임상의과학과 석사 학위논문

급성호흡곤란증후군 환자에서 혈청 Activin-A 농도의 임상적 의미

Role of serum Activin-A levels in ARDS patients

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서울대학교 대학원
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Mater of Science in Clinical Medical Science

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급성호흡곤란증후군 환자에서 혈청 **Activin-A**가 갖는 임상적 의미

지도교수 **이 상 민**

이 논문을 의학석사 학위논문으로 제출함

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임상의과학과

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김지민의 의학석사 학위논문을 인준함

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Abstract

Role of serum Activin-A levels in ARDS patients

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Background:

There are limited data regarding serum activin-A as a biomarker for ARDS. We aimed to evaluate whether serum activin-A levels are elevated and it has any role in predicting severity and prognosis in ARDS patients.

Methods:

Retrospective cohort study was performed with patients who were admitted to MICU with diagnosis of ARDS and have serum samples stored within 48 hours of ICU admission between March 2013 and December 2016 at a single tertiary referral hospital. Serum activin-A levels were measured with ELISA kit, and were

compared with those of normal healthy control and non-ARDS sepsis patients.

Results:

Serum activin-A levels of total 97 patients with ARDS were measured. Levels of Activin-A were elevated in ARDS patients compared to those of healthy controls (2.34 vs. 2.89, $p<0.001$) and non-ARDS sepsis patients (2.73 vs. 2.89, $p=0.002$). Activin-A was not correlated with severity of ARDS at the time of ICU admission, but showed statistically significant correlation with in-hospital mortalities (In-hospital survivors 676.2 vs. non-survivors 897.9, $p=0.047$). In predicting in-hospital mortality, serum activin-A concentrations showed superior AUC compared to that of APACHE II scores (0.653; 95% CI [0541, 0.765] vs. 0.591, 95% CI [0.471, 0.710]). With cut-off level of 708pg/mL, those with high serum activin-A levels had more than twofold increased risk of in-hospital mortalities.

Conclusions:

Serum activin-A levels in ARDS patients are elevated. Those with high serum activin-A levels tend to have poor prognosis.

Keywords: Respiratory Distress Syndrome, adult, Hospital Mortality, Activins

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Introduction

Acute Respiratory Distress Syndrome (ARDS), characterized by diffuse inflammation and increased pulmonary vascular permeability with widespread fibrosis later on, continues to be a major healthcare burden with a mortality of 27-45% depending on reports.(1) Several scoring systems have been proposed for early identification of patients at risk of developing ARDS and prediction of survival in ARDS patients. Those tools include Lung Injury Prediction Score (LIPS), Early Acute Lung Injury (EALI) score, and Surgical Lung Injury Prediction (SLIP), but their use is limited in real clinical world for they have low positive predictive value and some of these scoring systems are only for pre-operative patients.(2-4) For evaluating severity and predicting prognosis of ARDS patients, Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores are widely used, but these instruments have shortcomings in that they are complex, time-consuming to calculate, and they are not specifically designed for ARDS patients.(5)

For these reasons, there have been increasing needs for biomarker which could reflect severity or prognosis of ARDS patients. Serum activin-A, a member of transforming growth factor (TGF-b) superfamily, is a pleiotrophic regulator of cell development and function and its level is elevated in both acute and chronic inflammation.(6, 7) It has already been studied that serum activin-A has a prognostic role in sepsis.(5) Furthermore, there are increasing evidence that

activin-A plays an important role in several lung diseases including ARDS. In murine model, selective overexpression of activin-A in airway caused pulmonary pathology which was similar to acute lung injury(ALI)/ARDS. In human, it has been reported that patients with ARDS have increased level of activin-A levels in broncho-alveolar lavage(BAL) fluid.(8) However, levels of activin-A in serum, which is more convenient to measure than performing BAL in clinical practice, in ARDS patients has not been elucidated. Moreover, its relationship with ARDS severity or prognosis is rarely known. We aimed to elucidate whether serum activin-A concentration is a useful predictor of sepsis severity and a prognostic marker in critically ill patients with ARDS.

Materials and methods

Study design and Participants

We performed a retrospective cohort study with patients who were admitted to medical intensive care unit (ICU) and have serum samples stored within 48 hours of ICU admission between March 2013 and December 2016 in Seoul National University Hospital. Among those patients, we retrospectively enrolled patients who were diagnosed with ARDS at the time of ICU admission. ARDS was defined according to the 2012 Berlin definition.(9) For comparing serum activin-A level of ARDS patients with those of non-ARDS critically ill patients, we retrospectively selected patients for non-ARDS ICU controls who were admitted to medical ICU for sepsis without ARDS and had stored blood samples within 48 hours. Furthermore, for comparing serum activin-A level of ARDS patients with those of healthy people, we selected another group of normal controls who visited healthcare center for routine health screening examinations. All biospecimen for this study was provided by Seoul National University Hospital Human Biobank, a member of National Biobank of Korea, which is supported by the Ministry of Health and Welfare. All samples derived from National Biobank of Korea were obtained with informed consent under institutional review board-approved protocols. This study was performed in accordance with the tenets of the Declaration of Helsinki.

The APACHE II score, SOFA score, Simplified Acute Physiologic Score (SAPS II)

score were calculated for each patient. Physiological variables such as arterial oxygen tension (PaO2)/fractional inspired oxygen (FiO2) ratio and laboratory data, such as serum C-reactive protein and white blood cell counts were recorded at the nearest time of blood sampling for measurement of serum activin-A level. Electronic medical records were reviewed for identifying the cause of ARDS.

Measurement of serum activin-A concentrations

Blood samples were centrifuged at 2500 rpm/min for 10 minutes and strored at -80°C immediately at the time of collection, and were thawed right before the assays. An enzyme-linked immunosorbent assay (Quantikine Human/Mouse/Rat Activin-A Immunoassay;R&D Systems, Abingdon, UK) was performed to measure the activin-A concentration. To determine intra-assay precision, all samples were assayed in duplicate. The intra-assay coefficients of variation for activin-A was 4.2%, and the lower level of detection was 56.1pg/mL. Measurement of activin-A level was performed by an investigator blinded to the clinical records of the patients.

Outcomes and statistical analysis

The primary outcome was prognostic value of serum acitivin-A levels in ARDS patients. ICU/ hospital mortality, ICU/hospital length of stay were used as a clinical

outcome variables. The secondary outcome was the diagnostic value of serum activin-A concentrations as a biomarker for discriminating severity of ARDS. The data are presented as mean (±standard deviation) or median (interquartile range) for continuous variables and as number (percentage) for categorical variables.

The Mann-Whitney *U* test was used to compare differences in characteristics between survivors and non-survivors. The association between serum activin-A concentrations and mortality rates were investigated using Cox proportional hazard analysis. For comparing serum activin-A levels of ARDS patients with control groups, 1:1 propensity score matched Cox proportional hazard analysis was adopted. A receiver-operating characteristic (ROC) curve and multivariate logistic regression were used to evaluate the predictive power for ICU/Hospital mortality of serum activin-A concentration. Correlations between serum activin-A concentration and other prognostic, physiological, and biochemical variables were evaluated by logistic regression. Odd ratios (OR) and adjusted OR (aOR) were presented with 95% confidence intervals (CI). *P* value less than 0.05 was determined to have statistical significance. SPSS version. 23 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Baseline characteristics and clinical features of ARDS patients

Among 577 patients who were admitted to medical ICU and had serum samples stored within 48hours of admission from May 2013 to December 2016, 97 patients were diagnosed with ARDS at the time of ICU admission and were eligible for inclusion. (Figure 1) Baseline characteristics and clinical features of ARDS of the study population are presented in Table 1. Median age of study population was 67.2, and 64.3% were male. About 17.4% had underlying lung cancer, 7.1% had COPD or IPF, and 5% had metastatic cancer to lung Their mean white blood cell count was 15318/uL and C-reactive protein was 15.2mg/dL at the time of ICU admission. 91 patients (92.9%) received mechanical ventilation, while 8 patients survived through ARDS with non-invasive ventilation such as high flow nasal cannulas. Most of the patients received mechanical ventilation for type 1 respiratory failure. 85.7% of patients had direct lung injury for the cause of ARDS, and majorities of direct lung injury were pneumonia. 14.3% of patients had indirect lung injury and most of them were related to sepsis. About 67.3% of patients had severe ARDS; their P/F ratio at the time of ICU admission was less than 100. Their mean APACHE II, SOFA, SAPS II score were 23.9, 9.2 and 37.8, respectively.

Clinical course of ARDS patients

66.3% of patients received inotropics at some point of ICU care, and about half the patiens (46.9%) received Nitric Oxide in addition to mechanical ventilation. 81.6% of patients received corticosteroids for some reasons; ARDS, sepsis, Pneumocystic jiverocii pneumonia, acute exacerbation of idiopathic pulmonary fibrosis, etc. Their average durations of mechanical ventilation were 25 days. Successful extubation was done in 41 patients (41.8%), and 26 patients (26.5%) ended up receiving tracheostomy. Average length of ICU and hospital stays were 15 and 44 days, respectively. 58.2% of patients died in ICU, and 64.3% of patients died in hospital. (Table 2)

Levels of serum activin-A in ARDS patients

Average concentration of activin-A in ARDS patients was 1525.62pg/mL, ranging from 219 to 51412pg/mL. Due to its wide distribution, log transformation was done to compare its value with control groups. To evaluate whether serum activin-A level is elevated in ARDS patients, we measured serum activin-A levels of 14 healthy controls who were age and sex-matched with ARDS patients. Compared to healthy control, serum levels of activin-A were significantly elevated in ARDS (2.34 vs. 2.89, $p<0.001$). (Fig 2) For confirming whether serum activin-A levels are elevated in ARDS patients compared to non-ARDS ICU patients, we selected age, sex, and APACHE II score-matched ICU patients who were admitted to ICU for sepsis without ARDS. Of propensity score-matched 97 patients with sepsis, there

were no difference in age, sex, and APACHE II score compared to those of ARDS patients. Patients with ARDS had serum levels of activin-A that were higher than those of non-ARDS sepsis patients, which was statistically significant (2.73 vs. 2.89, p=0.002). (Figure 2)

Discriminant power of serum activin-A levels in ARDS patients and its association with other clinical variables

After confirming that serum activin-A levels are elevated in ARDS patients compared to either healthy controls or critically-ill patients without ARDS, we intended to evaluate whether levels of serum activin-A could discriminate severity of ARDS. Serum activin-A levels in patients with severe ARDS tends to be higher than those in patients with mild to moderate ARDS, but there was no statistical significance. (1833.92 vs. 899.4pg/mL, p=0.410). There was no significant correlation between serum activin-A levels and P/F ratio at ICU admission. (Figure 3). When evaluating association between serum activin-A levels with other variables that are known to reflect severity of disease, serum activin-A levels showed statistically significant association between SAPS II score, but showed no significant association with APACHE II, SOFA score, or level of C-reactive protein. (Table 3).

Prediction of clinical outcomes with serum activin-A levels

Serum activin-A levels were compared between survivors and non-survivors. Those who died during ICU stay or after ICU stay within hospitalization tended to have higher serum activin-A levels compared to those who survived, but there were no statistical significance. Because some patients showed extremely high serum activin-A levels (>3000pg/mL), we performed another analysis after excluding those outliers (all those 5 patients with extremely high serum activin-A levels were ICU/Hospital non-survivors). When excluding these outliers, there was significant difference in serum activin-A levels between survivors and non-survivors during hospitalization. (Table 4, Figure 4). When dividing patients into 4 quartiles according to their serum activin-A levels, Quartile 4 showed highest in-hospital mortality and shortest median survival days while Quartile 1 showed lowest in-hospital mortality and longest median survival days. (Table 5).

A ROC curve was used to evaluate whether the serum activin-A levels could be useful to predict in-hospital mortality. Predicting the mortality in the study population, the area under the ROC curve (AUC) was calculated as 0.635 (95% CI: 0.252, 0.745, p=0.024). This was higher than that of APACHE II score, of which AUC was calculated as 0.548 (95% CI: 0.432, 0.665, p=0.418). (Table 6, Figure 5). The cut-off level of 708pg/mL for serum activin-A concentration had a sensitivity of 55.8% and specificity of 67.2%. In patients with serum activin-A levels of 708pg/mL or higher, the risk of in-hospital mortality was 2.61-fold higher than in

those with serum activin-A levels less than 708pg/mL in the univariate analysis. This result was consistent in the multivariate analysis (aOR 2.64, 95% CI: 1.04-6.70, p=0.041). (Table 7)

Table 1. Baseline demographics and clinical features of ARDS patients

Variables	Total patients (n=97)
Baseline demographics and lab findings	
Age, years	67.2 (64.3-70.1)
Sex, Male, N(%)	63 (64.3%)
BMI, kg/m^2	22.5 (21.7-23.4)
Underlying lung disease, N(%)	
Lung cancer	17 (17.4%)
Chronic obstructive lung disease	7 (7.1%)
Idiopathic pulmonary fibrosis	7 (7.1%)
Tuberculosis-destroyed lung	4 (4.1%)
Metastatic cancer to lung	5 (5.1%)
Others	15 (15.3%)
Comorbidities, N(%)	
Hypertension	39 (39.8%)
Diabetes mellitus	25 (25.5%)
Cardiovascular disease	32 (32.7%)
Cerebrovascular disease	10 (10.2%)
Malignancy	51 (52.0%)
Liver cirrhosis	9 (9.2%)
Chronic kidney disease	18 (18.4%)
Blood test	
White blood cell, /uL	15318 (9538-21098)
Hematocrit, %	312 (30.0-32.4)
Creatinine, mg/dL	1.25 (1.03-1.48)
C-reactive protein, mg/dL	15.2 (13.2-17.3)
Albumin, mg/dL	2.8 (2.7-2.9)
Sodium, mEq/L	136.5 (135.1-137.9)
Clinical Features of ARDS	
Intubation, N(%)	91 (92.9%)
Indication for intubation, N(%)	
Type 1 respiratory failure	83 (84.7%)
Type 2 respiratory failure	8 (8.2%)
Cause of ARDS, N(%)	
Direct lung injury	86 (87.8%)
Indirect lung injury	11 (12.2%)
Severity of ARDS	
Mild	3 (3.1%)

Moderate	29 (29.6%)
Severe	65 (67.3%)
APACHE II score	23.9 (21.7-26.1)
SOFA score	9.2 (8.2-10.3)
SAPS II score	37.8 (33.6-42.1)
LIPS at hospital admission	5.5 (4.9-6.1)
Initial ventilation mode	
Pressure control ventilation	69 (70.4%)
Other than pressure control ventilation	22 (22.4%)
Mechanical ventilation setting	
FiO2	0.7 (0.6-0.8)
PaO2/FiO2 ratio	93 (85-101)
Peak inspiratory pressure, cmH20	25 (24-26)
Tidal volume, mL	468 (443-494)
Minute volume, L	10.5 (10.0-11.0)
Positive end-expiratory pressure, cmH20	8 (7-9)
Serum Activin-A concentration (pg/mL)	1525.62 (472.60-2578.64)
Serum Activin-A concentration[a]	2.89 (2.82-2.96)

Abbreviations : BMI, body mass index; ARDS, Acute Respiratory Distress Syndrome; APACHE, Acute Physiologic and Chronic Health Evaluation; SOFA, Sepsis-related organ failure; SAPS, simplified acute physiologic score; LIPS, lung injury prediction score; FiO2, Fraction of inspired oxygen; PaO2, patial pressure arterial oxygen.

[a]log transformation of levels of serum activin-A was done.

Table 2. Clinical course of ARDS patients

Variables	Total patients (n=97)
Use of adjunctive therapies, N(%)	
Inotropics	65 (66.3%)
Corticosteroid	80 (81.6%)
Nitric Oxide	46 (46.9%)
Prone position	17 (17.3%)
Continuous renal replacement therapy	21 (21.4%)
Extracorporeal membrane oxygenation	6 (6.1%)
Duration of mechanical ventilation	25 (3-47)
Extubation, N(%)	41 (41.8%)
Tracheostomy, N(%)	26 (26.5%)
ICU length of stay, days	15 (12-18)
Hospital length of stay, days	44 (31-57)
ICU mortality, N(%)	57 (58.2%)
Overall In-hospital mortality	63 (64.3%)
30-day in-hospital mortality	45 (45.9%)
60-day in-hospital mortality	60 (61.2%)

Abbreviations: ICU, intensive care units

Table3. Association between other variables with serum activin-A

Variables	Univariate		Multivariate[a]	
	ß±SE	p-value	ß±SE	p-value
Prognostic values				
APACHE II score	93.3 ± 47.9	0.054	92.9 ± 48.3	0.057
SOFA score	40.9 ± 101.4	0.687	-228.1 ± 151.9	0.137
SAPS II score	54.2 ± 25.0	0.033	92.2 ± 26.7	0.001
PaO2/FiO2 ratio, mmHg	-10.0 ± 13.3	0.450	-6.87 ± 13.5	0.612
Serum C-reactive protein	30.9 ± 53.7	0.437	30.9 ± 53.9	0.567
Serum albumin	-178.9 ± 711.5	0.802	-62.9 ± 720.5	0.931

Abbreviations : APACHE, acute physiologic and chronic health evaluation; SOFA, Sepsis-related organ failure; SAPS, simplified acute physiologic score; FiO2, Fraction of inspired oxygen; PaO2, patial pressure arterial oxygen.

[a]Adjusted by age, sex, APACHE II score

Table 4. Prognostic value of serum activin level

ICU mortality	**No (n=40)**	**Yes (n=57)**	**p-value**
Serum activin (pg/mL)	705.0	2010.5	0.197
In-hospital mortality	**No (n=34)**	**Yes (n=63)**	**P-value**
Serum activin (pg/mL)	676.2	1984.1	0.241

ICU mortality	**No (n=40)**	**Yes (n=52)**	**p-value**
Serum activin (pg/mL)	705.0	901.3	0.072
In-hospital mortality	**No (n=34)**	**Yes (n=58)**	**P-value**
Serum activin (pg/mL)	676.2	897.9	0.047

Abbreviations: ICU; intensive care units

Table 5. Difference in survival during hospitalization among Quartiles of serum activin level.

	Hospital mortality, N(%)	Median survival, days
Quartile 1	12 (50.0%)	46 ± 12
Quartile 2	14 (58.3%)	44 ± 19
Quartile 3	15 (62.5%)	44 ± 13
Quartile 4	22 (88.0%)	23 ± 5

Table 6. ROC curve of serum activin, APACHE II score in predicting in-hospital, ICU mortality

	In-hospital mortality			ICU mortality		
Parameter	AUC	95% CI	p-value	AUC	95% CI	p-value
Activin-A	0.653	0.541, 0.765	0.013	0.635	0.525, 0.745	0.024
APACHE II	0.591	0.471, 0.710	0.142	0.548	0.432, 0.665	0.418

Abbreviations : ICU; intensive care units, APACHE; acute physiologic and chronic health evaluation

Table 7. Serum activin-A level in predicting in-hospital mortality

Variables	Univariate		Multivariate[a]	
	Unadjusted OR	*P* value	Adjusted OR	*P* value
Prognostic values				
APACHE II score	1.03 (0.99, 1.08)	0.147	1.05 (0.99, 1.10)	0.061
SOFA score	1.03 (0.95, 1.12)	0.443	1.06 (0.97, 1.16)	0.186
SAPS II score	1.02 (0.99, 1.04)	0.103	1.01 (0.99, 1.04)	0.278
High serum activin (>708pg/mL)	2.61 (1.09, 6.26)	0.031	2.64 (1.04, 6.70)	0.041

Abbreviations : APACHE, acute physiologic and chronic health evaluation; SOFA, Sepsis-related organ failure; SAPS, simplified acute physiologic score

[a]Adjusted by APACHE II, SOFA, SAPS II score, and serum activin-A concentrations

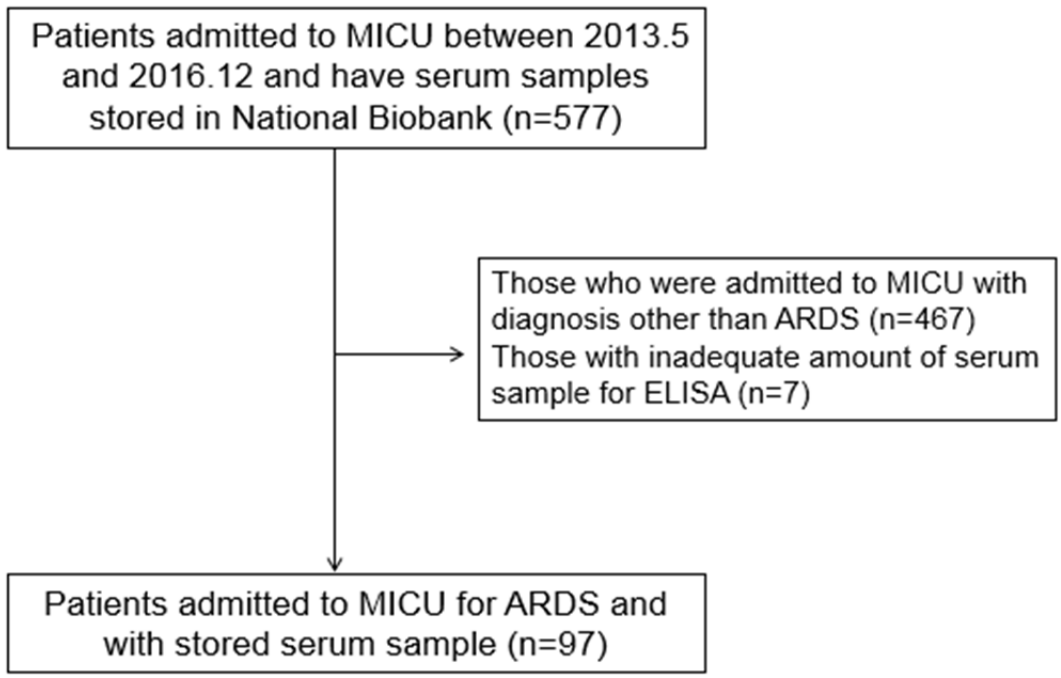

Figure 1. Flow diagram of the study population

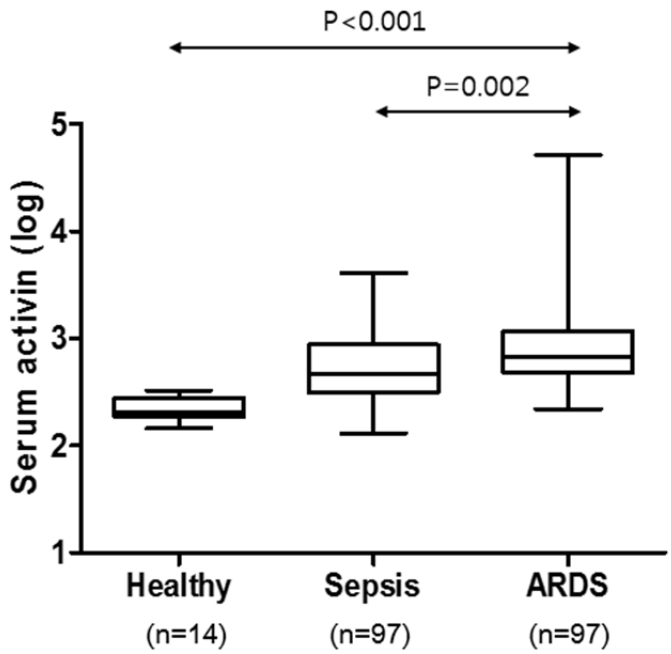

Figure 2. Comparison of concentration of serum activin-A among healthy controls, critically-ill patients with sepsis, and patients with ARDS.

Serum activin-A levels are log transformed. Healthy controls are age and sex-matched with ARDS patients. Those with sepsis patients were age, sex, and APACHE-II score matched with those of ARDS patients.

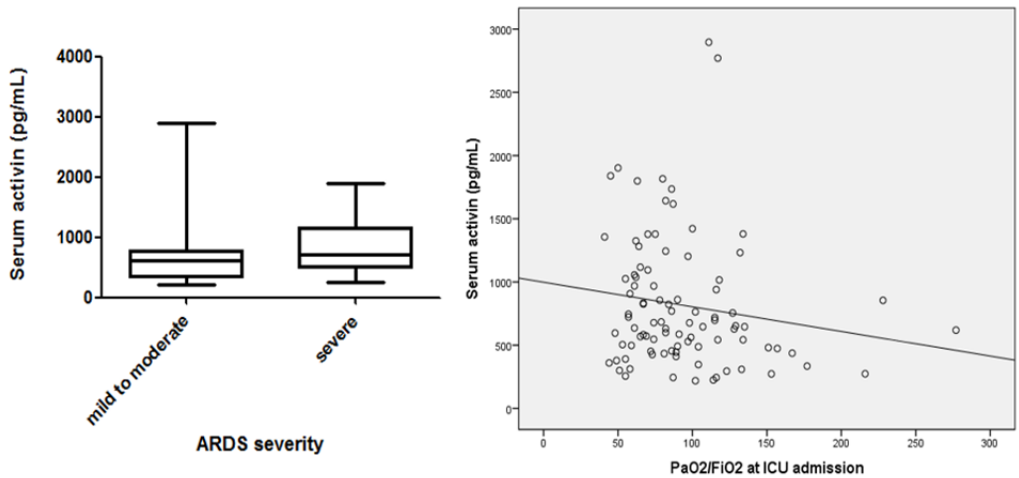

Figure 3. Serum activin-A concentration according to ARDS severity and P/F ratio. (a) There are no statistically significant differences in serum activin-A levels between those with mild to moderate ARDS and severe ARDS. (b) There are no statistically significant differences between serum activin-A levels and P/F ratio at the time of ICU admission.

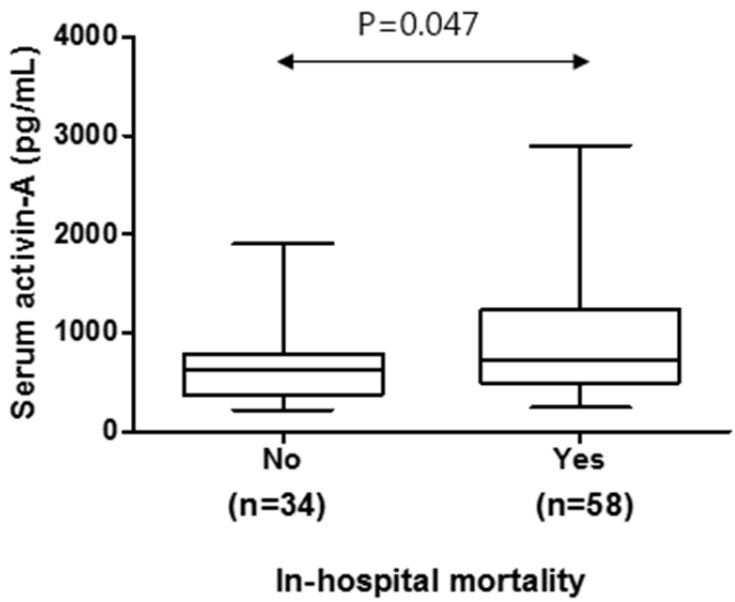

Figure 4. Serum activin-A concentration according to hospital outcomes.

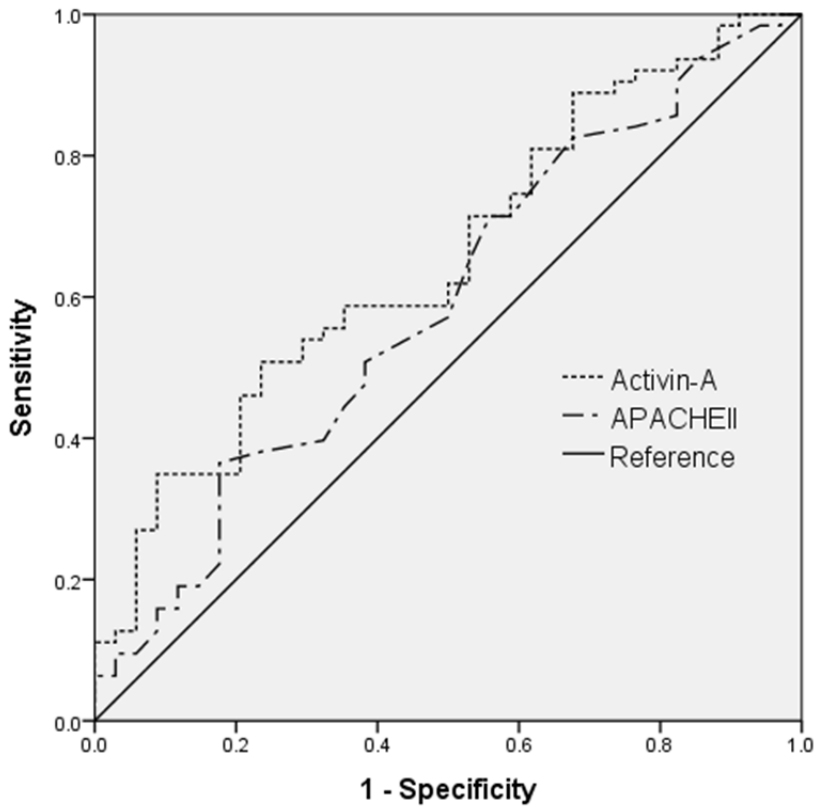

Figure 5. Receiver-operating characteristic curves for predicting in-hospital mortality. Serum activin-A level is presented as dotted line, APACHE II score as chain line, and reference value as solid line.

Discussion

In this study, we found that serum activin-A levels are elevated in ARDS, and its higher levels are associated with increased in-hospital mortality.

There are few biomarkers that have been proposed to reflect early identification and predicting prognosis of ARDS. In one study, plasma concentration of angiopoietin-2 in combination with LIPS score improved predictability of ARDS than using LIPS score alone.(10, 11) In another study, lower uric acid was associated with lower in-hospital mortality with a cut-off level of uric acid as 3.0mg/dL. (12) However evidence regarding these biomarkers are scarce so they are not in widespread use in clinical field. Activin-A is a member of transforming growth factor-ß superfamily and is a pleiotropic regulator of cell development and function.(6) It is known to be involved in both proinflammatory, antiinflammtory reaction, and tissue-remodeling activities.(13, 14) Increasing evidences have shown that activin-A plays an important role in various pulmonary diseases, such as asthma and chronic obstructive lung disease.(7, 15) Role of activin-A in ARDS has been proposed in murine models. Apostolous *et al* reported that overexpression of activin-A in mouse airways caused pulmonary pathology reminiscent of acute lung injury. Furthermore, broncho-alveolar lavage fluid of ARDS patients showed high activin-A levels compared to those in non-ARDS controls.(8) However, little is known about the change of serum activin-A levels in ARDS patients.

Compared to both healthy controls and critically ill patients with sepsis, patients with ARDS had a significantly higher levels of serum activin-A. Although there were no differences of serum activin-A levels according to ARDS severity, those with higher serum activin-A levels showed higher in-hospital mortality. Cut-off value of serum activin-A 708pg/mL or higher was associated with more than twofold increase in in-hospital mortality. Although serum activin-A concentration was not correlated with ARDS severity, those with activin-A levels higher than 708pg/mL had significantly lower P/F ratio which implies more severe disease than those with lower activin-A levels. Majority of enrolled patients had direct lung injuries.

One of limitations in this study is that we did not measure sequential levels of activin-A. In order to further elucidate the prognostic role of activin-A, comparing serial changes in activin-A between survivors and non-survivors would be helpful. In addition to acute inflammation, activin-A is known to play a role in late phase of inflammation and airway remodeling.(16, 17) Thus, it would be important to see whether serum activin-A increases in late fibrotic phase in ARDS and if its levels are modulated by administrating anti-inflammatory drugs such as corticosteroids. Another limitation of this study is that we could not find proper explanation for patients with extremely high serum activin-A concentrations. Of 97 patients, 5 patients showed very high serum activin-A concentrations; that is, activin-A over 3000pg/mL. All of them had ARDS after direct lung injuries. 4 patients had severe ARDS and 1 patient had mild to moderate ARDS at the time of ICU admission. All

of them did not survive through ARDS and died in ICU. We tried to find out shared factors among these patients which could contribute to extremely high serum activin-A levels but could not find any. Future studies are needed to explain these unusually high levels of serum activin-A levels. Lastly, unlike many studies that ARDS after direct lung injury had unfavorable prognosis compared to ARDS after indirect lung injury, there were no difference in serum activin-A levels or in-hospital mortalities among ARDS patients in this study.(18-20) Because this study was performed in medical ICU, majority of patients had ARDS related to direct lung injuries. ARDS patients with indirect lung injuries, for example post-op ARDS, transfusion-related ARDS, trauma-related ARDS, could have been missed for those with indirect lung injuries are generally admitted to surgical ICU. Further studies are needed to compare serum activin-A levels between direct and indirect lung injuries.

In conclusion, serum activin-A concentrations are elevated in ARDS, and its higher levels are associated with increased in-hospital mortality. Further studies are required to evaluate the practicability and clinical benefit of this biomarker.

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요약 (국문초록)

서론

이전부터 급성호흡곤란증후군 환자들의 예후를 적절히 반영해주면서 임상에서 쉽고 빠르게 측정이 가능한 혈청지표의 필요성이 대두되어 왔다. 이에 본 연구는 혈청지표로서 액티빈-A가 어떠한 의미를 가지며 급성호흡곤란증후군 환자의 진료에 있어서 어떤 도움을 줄 수 있는지를 알아보고자 하였다.

방법

본 연구는 2013년부터 2016년까지 서울대학교병원 내과계중환자실에 입실한 급성호흡곤란 증후군 환자 중 입실 48시간 이내 혈액 샘플이 인체자원은행에 보관되어 있는 환자를 대상으로 하였다. 혈청 액티빈-A 농도는 ELISA를 통해 측정하였으며 급성호흡곤란 증후군 환자의 액티빈-A 농도와 비교하기 위해 건강한 대조군 및 패혈증 환자들의 액티빈-A 농도를 함께 측정하였다.

결과

97명의 급성호흡곤란증후군 환자가 분석에 포함되었다. 급성호흡곤란 증후군 환자의 혈청 액티빈-A농도는 정상인 (2.34 vs. 2.89, $p<0.001$) 및 패혈

증 환자 (2.73 vs. 2.89, p=0.002) 에 비해 모두 통계적으로 유의하게 증가되어 있었다. 혈청 액티빈-A농도는 중환자실 입실 당시의 급성호흡곤란증후군의 중증도와는 유의한 연관성이 없었다. 병원내 사망자의 경우 비사망자에 비해 혈청 액티빈-A의 농도가 유의하게 높은 경향을 보였다. (897.9 vs. 676.2pg/mL, p=0.047) 이를 통해 병원내 사망에 대한 액티빈-A의 ROC curve를 그려보았을 때 액티빈-A의 AUC는 APACHE-II score의 AUC 보다 높은 것을 확인하였다. (0.653;95% CI[0.541,0.765] vs. 0.591;95% CI[0.471, 0.710]). 혈청 액티빈-A 농도를 708pg/mL기준으로 고농도군과 저농도군으로 분류하였을 때 고농도군에서 병원내 사망률에 대한 위험비율이 2배 이상 증가하는 것을 확인하였다.

결론

급성호흡곤란증후군 환자에서 혈청 액티빈-A의 농도는 증가되어있으며 높은 혈청 액티빈-A의 농도는 나쁜 예후와 연관이 있다.

주요어 : 급성호흡곤란증후군, 원내사망률, 액티빈

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