Research Square

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Lung-heart pressure index is a risk factor for acute respiratory distress syndrome (ARDS): A machine learning and propensity score-matching study.

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Research

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Abstract

Background

Ventilator-induced lung injury (VILI) and haemodynamic instability play vital roles in acute respiratory distress syndrome (ARDS). The principle of driving pressure (DP) is the response to “volutrauma”, and the mean arterial pressure (MAP) is a haemodynamic systemic manifestation. In this study, we explored a novel lung-heart pressure index (LHPI) based on DP and MAP and explored its prognostic value in patients with ARDS.

Methods

This is a retrospective study based on the MIMIC-III database. ARDS patients who had undergone mechanical ventilation for more than 48 hours were selected through structured query language. The focus of the study was whether a high LHPI was associated with 30-day mortality and whether its predictive power was better than that of DP and mechanical power (MP). We used random forest, propensity-score matching, and logistic regression to test our hypothesis.

Results

A total of 448 ICU ARDS patients were enrolled. The mortality rate of ARDS patients was 29.02%. The LHPI was more important than DP and MP in the random forest. A significant adverse effect of high LHPI on 30-day mortality was observed in the high-LHPI group compared to the effect observed in the low-LHPI group (OR=1.86, 95% CI 1.08–3.26, p =0.027). More importantly, LHPI was significantly better than DP (NRI=0.054, 95% CI (0.014-0.094), P=0.008; IDI=0.011, 95% CI (0.002-0.019), P=0.014) and MP (NRI=0.061, 95% CI (0.001-0.122), P=0.049; IDI=0.047, 95% CI (0.022-0.071), P<0.001) in predicting mortality.

Conclusions

The study showed that the LHPI was a powerful prognostic indicator of 30-day mortality in ARDS patients, and its predictive discrimination was better than that of DP and MP. Further experimental trials are needed to investigate whether adjusting treatment decisions according to the LHPI will significantly improve clinical outcomes.

Background:

Acute respiratory distress syndrome (ARDS) is present in 10% of ICU patients[1]. Currently, mechanical ventilation remains the primary treatment for patients with ARDS[2]. However, despite "lung-protective ventilation," ARDS has been associated with a high mortality rate of 30–40% in most studies, despite some improvements over the past decades[3]. Therefore, we must quickly identify the subgroup of patients with a high risk of death to optimize the provision of respiratory support and to provide treatment to those at risk.

The causes of the high mortality in ARDS patients are complex and multifactorial. Ventilator-induced lung injury (VILI) is a significant cause of mortality in ARDS patients, and lung strain plays a vital role in VILI[4]. In addition to lung strain, the ventilator parameter settings also affect haemodynamic[5], which appears to be the main factor associated with mortality [6].

Several studies have shown that driving pressure (DP)[7–9],as a specific manifestation of lung strain, and MAP[10, 11] are independent risk factors for ARDS mortality. However, related research on ARDS has not reported an integrated indicator based on DP and MAP, which may better reflect the comprehensive impact of mechanical ventilation on the respiratory and circulatory systems.

In our study, a novel integrated indicator, based on DP and MAP, was defined as the lung-heart pressure index (LHPI). We hypothesized that predicting ARDS mortality based on LHPI might be significantly better than the prediction based on known risk factors such as DP and mechanical power (MP).

First, we used LHPI as a continuous variable to verify whether it was more important than DP and MP using the random forest model. Second, we used LHPI as a categorical variable and adjusted the variables by propensity-score matching to verify whether it was an independent predictor, and we explored whether LHPI played the same role in the ARDS cohorts with different severities. Finally, we further assessed the predictive power of LHPI, DP, and MP through the net reclassification index (NRI) and integrated discrimination of improvement (IDI).

Methods:

Study Cohort

We searched the Medical Information Mart for Intensive Care III (MIMIC,v1.4) database developed and maintained by the MIT Computational Physiology Laboratory[12], which is an extensive, free, public database of hospitalization information for more than forty thousand identified patients who stayed in the critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012. The database includes demographics, hourly vital signs, laboratory test results, treatment procedures, medications, nursing records, imaging data, and information, including in-hospital or out-of-hospital mortality. We completed the required courses for the used of the database and obtained the corresponding certificate (researcher certification number 1605699 and record id 27752407).

We conducted a single-centre, retrospective study of ARDS patients in Berlin who were in the ICU for the first time according to the method established by Johnson et al[13, 14].

Data were extracted from the database using structured query language (SQL). The following demographic data (using the mean value from the second day of admission data) were collected: age, sex, ethnicity (white, black, other), body mass index (BMI), smoking status, ARDS severity (according to the Berlin definition), disease severity scores (Sequential Organ Failure Assessment [SOFA]), vital signs (MAP, respiratory rate [RR], heart rate [HR], Pao2/Fio2), laboratory values (pH, lactate, red cell volume

distribution width [RDW]) and ventilator parameters (lung-heart pressure index (LHPI, [100%*DP/MAP]), DP, MP, platform pressure (Pplat)).

Outcome

The primary outcome of the study was 30-day mortality from the date of ICU admission. We collected patient mortality information from the social security database.

Random forest machine

Random forest is an ensemble-based method that focuses only on ensembles of decision trees[15]. This method combines the base principles of bagging with random feature selection to add additional diversity to the decision tree models. After the ensemble of trees (the forest) is generated, the model uses a vote to combine the trees' predictions. The advantage of random forest is that it could correct for the decision tree habit of overfitting to their training set, handle noisy or missing data as well as categorical or continuous features, select only the most critical features and estimate the importance of variables in determining a classification.

In our study, the whole dataset was split 3:1 into training data and testing data sets. The variables, including LHPI, DP, MP, the ratio of MP to MAP (MP/MAP), platform pressure, age, ethnicity, RR, HR, BMI, smoking status, SOFA, RDW, pH, Pao_2/Fio_2 and lactate, were entered into a random forest model. The random forest model was trained on the training data and tested on the testing data. We used repeated 10-fold cross-validation ten times to determine the best mtry value for the random forest. After we submitted the final model, we evaluated the importance of variables in the model and the effect of variables on mortality.

Random Forest was performed by using the “randomForest” package in R.

Propensity score matching

We determined the optimal cut-off point by setting up the Receiver Operating Characteristic (ROC) curve and finding the largest Youden index (through the "OptimalCutpoints” package in R). Then, baseline characteristics of the original cohort were stratified by LHPI, matching low-LHPI patients based on estimated propensity scores with high-LHPI patients as the standard group[16]. The propensity score for an individual was determined based on the given covariates of age, sex, ethnicity, BMI, MAP, RR, HR, ARDS severity, smoking status, SOFA, pH, RDW, and lactate using a logistic regression model. This method consisted of ranking the high-LHPI patients and low-LHPI patients, then selecting the patient with the highest LHPI, and finding the low-LHPI patient with the closest propensity score. Both patients were then removed from consideration for matching, and the next highest patient was selected.

After matching, to assess the balance between the two groups, the standardized mean differences (SMDs) between the low-LHPI cohort and the high-LHPI cohort were calculated. Continuous variables are shown by means and standard deviations, and categorical variables are represented by total and proportion. For continuous variables, we used the non-parametric test or the Wilcoxon rank-sum test. For the categorical variables, we used the chi-square test or Fisher's exact test.

We used random forest imputation to process missing data (in Additional file 1: Fig S1)[17].

Comparing ventilator parameters

NRI is the improvement in reclassification that could evaluate the improvement in predictive performance obtained by adding or changing a predictor to a predictive model, and it is the sum of the differences in proportions of individuals moving up minus the proportion moving down for those with the outcome, and the proportion of individuals moving down minus the proportion moving up for those without the outcome[18]. Additionally, we evaluated predictive performance through IDI, which is a measure that integrates net reclassification of all possible cutoffs for the probability of the outcome[18].

In this study, we entered age, sex, DP, MAP, Pao2/Fio2, SOFA, RR, BMI, RDW, and pH into a logistic regression model. Based on the selection of the best model, the area under the receiver operating characteristic curve (AUROC), NRI, and IDI were analysed between different models containing LHPI, DP, and MP, respectively. The NRI cutoff point of 60% was selected a priori to define probabilities for mortality.

Sensitivity analysis

We carried out a series of sensitivity analyses, including a logistic regression-based matched cohort, the cohort with missing data, and the cohort after imputation, to assess the outcomes. We also conducted a sensitivity analysis focusing on patients with mild-moderate ARDS and severe ARDS.

Statistical significance was considered to be indicated by a two-sided $p < 0.05$. All statistical analyses mentioned above were performed using RStudio (Version 1.2.5001).

Results:

After reviewing 61532 subjects from MIMIC-III, we identified ARDS in 1349 subjects according to the Johnson et al. methodology[13], in which ARDS patients were selected based on the Berlin Definition. Readmission, age < 16 years, ventilation duration < 48 hours, bad data, key data outliers and missing key data were reasons for exclusion; finally, 448 patients were enrolled (Fig. 1).

The mortality of ARDS patients was 29.02% (in Additional file 3: Table S1). Patients who died were older, had higher LHPI, had higher SOFA scores, and had higher lactate.

Random forest machine learning

A random forest machine learning algorithm was trained on the variables of age, ethnicity, BMI, smoking, SOFA, heart rate, laboratory values (pH, lactate, RDW), and ventilator parameters (LHPI, driving pressure, mechanical power, platform pressure). With a Kappa of approximately 0.342, the random forest model with ntree = 500 and mtry = 8 was the final model. The AUROC of the random forest model was 0.708 (95% CI, 0.601–0.816). The training process showed that the LHPI was more important than DP and MP (Fig. 2).

Propensity score matching

The propensity score for an individual was estimated based on the given covariates of age, sex, ethnicity, BMI, HR, RR, smoking status, ARDS severity, SOFA, pH, RDW, and lactate using a logistic regression model. We divided the cohort into a low-LHPI group and a high-LHPI group (Table 1) with a value of LPHI of 19% as the cut-off point (in Additional file 2: Fig S2). Almost all covariates were considered balanced in the PSM cohort (Fig. 3). Thus, logistic regression was performed. The adjusted OR showed an adverse correlation between high LHPI and 30-day mortality (OR = 1.86, 95% CI 1.08–3.26, p = 0.027) (Table 3).

Table 1

Baseline characteristics of the original cohort and the matched cohort

Variables		Low LHPI	High LHPI	SMD	Low LHPI	High LHPI	SMD
		318	130		163	163	
Age (mean (SD))		55.03 (17.40)	62.68 (17.20)	0.059	57.74 (16.79)	57.93 (17.98)	0.011
Sex (%)				0.142			0.025
	F	132 (41.5)	53 (40.8)		75 (46.0)	73 (44.8)	
	M	186 (58.5)	77 (59.2)		88 (54.0)	90 (55.2)	
Race (%)				0.272			0.080
	White	223 (70.1)	64 (49.2)		102 (62.6)	96 (58.9)	
	Black	20 (6.3)	8 (6.2)		11 (6.7)	11 (6.7)	
	Other	75 (23.6)	58 (44.6)		50 (30.7)	56 (34.4)	
BMI ≥ 30 kg/m^2(%)				0.148			0.027
	No	223 (70.1)	102 (78.5)		115 (70.6)	113 (69.3)	
	Yes	95 (29.9)	28 (21.5)		48 (29.4)	50 (30.7)	
RR (%)		19.76 (5.98)	20.84 (6.96)	0.217	20.78 (5.98)	20.14 (6.31)	0.103
HR (%)		89.28 (17.08)	87.79 (19.23)	0.183	89.89 (18.27)	89.52 (18.35)	0.020
Smoking (%)				0.204			0.077
	NO	84 (26.4)	24 (18.5)		38 (23.3)	34 (20.9)	
	Yes	166 (52.2)	60 (46.2)		81 (49.7)	87 (53.4)	
	Unknown	68 (21.4)	46 (35.4)		44 (27.0)	42 (25.8)	

Abbreviations: LHPI lung-heart pressure index, SMD standardized mean difference, BMI body mass index, RR respiratory rate, HR heart rate, SOFA sequential organ failure assessment, RDW red cell distribution width.

a. All covariates are reported as the mean, standard deviation and SMD.

b. A balance between variables was considered when SMD was < 0.1.

Variables		Low LHPI	High LHPI	SMD	Low LHPI	High LHPI	SMD
		318	130		163	163	
ARDS severity (%)				0.057			0.030
	1	27 (8.5)	11 (8.5)		13 (8.0)	14 (8.6)	
	2	161 (50.6)	53 (40.8)		82 (50.3)	83 (50.9)	
	3	130 (40.9)	66 (50.8)		68 (41.7)	66 (40.5)	
SOFA (mean (SD))		7.09 (3.11)	8.89 (4.00)	0.312	7.75 (3.53)	7.77 (3.45)	0.007
RDW (mean (SD))		15.04 (2.01)	15.97 (2.29)	0.178	15.61 (2.45)	15.47 (1.96)	0.064
pH (mean (SD))		7.39 (0.06)	7.36 (0.08)	0.216	7.38 (0.06)	7.38 (0.07)	0.023
Lactate (mean (SD))		1.83 (0.90)	2.72 (2.47)	0.289	2.03 (1.11)	2.00 (1.03)	0.025
Abbreviations: LHPI lung-heart pressure index, SMD standardized mean difference, BMI body mass index, RR respiratory rate, HR heart rate, SOFA sequential organ failure assessment, RDW red cell distribution width.							
a. All covariates are reported as the mean, standard deviation and SMD.							
b. A balance between variables was considered when SMD was < 0.1.							

Predictive performance of LHPI, DP and MP

The best logistic regression model included the variables of DP, age, and SOFA. We replaced the DP in the model with LHPI and MP, successively (the three models were called the LHPI model, the DP model, and the MP model). As shown in Table 2, the AUROCs of the LHPI, DP and MP models were 0.719 (0.665–0.773), 0.715 (0.661–0.770), and 0.686 (0.631–0.741), respectively, for 30-day mortality. Moreover, reclassification statistics showed that the NRI and IDI between the LHPI and DP models were 0.054 (P = 0.008) and 0.011 (P = 0.014), and between the LHPI and MP models, the NRI and IDI were 0.061 (p = 0.049) and 0.0466, respectively (p < 0.001).

Table 2
Reclassification results for 30-day mortality.

	LHPI vs DP	P value
AUROC	0.719 (0.665–0.773) vs 0.715 (0.661–0.770)	0.545
NRI	0.054	0.008
IDI	0.011	0.014
	LHPI vs MP	
AUROC	0.719 (0.665–0.773) vs 0.686 (0.631–0.741)	0.051
NRI	0.061	0.049
IDI	0.466	< 0.001

Table 3
Summary of results of the primary outcome and sensitivity analysis.

Cohort	Adjusted OR (95% CI)	P value
Original Cohort	2.76 (1.26–6.19)	0.012
Post-imputation Cohort	1.97 (1.23–3.18)	0.005
Matched Cohort	1.86 (1.08–3.26)	0.027
Mild-moderate ARDS Cohort	1.04 (0.99–1.10)	0.135
Severe ARDS Cohort	1.12 (1.06–1.20)	< 0.001

Sensitivity Analysis

We performed some sensitivity analyses, as summarized in Table 3. We analysed all three cohorts, including the matched cohort, the post-imputation cohort, and the original cohort, and reached the same conclusion: ARDS patients with higher RDW had higher 30-day mortality. In addition, we applied a post hoc sensitivity analysis using the data of the patients with mild-moderate and severe ARDS (Table 3). LHPI was associated with an increased risk of mortality (OR 1.12; 95% CI 1.06–1.20; $p < 0.001$) from severe ARDS but not with an increased risk of mortality (OR 1.04; 95% CI 0.99–1.10, $p = 0.135$) from mild-moderate ARDS (Fig. 4).

Discussion:

Multiple studies have shown the prognostic significance of DP and MAP in patients with ARDS[7–11]. In our study, LHPI was a novel indicator constructed based on DP and MAP and was shown to be an independent predictor of mortality. Its predictive power proved to be superior to that of DP and MP. Moreover, the LHPI could be easily and simply obtained in the clinic. Therefore, it is possible to use LHPI as a predictor of ARDS mortality, which might give clinicians a more meaningful reminder to make accurate and early decisions based on this indicator to customize the most effective treatment.

The LHPI is an integrated indicator, as it is the ratio of DP to MAP. The predictive value of the LHPI for ARDS mortality might be elucidated by the ventilator setting, which not only affects the occurrence of VILI but also affects the haemodynamic stability and plays a vital role in the initiation of mortality[5, 19]. Patients with elevated LHPI usually have high DP and low MAP. DP is the surrogate for cyclic lung strain[20], and high DP indicates excessive tidal volume and lung strain relative to "baby lungs," resulting in VILI[21, 22].

VILI mainly includes “barotrauma” and “volutrauma." If the stress exceeds the tensile properties of the collagen fibres up to “stress at rupture,” the lung undergoes the classic "barotrauma." When the stress causes the strain to be too large but does not reach the levels of physical rupture, “volutrauma” will occur. To avoid “volutrauma," we should consider not merely the tidal volume but the strain. Amato and his colleagues corroborated this view through a retrospective study[7]. In addition to VILI, positive-pressure ventilation could cause changes in intrapleural pressure[23], which could affect the haemodynamic stability[24]. The increase in intrapleural pressure transiently decreases venous return to the right ventricle and eventually to the left ventricle, and small changes in intrapleural pressure can exert relatively large effects on cardiac output. Moreover, the reduction in MAP would exacerbate the imbalance of the distribution of alveolar ventilation and perfusion, thereby worsening the condition of patients with ARDS[25–27].

All of these factors might cause tissue and organ ischaemia and hypoxia and increase the SOFA score and mortality.

Although there is some evidence that lower DP is associated with improved lung function[8, 9, 28, 29], the results of some studies have been negative[30]. In the present study, we observed that the discrimination of DP in predicting mortality was significantly lower than that of LHPI. This result indicated that DP did not fully reflect the true situation of ARDS patients. Recently, the development of MP was shown to be related to mortality in patients on mechanical ventilation, which included all aspects of ventilator parameters[14]; however, in our study, the discrimination of MP was also lower than that of LHPI. This result might be related to the MP itself still having some problems[22], such as the power not normalizing[31], the lack of ascertainment of the impact of MP throughout the lung, and the effect of expiratory phase on MP[32]. In our study, we observed that LHPI played a relatively important role in the random forest model. When we further explored the mortality predictive potential of LHPI after adjusting variables through the PSM cohort, we found that the LHPI was an independent risk factor for 30-day mortality. In addition, a multivariable regression model was trained in the mild-moderate ARDS group and

the severe ARDS group (Table 3). The results indicated that the negative impact of a higher LHPI was dependent on the severity of ARDS. Finally, the results of NRI and IDI further demonstrated that the predictive ability of LHPI was better than that of DP and mechanical power.

In summary, our analysis suggested that LHPI might be a powerful prognostic marker for ARDS, especially in patients with severe ARDS. In addition, its predictive discrimination was better than that of DP and MP.

The present analysis had some limitations. First, our study was a single-centre retrospective observational study resulting in the inherent bias of the analysis. Data from different centres might have different results. Therefore, the results of this study require large multi-centre prospective studies for further validation. Second, we used the PSM analysis method to overcome some potential selection biases, but some biases are inevitable. Third, we only analysed the average of the indicators for the second day, and all of the variables, such as other clinical indicators, will change dynamically with the course of treatment, and our study only explored the predictive power of the LHPI in static conditions. In addition, DP is generally considered to require sufficient sedation or inhalation pauses, so DP acquisition might have been biased. Finally, although our findings suggested that the prognosis of ARDS was related to LHPI, the strength of the evidence was insufficient, and strong evidence, such as that from randomized controlled trials, is still needed to confirm.

Conclusion:

To the best of our knowledge, this is the first report to demonstrate the prognostic value of the LHPI for patients with ARDS. We showed that LHPI was an excellent variable for predicting mortality in ARDS patients, and its predictive ability was better than that of DP and MP. The increased risk of mortality in ARDS patients with high LHPI may be related to the occurrence of VILI and haemodynamic instability. However, these findings require further confirmation from a multi-centre prospective study to validate the clinical significance of the LHPI in ARDS.

Abbreviations

ARDS Acute Respiratory Distress Syndrome

AUROC Area Under the Receiver Operating Characteristic Curve

BMI Body Mass Index

DP Driving Pressure

HR Heart Rate

IDI Integrated Discrimination Improvement

LHPI Lung-Heart Pressure Index

MAP Mean Arterial Pressure

MP Mechanical Power

NRI Net Reclassification Index

Pplat Platform Pressure

RDW Red Cell Volume Distribution Width

ROC Receiver Operating Characteristic

RR Respiratory Rate

SOFA Sequential Organ Failure Assessment

SQL Structured Query Language

SMD Standardized Mean Differences

VILI Ventilator-Induced Lung Injury

Declarations

Ethics approval and consent to participate

The MIMIC-III database is a freely used critical care medical database designed by MIT and MIDMC. Although all information related to patient privacy contained in the MIMIC-III is specially processed to be deidentified, researchers still have to pass the “Data or Specimens Only Research” online course (researchers certification number 1605699 and record id 27752407).

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

XSY designed this study, collected and analysed data, and drafted the manuscript; XJP designed this study, collected data, and drafted and revised the manuscript; ZQC collected, compiled and analysed the data; YFH analysed the data, interpreted the results and reviewed the manuscript; JS and SYX contributed with the study design and interpreted results; XWZ and HJ interpreted the results and reviewed the manuscript; WJC and YCY collected and compiled data; and JYP designed and supervised this study and obtained funding. All authors read and approved the final manuscript.

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Additional Files

Additional file 1:

Fig S1. Pattern of missing data in variables of interest.

Additional file 2:

Fig S2. Receiver-operating characteristics (ROC) curve analysis of the best cut-off of mechanical power. The best cut-off was about 19.0%.

Additional file 3:

Table S1. Baseline Characteristics of original cohort. The data was divided into survivor cohort and death cohort.

Table S2. The cohort of mild-moderate ARDS patients and severe ARDS patients.

Table S3. Reclassification results for 30-day mortality. LHPI model: LHPI replaces DP in the best model. VT/PBW model: VT/PBW replaces DP in the best model. MP/DP model: MP/DP replaces DP in the best model.

Figures

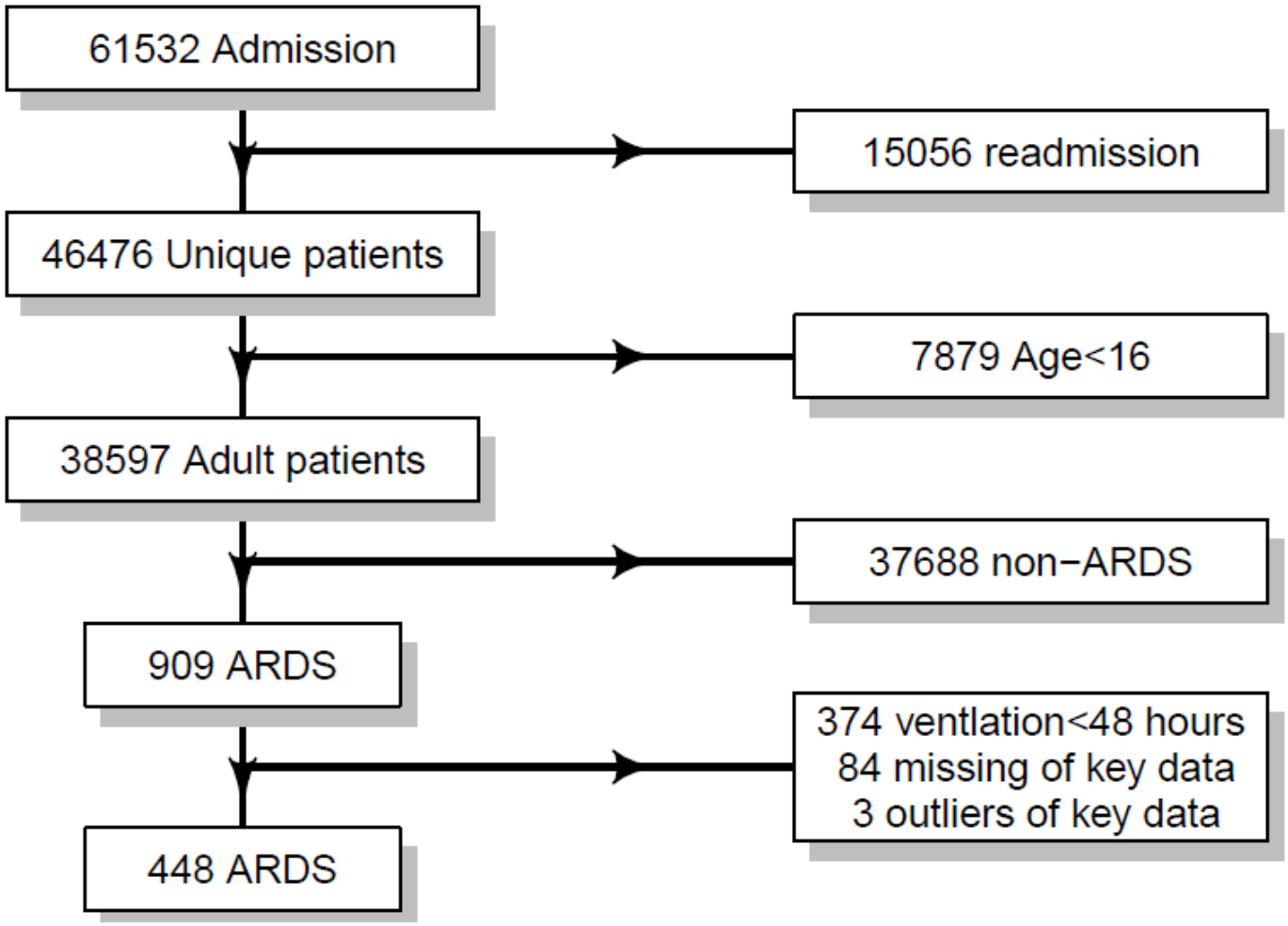


Figure 1

Flow Chart Illustrating the Inclusion and Exclusion Criteria of the Study Groups.

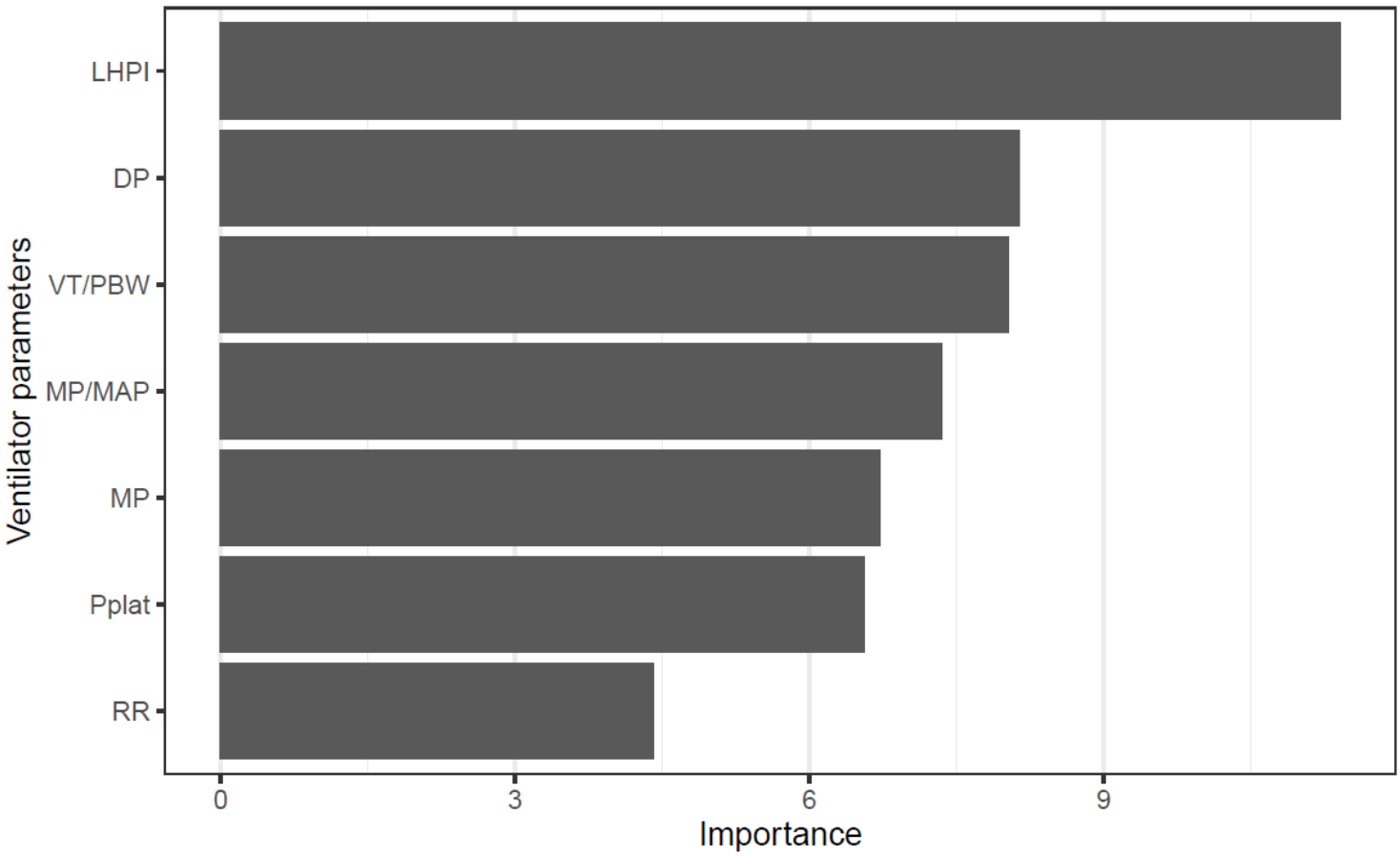


Figure 2

The importance of ventilator parameters in the Random Forest model.

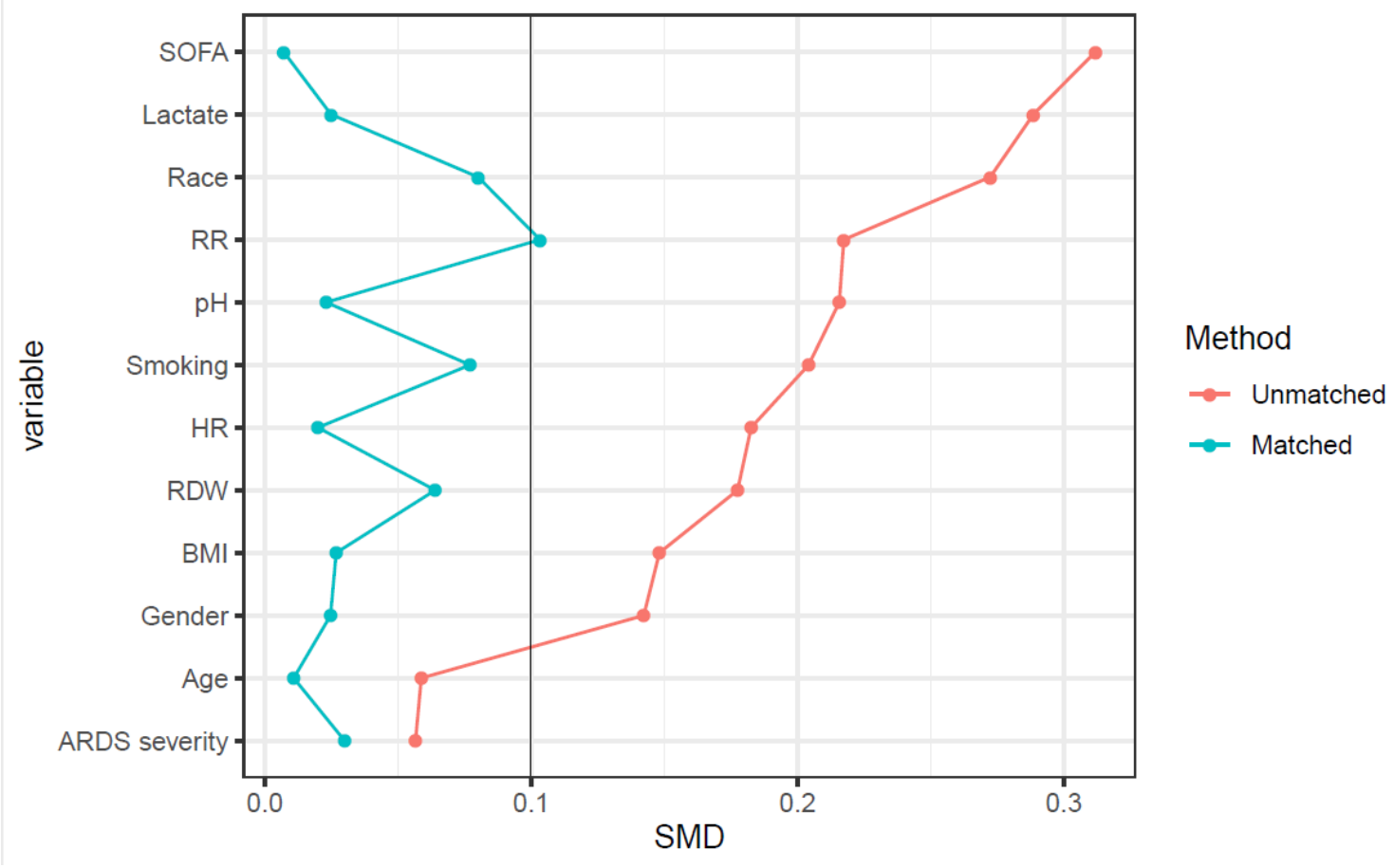


Figure 3

Standardized mean difference (SMD) of variables between original and PSM cohorts.

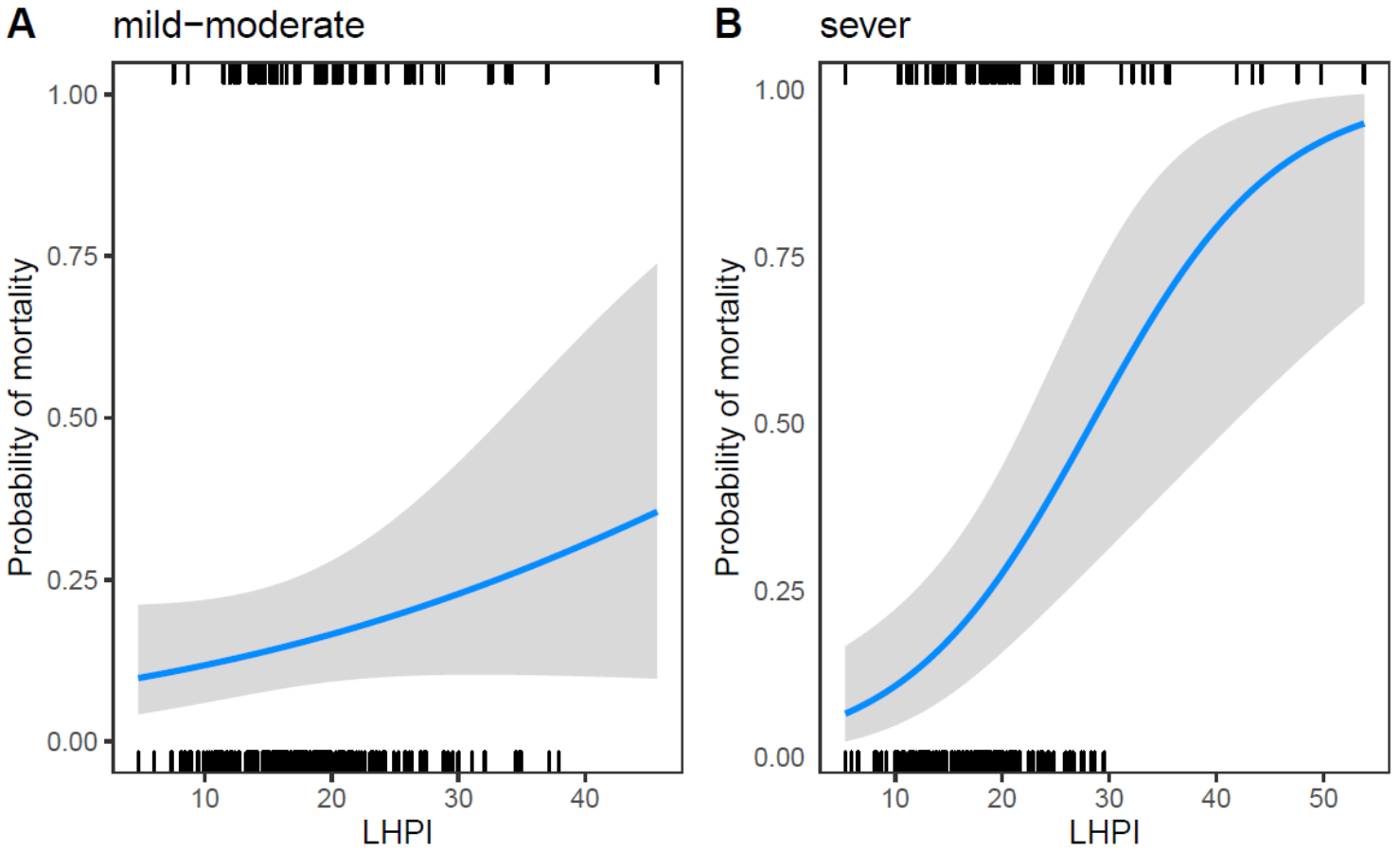


Figure 4

Interaction between LHPI and ARDS severity. The LHPI was associated with an increased risk of mortality (OR 1.12; 95% CI 1.06-1.20; p<0.001) from severe ARDS but not with an increased risk of mortality (OR 1.04; 95% CI 0.99-1.10, p=0.135) from mild-moderate ARDS.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additional2.tiff
- Additional3.docx
- Additional1.tiff