

ESM-1 Levels and ARDS Prediction Score for Predicting ARDS Occurrence in Sepsis Patients

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Research

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Abstract

Background: Acute respiratory distress syndrome (ARDS) development is overtly associated with elevated mortality. This study aimed to determine the parameters predicting ARDS in sepsis patients.

Methods: This was a retrospective case control study. The sepsis patients admitted to the intensive care unit were divided into the ARDS and non-ARDS groups according to ARDS occurrence within 72 hours. Plasma endothelial cell specific molecule-1 (ESM-1), white blood cell (WBC), C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT) were assessed on the first day. PaO₂/FiO₂ ratio was determined on the first two days. Pearson correlation analysis and logistic regression analysis were carried out.

Results: The ARDS and non-ARDS groups included 12 and 42 patients respectively. ESM-1 levels in the ARDS group on the first day were significantly lower than those of the non-ARDS group ($P=0.009$). ESM-1 levels and PaO₂/FiO₂ ratio were positively correlated. Logistic regression analysis showed that ESM-1, CRP and IL-6 levels on the first day were associated with ARDS. The areas under the receiver operating characteristic curve (ROC) curves (AUCs) for ESM-1, CRP and IL-6 were 0.750, 0.736 and 0.736, respectively. A regression equation was established based on the coefficients of plasma ESM-1, CRP and IL-6 levels to derive an ARDS prediction score with an AUC for predicting ARDS of 0.895.

Conclusion: Plasma ESM-1, CRP and IL-6 levels on the first day are associated with ARDS in sepsis. The novel ARDS predictive score is obviously better than ESM-1, CRP and IL-6 in predicting ARDS in sepsis patients.

Background

Sepsis represents a serious life-threatening ailment that occurs consecutively to an abnormal response to infection [1]. It has a high mortality rate, for causing immune disorders and organ dysfunction [2, 3]. Indeed, acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) are two major complications of sepsis [4]. In sepsis patients, the rate of ARDS is as high as 25%~50%, and ARDS causes death in up to 40% of affected cases [5]. Currently, markers for early diagnosis and severity assessment in ARDS are scarce.

Sepsis is a relatively complex process involving immune reactions, inflammation and coagulation activity [6]. Recent findings suggest that changes in the structure and function of endothelial cells may be associated with the occurrence and development of sepsis, playing a core role in organ dysfunction and patient death; therefore, endothelial cell injury and dysfunction attract increasing attention in sepsis [7].

Endothelial cell-specific molecule-1 (ESM-1), a molecule secreted by endothelial cells, is a 50 kDa soluble proteoglycan containing a polypeptide of 165 amino acids and a single cutaneous sulfate chain covalently bound [8]. Under normal physiological conditions, only small amounts of ESM-1 are detected in

serum, averaging 1.081 ng/ml in healthy individuals [9]. ESM-1 is secreted by activated endothelial cells, and is specifically expressed in the lung, kidney and some tumors [10–13]. Recent studies have shown that ESM-1, which reflects endothelial injury, is associated with the severity and prognosis of sepsis [14–17]. However, the relationship between plasma ESM-1 and the occurrence of septic ARDS remains largely undefined. Meanwhile, a recent study described procalcitonin (PCT) as an efficient serum marker of early neonatal sepsis, also demonstrating that simultaneous assessment of interleukin-6 (IL-6), C-reactive protein (CRP) and PCT could help predict sepsis in neonates [18].

Based on the above reports, this study aimed to explore the values of plasma ESM-1, CRP, IL-6 and PCT levels in timely predicting ARDS in patients with sepsis. Since our results showed that plasma ESM-1, CRP and IL-6 levels were independently associated with ARDS in sepsis, we further established a regression equation combining plasma ESM-1, CRP and IL-6 levels to improve the accuracy of ARDS occurrence prediction.

Methods

Participants and study

This retrospective case control study was performed from June 2016 to June 2018 at the intensive care unit (ICU) in Shanghai East Hospital. The inclusion criteria were: (1) age \geq 18 years; (2) diagnosis of sepsis within 24 h of admission to the ICU, according to the criteria of the Surviving Sepsis Campaign in 2016 [19]. The exclusion criteria were: (1) malignant tumors; (2) immune system diseases; (3) blood system diseases; (4) cardiopulmonary resuscitation; (5) end-stage liver or renal failure; (6) death within 24 hours of admission; (7) lung infection or ARDS on admission to the ICU. Patients were divided into the non-ARDS and ARDS groups according to whether ARDS occurred within 72 hours after admission to the ICU. The study was approved by the Ethics Committee of East Hospital Affiliated to Tongji University. Informed consent was waived because of the retrospective nature of the study.

Data collection

Age, sex and diagnoses were recorded. ESM-1, WBC, CRP, IL-6 and PCT were tested on the first day of enrollment. Meanwhile, Acute Physiology and Chronic Health Evaluation system II (APACHE II) [20] and Sequential Organ Failure Assessment (SOFA) [21] scores were determined. Arterial blood gas analysis was performed, and the PaO₂/FiO₂ ratio was determined on the first two days after admission to the ICU. The rate of organ failure, ICU length of stay, hospitalization days and mortality at 28 days were recorded as well.

Assays for biomarker assessment

A total of 3 ml venous blood was collected in EDTA tubes, and centrifuged at 4 °C for 15 minutes at 1000 × g within 30 minutes after collection. The supernatant (plasma) was stored at -80 °C until use. ESM-1 levels were assessed by sandwich ELISA with the ESM-1 ELISA kit (MyBiosource, MBS7051917, USA).

PCT and IL-6 were evaluated by an automatic immunoassay analyzer (Roche, cobas e411, Switzerland). CRP was quantitated with a whole-process C-reactive protein quantitative detection kit (Shanghai Opu Biological Medicine; shanghai, China). Arterial blood gas analysis was performed on an automatic blood gas analyzer (Radiometer, ABL800 FLEX, Denmark).

WBC were evaluated in the hospital's central laboratory on a Mindray automatic blood cell analyzer (Shenzhen Mindray Biomedical Electronics; BC-6800; Shenzhen, China). Cell subtypes were classified and counted by flow cytometry based on sheath impedance, laser scattering and fluorescence staining.

Statistical analysis

Measurement data with normal distribution were expressed as mean \pm standard deviation (SD), and pairwise comparisons were conducted by independent samples t test. For measurement data with skewed distribution, the Mann-Whitney rank sum test was used for comparisons. Categorical variables were presented as frequencies (percentages), and compared by the chi-squared test. Pearson correlation coefficients were determined for parameter correlation analysis. Logistic regression analysis was carried out to screen factors independently associated with ARDS.

Then, a regression equation was established based on the coefficients of markers with independent predictive values in the final step of the logistic regression:

$$\text{logit}(p) = 3.551 + (0.041 \times \text{CRP}) + (0.001 \times \text{IL-6}) - (0.328 \times \text{ESM-1}).$$

To determine the probability of ARDS occurrence in sepsis, $\text{logit}(p)$ was converted to an outcome probability by the following equation:

$$\text{ARDS prediction score} = \text{ARDS prediction probability} = [e^{\text{logit}(p)} / (1 + e^{\text{logit}(p)})] \times 100.$$

Finally, each factor independently predicting ARDS as well as the new ARDS prediction score were evaluated for their values in predicting ARDS.

The R software package version 3.4.4 and SPSS version 22.0 (IBM, Armonk, NY, USA) were employed for statistical analysis.

Results

Baseline characteristics of the enrolled patients

A total of 88 patients were enrolled in this study, and 34 were excluded for various reasons listed in Fig. 1. Finally, 54 cases were analyzed. Four patients developed ARDS within 24 h of enrollment, 7 additional patients within 48 h, and another patient within 72 h. The patients were divided into the non-ARDS ($n = 42$) and ARDS ($n = 12$) groups according to whether ARDS occurred within 72 hours after admission to the ICU. The baseline features of the patients are presented in Table 1, and were similar in both groups ($P > 0.05$).

Relationship between plasma ESM-1 levels and the PaO₂/FiO₂ ratio

The PaO₂/FiO₂ ratio is an important factor for diagnosis and severity evaluation in ARDS. Therefore, the correlation between plasma ESM-1 concentration and the PaO₂/FiO₂ ratio was evaluated. There was a positive correlation between plasma ESM-1 concentration and the PaO₂/FiO₂ ratio on Day 2, but not on Day 1 (Fig. 2). This may be because the lower the plasma ESM-1 concentration at the time of admission to the ICU, the more likely ARDS occurs.

Factors independently associated with ARDS occurrence

ESM-1 (12.14 ± 7.27 vs. 6.17 ± 2.63 ng/mL; P = 0.009), CRP (114.31 ± 44.45 vs. 152.58 ± 37.76 mg/L; P = 0.019), IL-6 (1088.88 ± 1809.13 vs. 2048.40 ± 2052.92 pg/mL; P = 0.018) and Day 1 PaO₂/FiO₂ ratio (360.36 ± 46.84 vs. 315.50 ± 52.40 mmHg; P = 0.029) showed significant differences between the two groups (Table 2). WBC and PCT showed comparable values in both groups (Table 2).

Binary multi-factor logistic regression analysis was performed to determine factors independently associated with ARDS occurrence. First, a regression model was constructed using the four indexes above as covariates. The Hosmer-Lemeshow test yielded a *P* value of 0.842 (Chi-square = 4.169, df = 8), and the null hypothesis could not be rejected. Therefore, the fitting effect of the equation based on the data was very good. After the system default input method was adopted with confounding factors excluded, plasma ESM-1 (odds ratio [OR] = 0.721, 95% confidence interval [CI] 0.535–0.971; P = 0.031), CRP (OR = 1.041, 95%CI 1.008–1.077; P = 0.016) and IL-6 (OR = 1.001, 95%CI 1.000–1.001; P = 0.044) showed statistical significance. These findings indicated that ESM-1, CRP and IL-6 were independently associated with ARDS occurrence in sepsis patients (Table 3).

The values of ESM-1, CRP and IL-6 levels, and the novel ARDS predictive score in predicting ARDS

Next, the above factors independently associated with ARDS occurrence, including plasma ESM-1, CRP and IL-6 levels, were evaluated via receiver operating characteristic (ROC) curves (Fig. 3). The areas under the ROC curves (AUCs) for ESM-1, CRP and IL-6 were 0.750, 0.736 and 0.736, respectively. A regression equation was established based on the coefficients of plasma ESM-1, CRP and IL-6 levels to derive an ARDS prediction score with an AUC for predicting ARDS of 0.895. Detailed ROC curve analysis is summarized in Table 4.

Discussion

The present study demonstrated that plasma ESM-1, CRP and IL-6 levels on the first day are independently associated with ARDS in sepsis. Based on these data, a novel ARDS prediction score was developed, with obviously improved value than ESM-1, CRP and IL-6 in predicting ARDS in sepsis cases.

In this study, the incidence of sepsis-induced ARDS was 35.21%. Among ARDS patients, the case fatality rate was 58.1% versus 23.8% in the non- ARDS group ($P = 0.027$), corroborating previous reports^[22-23]. Therefore, it is very important to timely predict and subsequently prevent the occurrence of ARDS in sepsis cases.

In a previous study, Scherpereel et al.^[24] demonstrated a correlation between plasma ESM-1 levels and the severity of sepsis in patients admitted to the ICU. However, these authors did not indicate a relationship between plasma ESM-1 levels and the subsequent development of organ failure. In a small sample study in 2015, Palud et al.^[25] firstly reported that patients with severe sepsis and low blood ESM-1 levels develop respiratory failure on Day 3, but not those with high blood ESM-1 amounts. We further investigated whether low levels of plasma ESM-1 are actually associated with respiratory failure in sepsis. As shown above, plasma ESM-1 levels in individuals developing ARDS within 72 h were 6.17 ± 2.63 ng/mL on Day 1, which were significantly lower than those of sepsis patients without ARDS within 72 h (12.14 ± 7.27 ng/mL; $P = 0.009$). These experimental data confirmed that low plasma ESM-1 levels in sepsis patients may be associated with ARDS occurrence. It is generally admitted^[26,27] that ESM-1 secreted by endothelial cells protects lung injury by reducing the adhesion of white blood cells to endothelial cells. ESM-1 can bind to LFA-1 to prevent its interaction with ICAM-1. Therefore, ESM-1 inhibits LFA-1/ ICAM-1 dependent white blood cell adhesion during the inflammatory process, thereby reducing endothelial cell damage^[27]. In addition, De Freitas et al. proposed an explanation^[28] for this hydrolysis that ESM-1 is hydrolyzed into a specific segment (P14) with a molecular weight of 14000 by proteolysis of neutrophil-associated cathepsin G. *In vitro*, P14 was found to inhibit ESM-1 interaction with LFA-1, participating in the process of systemic inflammation. Therefore, during the acute phase of severe sepsis, insufficient endothelial cell amounts could lead to excessive infiltration of white blood cells into the lung, leading to ARDS.

The PaO₂/FiO₂ ratio is an important factor for the diagnosis and severity assessment of ARDS. Therefore, we evaluated the correlation between plasma ESM-1 amounts and the PaO₂/FiO₂ ratio. As shown above, plasma ESM-1 concentration was positively correlated with the PaO₂/FiO₂ ratio on Day 2, likely because the lower the plasma ESM-1 concentration at the time of enrollment, the more likely ARDS occurs. In addition, this study analyzed selected inflammatory biomarkers at the time of enrollment, including WBC count, and plasma CRP, IL-6, and PCT levels. In the ARDS group, CRP and IL-6 levels were higher than those of the non-ARDS group ($P = 0.019$ and $P = 0.018$, respectively), while no significant differences in WBC count and PCT levels were found between the two groups. Through binary logistic regression analysis, it was found that ESM-1, CRP and IL-6 amounts on Day 1 were independently associated with ARDS occurrence in sepsis patients. ROC curve analysis showed that Day 1's plasma ESM-1 (AUC = 0.75) was superior to CRP (AUC = 0.736) and IL-6 (AUC = 0.736) in predicting the occurrence of ARDS within 72 hours, in agreement with De Freitas et al.^[26]. With a cutoff plasma ESM-1 levels of 5.865 ng/mL, the sensitivity and specificity of this parameter were 0.786 and 0.583, respectively, in predicting ARDS occurrence in sepsis patients. The accuracy in predicting ARDS occurrence was

relatively high, with a low rate of missed diagnosis. However, the false positive rate was about 0.417, indicating the possibility of misdiagnosis.

Next, we evaluated the combined predictive value of plasma ESM-1, CRP and IL-6, by establishing a regression equation based on respective coefficients of the above parameters. The resulting predictive probability of ARDS (ARDS predictive score) was calculated for each enrolled patient. As shown above, the novel ARDS predictive score was overtly better compared with ESM-1, CRP and IL-6 in predicting ARDS in sepsis patients, indicating that it could be used to timely predict ARDS in patients with sepsis, selecting appropriate care and saving lives.

However, this study had certain limitations. First, it was a retrospective study, with inherent drawbacks. In addition, after excluding 13 patients with ARDS at the time of inclusion, only 12 cases were assessed to predict ARDS occurrence in sepsis patients within 72 hours. Although this corroborated other reports [28,29], the number of patients was low. Moreover, the single center design further reduces data generalizability. Finally, inflammatory factors were not assessed in an exhaustive manner, which deserves further attention. To address the above issues, larger well-designed multicenter are warranted.

Conclusions

The present study demonstrated that plasma ESM-1, CRP and IL-6 levels on the first day are independently associated with ARDS in sepsis cases within 72 h. Based on these three parameters, a novel ARDS predictive score was established, with obviously elevated potential in predicting ARDS compared with ESM-1, CRP and IL-6 in sepsis patients. This score may help clinicians initiate preventive treatment for ARDS at an early stage, thereby improving patient prognosis and saving lives.

Declarations

Ethical Approval and Consent to participate

The study was approved and consented by the Ethics Committee of East Hospital Affiliated to Tongji University (2014096). Informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of supporting data

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 conflicts of interest.

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Authors' contributions

XBW was guarantor of entire study, she designed the study and was a major contributor in writing the manuscript. TD analyzed and interpreted the patient data regarding the sepsis disease. HY and XJ collected the patient clinical data and plasma samples. HYY performed the clinical study and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table.1 Baseline characteristics of the patients

Variable	Non-ARDS group (n=42)	ARDS group (n=12)	<i>P</i>
Male, n (%)	23 (54.8%)	8 (66.7%)	0.470
Age (years)	72.95±12.03	61.33±20.29	0.160
Chronic comorbidities, n (%)			
Coronary heart disease	10 (23.8%)	5 (41.7%)	0.812
Diabetes	11 (26.2%)	3 (25.0%)	0.416
Hypertension	22 (52.4%)	5 (41.7%)	0.197
Site of infection, n (%)			
Skin and soft tissue	5 (11.9%)	1 (8.3%)	0.728
Biliary system	10 (23.8%)	1 (8.3%)	0.249
Abdomen	13 (31.0%)	7 (58.1%)	0.083
Urinary tract	8 (19.0%)	1 (8.3%)	0.389
Other	6 (14.3%)	2 (16.7%)	0.672
APACHE II	16.43±6.63	17.17±5.86	0.600
SOFA	7.381±4.56	6.25±5.07	0.270
Number of organ failure	2.167±1.54	3.333±2.42	0.130
ICU length of stay (days)	15.21±13.53	12.58±9.98	0.500
Hospitalization days	34.64±38.82	21.75±18.80	0.200
Mortality at day 28, n (%)	10 (23.8%)	7 (58.1%)	0.027

ARDS, acute respiratory distress syndrome; APACHE II, acute physiology and chronic health evaluation system II; SOFA, sequential organ failure assessment; ICU, intensive care unit.

Table.2 Comparison of biomarkers between the two groups

Variable	Non-ARDS group (n=42)	ARDS group (n=12)	P
ESM-1 (ng/mL)	12.14±7.27	6.17±2.63	0.009
WBC (×10 ⁹ /L)	14.81±9.94	17.06±8.73	0.279
CRP (mg/L)	114.31±44.45	152.58±37.76	0.019
IL-6 (pg/mL)	1088.88±1809.13	2048.40±2052.92	0.018
PCT (ng/mL)	35.07±36.52	36.04±45.81	0.502
Day 1 PaO ₂ /FiO ₂ ratio (mmHg)	360.36±46.84	315.50±52.40	0.029

ARDS, acute respiratory distress syndrome; ESM-1, endothelial cell specific molecule-1; WBC, white blood cells; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6; CI, confidence interval.

Table.3 Associations of various factors with ARDS occurrence in sepsis patients determined by multivariate analysis

Variable		B	Odds Ratio	95.0%CI		P
				Lower	Upper	
Step 1a	ESM-1	-0.328	0.721	0.535	0.971	0.031
	CRP	0.041	1.041	1.008	1.077	0.016
	IL-6	0.001	1.001	1.000	1.001	0.044
	PaO ₂ /FiO ₂ ratio	-0.026	0.975	0.949	1.001	0.057
	Constant	3.551	34.833			0.429

ESM-1, endothelial cell specific molecule-1; CRP, C-reactive protein; IL-6, interleukin-6; CI, confidence interval.

Table. 4 AUCs and other parameters obtained by analyzing the ROC curves of ESM-1, CRP and IL-6 levels for ARDS prediction

Variable	AUC	P-value	95%CI	Cut-Off	Sensitivity	Specificity	Youden's index
ESM-1	0.75	0.009	0.621-0.879	5.865	0.786	0.583	0.369
CRP	0.736	0.018	0.571-0.901	117.93	0.909	0.500	0.409
IL-6	0.736	0.018	0.585-0.886	257.80	0.909	0.605	0.514
ARDS predictive score	0.895	0.000	0.797-0.993	99.783	1	0.605	0.605

ARDS, acute respiratory distress syndrome; ESM-1, endothelial cell specific molecule-1; CRP, C-reactive protein; IL-6, interleukin-6; CI, confidence interval; AUC, areas under curve.

Figures

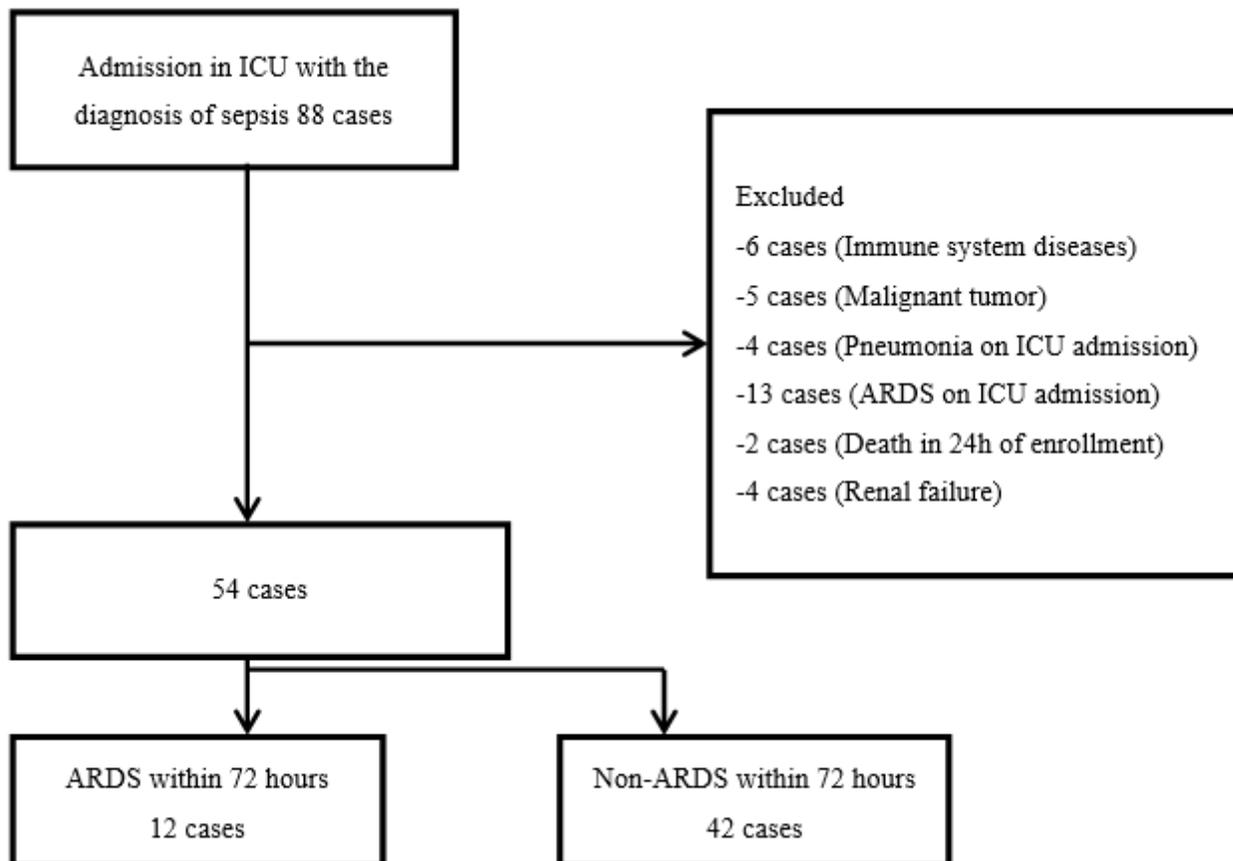


Figure 1

Study flowchart.

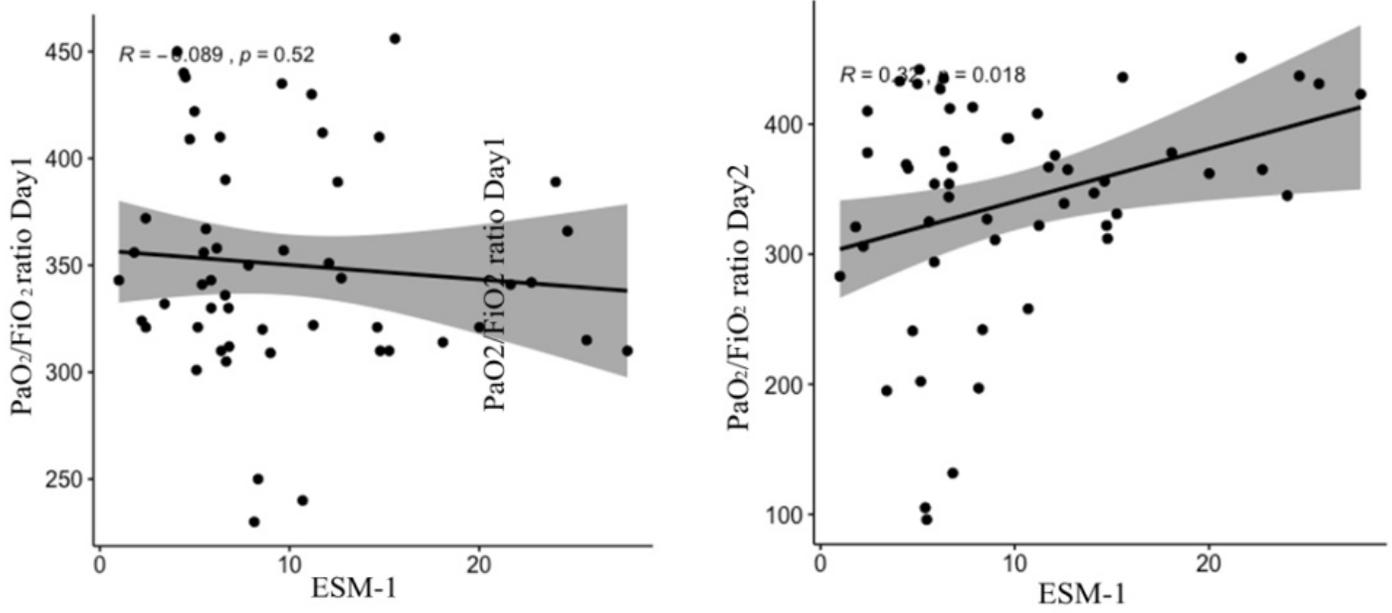


Figure 2

Correlation of ESM-1 with the PaO₂/FiO₂ ratio ESM-1, endothelial cell specific molecule-1

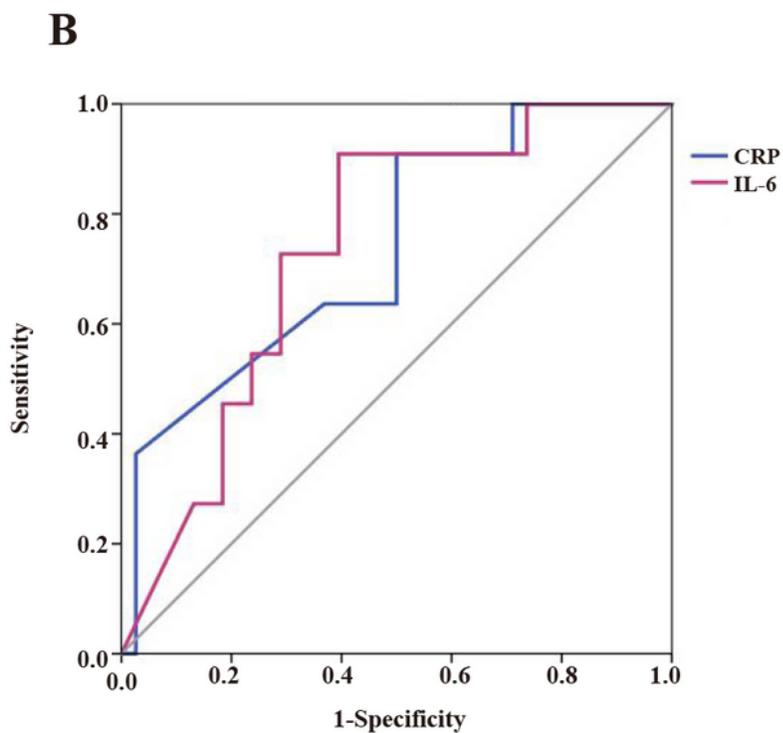
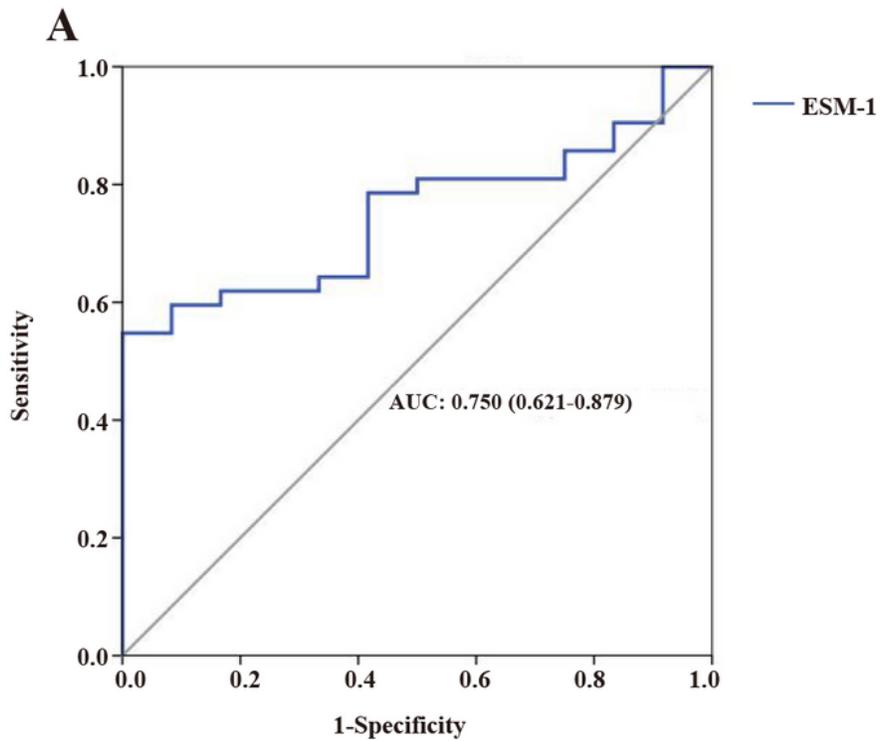


Figure 3

ROC curves of ESM-1, CRP and IL-6 levels. A. ESM-1; B. CRP and IL-6. ESM-1, endothelial cell specific molecule-1; CRP, C-reactive protein; IL-6, interleukin-6