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ORIGINAL ARTICLE

Predicting ARDS in critically ill patients: Creating a new score

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Abstract

Background: We intended to create a new acute respiratory distress syndrome (ARDS) prediction score in high-risk critically ill patients.

Methods: We recruited 200 patients [63 (43-70) years, 120 (60%) males] admitted to the ICU with APACHE-II scores of ≥15 and at least one ARDS risk factor, after excluding patients with ARDS on admission, cardiac patients, and readmissions. The presence of risk factors together with the admission and 48-hour CRP (CRP-0 and CRP-48) were tested in univariate then multivariate regression models for identifying significant predictors whose weights were assigned according to the β-coefficient of the regression model. Our score was compared with the score previously proposed by Trillo-Alvarez et al. on 2011 (LIPS-T). The primary and secondary outcomes were the development of ARDS and in-hospital mortality, respectively.

Results: ARDS developed in 88 patients (44%). Logistic regression revealed that pneumonia, tachypnoea, increased heart rate, and increased CRP-48 are significant ARDS predictors. The weight of each predictor was estimated according to its β-coefficient. The new score was 35.5 (27-44) and 14 (9-24.3) in ARDS and non-ARDS patients, respectively (p=0.000). The AUC of the new score was 0.827 compared with 0.74 for the LIPS-T (p=0.014). A score of 20 had a sensitivity and specificity of 82% and 71%, respectively, in predicting ARDS. Our score was significantly lower in survivors compared with non-survivors (p=0.000) and its AUC in predicting in-hospital mortality was 0.761 compared with 0.657 for the LIPS-T (p=0.0045).

Conclusions: We have created a new simple LIPS score which could be better than the scores previously proposed in terms of ARDS and in-hospital mortality prediction in critically ill patients.

Introduction

Acute respiratory distress syndrome (ARDS) is a known public health problem.[1] The reported high ARDS morbidity and mortality[2,3] and the lack of specific treatment options[4] paid the research attention towards the need for early identification of high-risk ARDS patients as targets for preventive studies.

Many researchers have created and validated lung injury prediction scores (LIPS)[5-7] that were seen to significantly predict the occurrence of ARDS. These studies recruited a wide range of emergency department (ED) and intensive care unit (ICU) patients who had at least one risk factor for ARDS. Additionally, they considered only clinical predictors without the involvement of biomarkers. The risk of ARDS development increases with a higher APACHE-II score.[7] Accordingly, the recruitment of patients with higher APACHE-II scores during LIPS creation is better for ICU practice. In addition, the enthusiasm of using biomarkers in diagnostic and prognostic perspectives directed our attention to the incorporation of a biomarker in the score. Theoretically, the use of a biomarker which is involved in ARDS pathogenesis increases the specificity of the score. However, the use of a biomarker which is commonly used during clinical practice might be better than the use of a more specific one which is not commonly used for a wide range of ICU patients. C-reactive protein (CRP) is commonly used in clinical practice for the follow-up of inflammatory conditions such as sepsis.[8] In addition, it was shown to be elevated in ARDS patients.[9]

This study was intended to create a score for the prediction of ARDS and in-hospital mortality in critically ill patients with APACHE-II score ≥15.

Patients and methods

This was a single-centre prospective observational cohort study including all patients older than 18 years who were admitted to the ICU with an APACHE-II score ≥15 and at least one of the predisposing conditions of ARDS during the period from

January 2016 to May 2017. We used standardised definitions for the included predisposing conditions (aspiration, pneumonia, pancreatitis, high-risk trauma, high-risk surgery, sepsis, shock, tachypnoea, hypoalbuminaemia, chemotherapy use, smoking, interstitial lung disease (ILD), alcohol abuse, and diabetes).[10-13] Tachypnoea was defined as a respiratory rate >30 breaths/min and hypoalbuminaemia as serum albumin <3.5 g/dl.[10] Samples for CRP levels on admission (CRP-0) and 48 hours later (CRP-48) were taken.

Patients with ARDS on admission, a supposed cardiac cause of hypoxaemia, and those with hospital readmission (within 7 days) were excluded from the study.

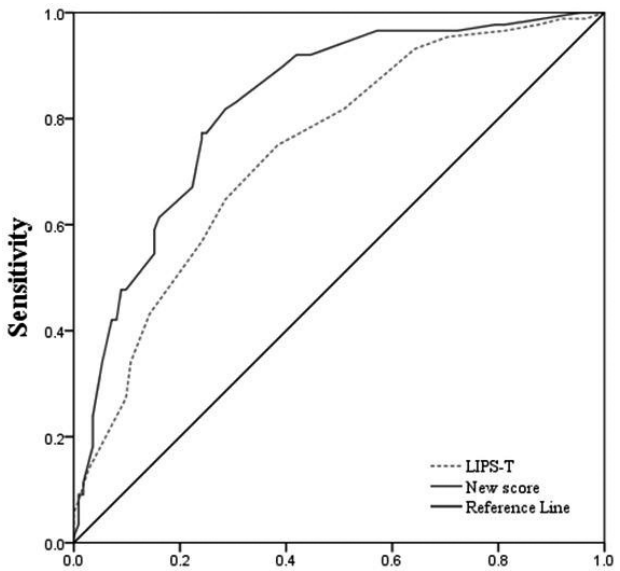
The reported predisposing conditions are used for the calculation of a new score to predict ARDS. The LIPS published by Trillo-Alvarez et al. in 2011 (reported in the text as LIPS-T)[6] was calculated to be compared with the new score.

The primary outcome of interest was the in-hospital development of ARDS according to the Berlin definition.[14] ARDS development was determined by two independent experts who were blinded to the data on the risk factors. The secondary outcome was in-hospital mortality.

The study protocol was approved by the institutional review board at Cairo University together with representatives from the site conducting the study. Informed consent was obtained from patients or first-degree relatives.

Statistical analysis

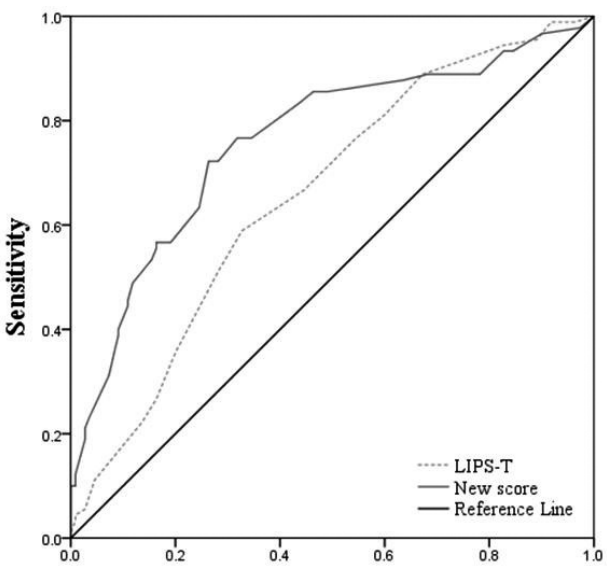
Data were prospectively collected and coded prior to analysis using the Statistical Package of Social Science (SPSS version 22). Normal distribution of dependent variables in relation to their independent variables was studied. Normally-distributed variables should have a p-value >0.05 in Shapiro-Wilk's test[15] and z-value of skewness and kurtosis between -1.96 and +1.96.[16] Most of our variables were non-normally distributed. We expressed continuous variables as median (25th-75th) percentiles [median (Q_1-Q_3)]. Categorical variables were expressed as frequency and proportion. The non-parametric test (Mann-Whitney U test) was used for comparison between two groups regarding quantitative variables, while the Chi-square test (x^2) was used for comparison between two groups regarding qualitative data. The exact test was used instead when the expected frequency was less than 5. Univariate and multivariate binary logistic regression analysis were performed for the independent predictors of ARDS. The relative weight of each predictor was estimated according to the β-coefficients from multivariate analysis. The regression model was validated using bootstrapping of 1000 samples. Receiver operator characteristic (ROC) analysis was performed to define cut-off values of the scores. The best cut-off values were calculated using the highest Youden's index. Comparison between the different areas under curve (AUC) was performed using the



	AUC	Standard Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LIPS-T	0.740	0.035	0.000	0.672	0.808
New score	0.827	0.029	0.000	0.769	0.884

Difference between Areas	0.0869
Standard Error	0.0354
95 % Confidence Interval	0.0175 – 0.156
Z statistics	2.456
P value	0.014

Figure 1. The ROC curves of the LIPS-T and the new score in predicting ARDS



	AUC	Standard Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LIPS-T	0.657	0.038	0.000	0.581	0.732
New score	0.761	0.035	0.000	0.693	0.830

Difference between Areas	0.105
Standard Error	0.0368
95 % Confidence Interval	0.0325 – 0.177
Z statistics	2.844
P value	0.0045

Figure 2. The ROC curves of the LIPS-T and the new score in predicting in-hospital mortality

Z statistics calculation according to DeLong et al.[17] MedCalc Statistical Software version 18.11 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) was used for its calculation as it cannot be calculated using the SPSS. Results were considered statistically significant if the p-value was ≤0.05.

Results

Initially, 280 patients were enrolled in the study. Eighty patients were subsequently excluded due to a cardiac cause of hypoxaemia (47 patients), ARDS on admission (25 patients), and a history of previous admission (8 patients). The remaining 200 patients [median age (Q1-Q3) 63 (43-70) years, including 120 (60%) males] formed the study sample. The APACHE-II score of the whole sample was 20 (18-24).

Of the sample, 44% (88 patients) developed ARDS, while the remaining 56% (112 patients) did not. ARDS developed after a median (Q1-Q3) of 4 (2-7) days. There was no difference between the two groups in terms of age or gender (p=0.98 and 0.6 respectively).

Hypoalbuminaemia, tachypnoea, lower systolic blood pressure, higher heart rate, higher shock index, sepsis, pneumonia, aspiration, high-risk surgery and CRP-48 were found to be significant predictors of ARDS in the univariate regression analysis. *Table 1* shows the predisposing conditions and CRP measurements in the study samples.

Multivariate binary logistic regression revealed only four significant predictors of developing ARDS. These predictors were pneumonia, tachypnoea, increased heart rate, and increased CRP-48 *(table 2)*. The derived logistic model equation was [- 4.966] + [1.512 x (tachypnoea)] + [(0.761) x pneumonia] + [(0.029) x HR] + [(0.009) x CRP-48] in which the presence of tachypnoea or pneumonia is scored as 1 and their absence is scored as 0 (Nagelkerke R^2 was 0.399 and Hosmer-Lemeshow test was 0.08) *(table 2)*. The weight of each predictor estimated to build up the score is shown in *table 3*.

The new LIPS was calculated in the study sample. It was significantly higher in ARDS patients *(table 1)*. The LIPS calculated according to Trillo-Alvarez et al. (LIPS-T) was also found to be significantly higher in patients who subsequently developed ARDS *(table 1)*.

The two scores were compared using the ROC curve. The AUC of the new score was 0.827 compared with 0.74 for the LIPS-T. This difference was statistically significant (p=0.014) *(figure 1)*.

A new score of more than 20 was found to be 82% sensitive and 71% specific in predicting ARDS development with 69% positive predictive value (PPV) and 83% negative predictive value (NPV).

Both scores were significantly higher in non-survivors. The new score was 35 (21.8-44) in non-survivors compared with 14 (10-27.3) in survivors (p=0.000) and the LIPS-T was 5 (3.5-6) and 3.5 (1.5-5) in non-survivors and survivors, respectively (p=0.000). The new score was superior in predicting mortality in our patients' sample. Its AUC was 0.761 compared with 0.657 for the LIPS-T (p=0.0045). New score of 26 was found to be 72% sensitive and 74% specific in predicting mortality with 69% PPV and 76% NPV *(figure 2)*.

Table 1. Predisposing conditions, CRP measurements and study scores in study samples

		ARDS (88 patients)	No ARDS (112 patients)	Total (200 patients)	P value
Hypoalbuminaemia [No (%)]		68 (77.3%)	61 (54.5%)	129 (64.5%)	0.001
Tachypnoea [No (%)]		56 (62.9%)	20 (18%)	76 (38%)	0.000
Diabetes [No (%)]		38 (43.2%)	44 (39.3%)	82 (41%)	0.58
Smoking [No (%)]		33 (37.5%)	47 (42%)	80 (40%)	0.52
Chemotherapy [No (%)]		7 (7.9%)	8 (7.1%)	15 (7.5%)	0.83
Interstitial lung disease [No (%)]		2 (2.3%)	3 (2.7%)	5 (2.5%)	1
Alcohol abuse [No (%)]		0 (0%)	3 (2.7%)	3 (1.5%)	0.26
SBP (mmHg) [(median (Q1-Q3)]		90 (73-120)	110 (90-120)	100 (80-120)	0.003
HR (bpm) [(median (Q1-Q3)]		110 (100-120)	100 (90-110)	105 (90-110)	0.000
Shock index [(median (Q1-Q3)]		1.2 (0.9-1.8)	0.9 (0.7-1.2)	1 (0.8-1.5)	0.000
Shock index score [No (%)]	< 1	30 (34.1%)	78 (69.6%)	108 (54%)	0.000
	1-1.5	33 (37.5%)	17 (15.2%)	50 (25%)	
	> 1.5	25 (28.4%)	17 (15.2%)	42 (21%)	
Sepsis [No (%)]		56 (63.6%)	43 (38.4%)	99 (49.5%)	0.000
Pneumonia [No (%)]		47 (53.4%)	33 (29.5%)	80 (40%)	0.001
Aspiration [No (%)]		28 (31.8%)	21 (18.8%)	49 (24.5%)	0.03
High risk surgery [No (%)]	Elective	5 (5.7%)	20 (17.9%)	25 (12.5%)	0.03
	Emergent	14 (15.9%)	12 (10.7%)	26 (13%)	
	Total	19 (22%)	32 (28.6%)	51 (25.5%)	
High-risk trauma [No (%)]		23 (26.1%)	27 (24.1%)	50 (25%)	0.7
Pancreatitis [No (%)]		0 (0%)	2 (1.8%)	2 (1%)	0.5
CRP-0 (mg/dl)		48 (24-48)	48 (24-48)	48 (24-48)	0.4
CRP-48 (mg/dl)		96 (67.5-150.3)	48 (24-96)	96 (48-96)	0.000
LIPS-T		5 (3.6-6.5)	3.5 (1.5-4.5)	4 (2.5-5.5)	0.000
New score		35.5 (27-44)	14 (9-24.3)	22 (12-38)	0.000

SBP = systolic blood pressure, HR = heart rate, CRP-0 = C-reactive protein at admission, CRP-48 = C-reactive protein at 48 hours. LIPS-T = Lung Injury Prediction Score calculated according to Trillo-Alvarez. Bold = statistically significant P value (P < 0.05)

Discussion

Identifying patients at higher ARDS risk for recruitment in preventive studies rather than the whole population might improve studies outcomes. Many authors have proposed

different scores for ARDS prediction within a wide range of ED or ICU patients.[5-7] In this study, we intended to create a simple and easy-to-measure ICU prediction score that applies to critically ill patients with relatively high APACHE-II scores using the previously identified predisposing conditions for ARDS[10,13,18,19] and the easy-to-measure, rapid, and readily available point-of-care CRP assay.

In a cohort of 200 patients, we identified tachypnoea, pneumonia, increased heart rate and increased CRP-48 as predictors of ARDS using a multivariate regression model. These factors represented the variables of the new score created from our data. Our new score had an AUC of 0.827 which was significantly higher than that proposed by Trillo-Alvarez[6] when applied on our cohort. A score higher than 20 was 82% sensitive and 71% specific in predicting ARDS in our sample. This new score also showed a significantly larger AUC for predicting mortality in our sample compared with Trillo-Alvarez's score.

Although many other predisposing conditions, apart from those we have identified, have been shown by other investigators to be significantly associated with higher risk of ARDS,[10-13] we could not elucidate this relation in our study. This might be explained by the nature of our sample, characterised by a high APACHE-II score and the small number of included patients with these predisposing conditions. For example, we had two patients with pancreatitis and five patients with interstitial lung disease.

The β-coefficient derived from the multivariable binary logistic regression model was used to assign weights for the four significant predictors of ARDS formulating a simple new score. The new score had an AUC of 0.827 with a score higher than 20 found to be 82% sensitive and 71% specific in predicting ARDS. We compared our score with the LIPS proposed by Trillo-Alvarez and his colleagues.[6] Trillo-Alvarez et al. derived their LIPS from a retrospective sample of all ICU patients and validated it on a prospective sample including ED patients. They identified a high AUC of 0.84 in both samples with a cut-off value of 3 to be 69% sensitive and 84% specific in predicting ARDS.[6] Applying their score on our more critically ill sample with high APACHE-II scores, it revealed an AUC of 0.740 which is significantly lower than that of our score (0.827).

Gajic et al.[7] developed and validated another score including all patients admitted to the ED with at least one ARDS risk factor. They identified an AUC of 0.8 for predicting ARDS development in both the derivation and the validation cohorts. They identified an optimum cut-off value of 4 to be 69% sensitive and 78% specific. Soto et al.[20] validated this score in all ICU patients and Bauman et al.[21] validated it in surgically ventilated patients. Soto et al.[20] found an AUC of 0.7 with a cut-off value of 4 to be 90% sensitive and 31% specific and identified a 31% increase in the likelihood of ARDS development for every point increase in LIPS, while Bauman et al. identified an AUC of 0.79 and found that every one-unit increase in LIPS is associated with 50% increase in the incidence of ARDS development.[21]

The proposed score was not only seen to predict the occurrence of ARDS but also the occurrence of in-hospital mortality. Because of the high mortality in patients with ARDS, identification of a prediction tool for mortality is important for family counselling and guiding clinical decision-making. The new score was significantly higher in non-survivors than in survivors with an AUC of 0.761. Although the LIPS developed by Trillo-Alvarez et al.[6] is also significantly higher in non-survivors, the AUC of our new score is significantly higher than that of LIPS-T. Using the LIPS proposed by Gajic et al.,[7] Soto and other investigators[20] also found that a higher LIPS is a significant mortality predictor in ICU patients at risk of ARDS. In addition, Bauman et al. found a 22% increase in the 30-day mortality rate for every one-unit increase in LIPS in surgical patients.[21]

Our study had the limitation of being a single-centre study with a small sample size. Other studies proposing LIPS scores had enrolled all ED or ICU patients with low incidence of ARDS development compared with our study that included critically ill patients with APACHE-II score ≥15 who have a higher incidence of ARDS. The incidence of ARDS in our study was 44%. The choice of serum CRP as the biomarker of the study could be considered a limitation by being non-specific. The use of other biomarkers involved in the pathophysiology of ARDS may be considered by some authors to be more valuable. We, however, used serum CRP as it is a commonly used biomarker that monitor the inflammatory process and can be used for screening rather than other more specific biomarkers. Validation of the new score on the same study sample was considered a study limitation. The authors used bootstrapping for validation of the regression model, yet it is required to be validated in another sample.

Table 2. The multivariate binary logistic regression of the significant ARDS predictors

	B	Standard error	P value	Odds ratio	95% Confidence interval	
					Lower	Upper
Tachypnoea	1.512	0.366	0.000	4.538	2.216	9.292
Pneumonia	0.761	0.362	0.036	2.140	1.052	4.352
Heart rate	0.029	0.012	0.014	1.029	1.006	1.053
CRP-48	0.009	0.003	0.003	1.009	1.003	1.015
Constant	-4.966	1.213	0.000			

CRP-48 = C-reactive protein at 48 hours

Conclusions

We present here a new simple ARDS prediction score based on only the presence of tachypnoea, pneumonia, heart rate, and CRP after 48 hours of admission. The new score could be better than the previously proposed scores in terms of ARDS prediction and in-hospital mortality in the subset of critically-ill ICU patients.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

Table 3. The weight of the ARDS predictors according to the β-coefficient

Predictor	Value	Weight	Value	Weight
Pneumonia	Absent	0	Present	8
Tachypnoea	Absent	0	Present	16
CRP-48 mg/l	0-10	0	11-20	1
	21-30	2	31-40	3
	41-50	4	51-60	5
	61-70	6	71-80	7
	81-90	8	91-100	9
	101-110	10	111-130	11
	131-140	12	141-150	13
	151-160	14	161-170	15
	171-180	16	181-190	17
	191-200	18	201-210	19
	211-220	20	221-230	21
	231-240	22	241-250	23
	251-260	24	261-270	25
	271-280	26	281-290	27
	291-300	28	301-310	29
	≥311	30		
Heart rate (bpm)	60-90	0	91-120	10
	121-150	19	151-180	28

CRP-48 = C-reactive protein at 48 hours

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