiratory rate (RR): 20 breaths·min^{-1} (median value), c) positive end-expiratory pressure (PEEP) level: 5 cmH_2O (low PEEP strategy), d) tidal volume (V_T): 450 mL (considering 6 mL·kg^{-1} in a 75 kg patient), e) resistive pressure (RP): 7 cmH_2O (median value) and f) MP: 18 J·min^{-1} [46]. Grey shaded areas represent 95% confidence intervals estimated for each odds ratio.

Failure of oxygenation to predict outcome

Our findings show that respiratory mechanics parameters (*i.e.* normalised elastance) and some variables of ventilation intensity (*i.e.* P_{plat}, DP and 4DP+RR) showed a significant independent association with ICU mortality, whereas oxygenation was neither independently associated with outcome nor useful in mortality prediction.

Although P_{plat} was lower than the protective cut-off of 30 cmH_2O, it was strongly associated with mortality, suggesting that lung stress may contribute to major outcomes in our population [25]. Furthermore, normalised elastance, DP and 4DP+RR showed the highest predictive performance of 90-day ICU mortality, with DP confirming findings by Chen *et al.* [26]. Although based on a different type of analysis, our findings are in line with recent data by Yehya *et al.* [14]. In a reanalysis of the ALVEOLI and ExPress trials, Yehya *et al.* [14] reported that the decrease in DP, but not the increase of P_{aO_2}/F_{IO_2}, was strongly associated with outcome. This further suggests that DP and its dynamic changes may represent actionable bedside variables for enrichment in ARDS clinical trials [27]. When mortality prediction was evaluated by using discrimination, normalised elastance, DP and 4DP+RR outperformed oxygenation, and this should be carefully considered given that the current definition of ARDS severity is based on oxygenation criteria [3]. Our findings should be interpreted considering the known limitations of

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the P_{aO_2}/F_{IO_2} ratio as a marker of lung injury severity. Several confounding factors, including the non-linear relationship between F_{IO_2} and venous admixture, may significantly affect oxygenation measurements and potentially alter ARDS severity classification based on P_{aO_2}/F_{IO_2} thresholds [28]. Moreover, the lack of standardisation regarding PEEP [29, 30] or mean airway pressure [31] levels during P_{aO_2}/F_{IO_2} assessment introduces further variability.

Recently, Catozzi *et al.* [32] reported that ARDS severity based on oxygenation impairment fails to capture VILI, an intermediate patient outcome, compared with DP. Our findings add to these findings, confirming the poor predictive performance of oxygenation in outcome prediction compared with normalised elastance and DP-related variables in a real-world observational study. Although P_{aO_2}/F_{IO_2} is used to classify ARDS severity, it does not reflect oxygen delivery, which is the main driver of tissue oxygenation; it depends on multiple parameters (*i.e.* cardiac output, haemoglobin levels and oxygen saturation) [33] and is a known contributor to mortality in critically ill patients [34]. Furthermore, ventilator settings, particularly high PEEP [35] and DP [36], can adversely affect cardiac output and pulmonary perfusion, further reducing the reliability of oxygenation indices as surrogates for tissue oxygen delivery.

MP and outcome

Recently, MP was proposed to unify the different individual components of VILI and quantify the contribution of mechanical ventilation on lung damage [12]. MP positively associates with ARDS severity using Berlin definition severity criteria [32]. However, MP was not associated with differential survival outcomes. In fact, MP had a low predictive performance for ICU mortality compared with normalised elastance and DP and 4DP+RR as observed by the analysis of the AUROCs. Our findings confirm data from Coppola *et al*. [37] in ARDS patients that reported no difference in MP between survivors and non-survivors. Furthermore, in a retrospective analysis of almost 5000 patients with ARDS, Dianti *et al*. [38] did not report a benefit by using MP compared with DP to weight the effect of VILI on death.

Role of components of MP: implications for PEEP, V_T and airway resistance

MP includes static and dynamic variables that contribute to VILI and may individually predict outcome [16]. PEEP is considered a linear static contributor to power. However, this does not account for the potentially protective effects of higher PEEP-induced lung recruitment, which may be particularly relevant in the presence of severe ARDS [18, 19, 39]. In experimental data, Collino *et al*. [40] suggested the potential detrimental role of too low or too high levels of PEEP: the first leading to derecruitment and atelectrauma, the second leading to lung overdistension. Recently, Schaefer *et al*. [17] reported in an elegant reanalysis of data from the clinical trial EPVent study that the inclusion of PEEP in MP is associated with a poor prediction of mortality (AUROC 0.51, 95% CI 0.29–0.74). In contrast, exclusion of the PEEP component led to a 31% increase in mortality prediction (AUROC 0.67, 95% CI 0.44–0.91). The authors hypothesised a U-shape behaviour of PEEP in relation to VILI because of the balance between atelectasis and overdistension [40, 41]. These studies support our findings in detecting a quadratic effect and a U-shape association between PEEP and ICU mortality, although we cannot exclude that high levels of PEEP may reflect underlying severity of lung injury, rather than contribute causally to outcome. This finding suggests that the contribution of PEEP to MP is non-linear and might explain why MP has no association with outcome. Of note, V_T, although considered linear in the MP equation, showed a quadratic effect, and it did not show any association with 90-day ICU mortality. Furthermore, our data show that the resistive component of MP was not associated with patient outcome. The dissipation of this component of pressure to the airway resistance is not transferred to the lungs. The lack of contribution to the outcome of V_T and resistive MP confirm the recent data reported by Costa *et al*. [20] in an ARDS population and Barbeta *et al*. [42] in a COVID-19 respiratory failure population.

DP and 4DP+RR: clinical implications

4DP+RR showed a similar predictive accuracy of DP alone, without allowing further significant predictive power in our cohort by the inclusion of RR. 4DP+RR focuses on the DP applied to the lung over time, which may prove to be useful in other settings. 4DP+RR above or below 76 (*i.e.* optimal cut-off to predict 90-day ICU mortality) dissects cohorts of patients with a significantly different risk of mortality using an empirical cumulative distribution function of time to ICU mortality. Whether changes in DP and RR to reach the same 4DP+RR will have the same impact on VILI and outcome, and whether this has a different association based on the compliance of the respiratory system, as reported by Costa *et al*. [20] and discussed by Beitler and Walkey [43], have yet to be demonstrated. DP and 4DP+RR may be a novel target to provide an enrichment strategy for clinical trials in ARDS [1].

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Strengths and limitations

This study has important strengths. The study evaluates the respective performance of indices of oxygenation, respiratory mechanics and ventilation intensity in a large and diverse prospective observational "real-world" cohort of patients with ARDS, making the findings relevant to clinical practice. There are also several limitations. First, the use of mortality as the common benchmark to compare the predictive accuracy of different indexes, while necessary due to the lack of lung imaging or histopathological data confirming VILI, is a limitation, because of the diverse contributors to mortality in critically ill patients with ARDS. In fact, the Berlin definition of ARDS demonstrated an AUROC for mortality in the original paper of only 0.58 (95% CI 0.56–0.59) [3]. This needs to be considered when considering that normalised elastance, DP and 4DP+RR had an AUROC of 0.63, 0.62 and 0.62, respectively, for mortality. Even if this value might appear low in absolute terms, any increase in the AUROC value may be associated to a mortality increase related to lung injury. Second, the retrospective design and the secondary analysis of the study mean that it may be underpowered to detect study aims. Third, missing data mainly about P_{plat} might limit the generalisability of our findings to patients who had P_{plat} measured. Specifically, patients included in our cohort showed a higher use of adjunctive measures [44], that was not associated with a difference in mortality, and a higher representation of middle-income countries, that similarly matched the proportion of the historical overall LUNG SAFE cohort of ARDS patients [45]. Fourth, we acknowledge that our findings rely on ventilatory data at baseline and we cannot exclude that dynamic ventilatory changes or events over time may have acted as mortality risk modifiers in ARDS considering its multifactorial aetiology and development. Finally, the exploratory nature of our findings cannot infer causal relations but prove different levels of association between the study indexes and the outcome.

Conclusions

Normalised elastance, DP and 4DP+RR, measured at day 1 of ARDS, were the most reliable predictors of 90-day ICU mortality in this large, prospective observational "real-world" cohort of patients with ARDS. These parameters consistently outperformed oxygenation metrics, supporting their role in stratifying ARDS severity. MP was not associated with mortality, likely due to confounding contributions from PEEP. In fact, PEEP showed a U-shaped adjusted association with mortality. These findings reinforce the relevance of targeting DP and 4DP+RR as key targets to limit lung injury and, together with normalised elastance, for enriching patient selection in future ARDS clinical trials.

Data availability: Data are available upon reasonable request to the LUNG SAFE steering committee (contact: jlaffey@universityofgalway.ie).

This study was prospectively registered with ClinicalTrials.gov with identifier number NCT02010073.

Ethics statement: National coordinators and site investigators (supplementary appendix) were responsible for obtaining ethics committee approval and patient consent (where required), and for ensuring data integrity and validity.

Conflicts of interest: The authors have no potential conflicts of interest to declare.

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