

# Levels of Soluble Receptor for Advanced Glycation End Products in Bronchoalveolar Lavage Fluid in Patients with Various Inflammatory Lung Diseases

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## Supplementary Issue: Current Developments in Interstitial Lung Disease

**ABSTRACT:** Receptor for advanced glycation end products (RAGE) is a multiligand receptor of S100/calgranulins, high-mobility group box 1, and others, and it is associated with the pathogenesis of various inflammatory and circulatory diseases. The soluble form of RAGE (sRAGE) is a decoy receptor and competitively inhibits membrane-bound RAGE activation. In this study, we measured sRAGE levels in bronchoalveolar lavage fluid (BALF) of 78 patients, including 41 with interstitial pneumonia, 11 with sarcoidosis, 9 with respiratory infection, 7 with ARDS, 5 with lung cancer, and 5 with vasculitis. Among them, sRAGE was detectable in BALF of 73 patients (94%). In patients with ARDS and vasculitis, the sRAGE levels were significantly higher than in the control subjects and those with interstitial pneumonia. The sRAGE levels were positively correlated with total cell counts in BALF and serum levels of surfactant protein-D, lactate dehydrogenase, and C-reactive protein. There was an inverse correlation between PaO<sub>2</sub>/FIO<sub>2</sub> ratio and sRAGE levels. These results indicate that sRAGE in BALF might be considered as a biomarker of lung inflammatory disorders, especially ARDS and vasculitis.

**KEYWORDS:** RAGE, bronchoalveolar lavage, ARDS, vasculitis, surfactant protein D

**SUPPLEMENT:** Current Developments in Interstitial Lung Disease

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## Introduction

Receptor for advanced glycation end products (RAGE), a member of the immunoglobulin superfamily, is a multiligand, pattern-recognition receptor, which can bind advanced glycation end products (AGEs), amyloid  $\beta$ -peptide, and S100 proteins.<sup>1,2</sup> AGEs are a class of compounds formed by non-enzymatic glycation and oxidation of proteins and lipids. RAGE has also been implicated in mediating the cytokine activity of high-mobility group box 1 (HMGB1), which is a late inflammatory mediator of sepsis or lipopolysaccharide (LPS) lethality.<sup>3</sup> RAGE–ligand interaction results in rapid and sustained cellular activation and gene transcription, in most cases culminating in the activation of nuclear factor- $\kappa$ B.<sup>4,5</sup> This cellular activation is related to inflammatory processes or tissue injury, such as diabetic microvascular injury or amyloidosis, and immune-inflammatory process.<sup>1,6</sup>

Structurally, RAGE consists of an extracellular, a transmembrane, and cytosolic domain (mRAGE). In addition, soluble forms exist, which act as decoy receptors since

they display similar affinity for ligands and thereby limit their availability to mRAGE.<sup>7</sup> Soluble forms are generated by two distinct mechanisms. First, by alternative splicing of the *AGER* gene, which leads to the formation of endogenous soluble RAGE (esRAGE).<sup>7</sup> Second, ectodomain shedding of mRAGE generates soluble form of RAGE (sRAGE), which lacks both the transmembrane and cytosolic domain.<sup>8</sup>

RAGE is highly expressed in the mature lung by type I pneumocytes when compared with other lung cells and other tissues.<sup>9</sup> Both sRAGE and esRAGE have been identified in the human lungs. As a pattern recognition receptor, RAGE has been implicated in the pathogenesis of various lung diseases such as chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and lung cancer.<sup>10–12</sup>

In this study, we aimed to evaluate the levels of sRAGE in the bronchoalveolar lavage fluid (BALF) that was collected from patients with various inflammatory lung disorders, including interstitial pneumonia, sarcoidosis, respiratory



infection, and ARDS. We also examined whether the sRAGE levels in BALF are correlated with other clinical parameters, such as oxygenation index, serum marker levels, and imaging scores of high-resolution computed tomography (HRCT).

## Methods

The study protocol was approved by the ethical committee of Keio University School of Medicine (2012–332). This study complied with the principles of the Declaration of Helsinki.

**Patient selection.** We retrospectively evaluated data from 78 consecutive patients who underwent bronchoalveolar lavage (BAL) at Keio University Hospital during the period from May 2011 to December 2012. Forty-seven (60%) of the study subjects were males, and the mean age was  $53.9 \pm 1.6$  years. The clinical diagnosis included interstitial pneumonia (IIP) in 41 patients, sarcoidosis in 11, respiratory infection in 9, ARDS in 7, vasculitis in 5, and lung cancer in 5. The patients who had received oral corticosteroids or immunosuppressive agents by the time of BAL were excluded. No patient with hypersensitivity pneumonia was included in the IIP group. Because no study subjects underwent surgical lung biopsy, more detailed classification of IIP could not be provided. The diagnosis of vasculitis was usually made by the lung pathology obtained with transbronchial lung biopsy. Otherwise, the diagnosis was made with lung imaging and pathology of other involved organs. Four nonsmoking healthy volunteers served as controls.

**Data collection.** We reviewed the medical records of all the patients evaluated for demographic, radiographic, BAL, and serum data. Radiographic evaluation included the scoring system using HRCT as previously described.<sup>13</sup> In sera, the levels of surfactant protein-D (SP-D), lactate dehydrogenase (LDH), KL-6, and C-reactive protein (CRP) were examined.

**BAL procedure and fluid processing for analysis.** In most cases, BAL was targeted toward affected lung segments as noted on chest CT. In most cases, the procedure was performed by wedging the bronchoscope in a subsegmental bronchus. Usually, three lavages were performed using 50 mL of 0.9% saline solution per lavage. The recovered fluid was placed on ice immediately. The BALF was pooled and filtered through sterile gauze to remove mucous strands. After the cell count was determined, the BALF was centrifuged at  $200 \times g$  for 5 minutes at  $4^\circ\text{C}$ . The cell pellets were used for the differential counts on Wright-Giemsa-stained preparations. The supernatants were aliquotted and frozen at  $-80^\circ\text{C}$  until the measurement.

**sRAGE measurement.** The levels of sRAGE in the BALF were measured using sandwich enzyme-linked immunosorbent assay kits (R&D Systems). The detection limit was 16.14 pg/mL.

**HRCT protocol.** All HRCTs were performed with 1.0- or 1.5-mm-thick sections taken at 1-cm intervals throughout

the entire thorax and were reconstructed using a high-spatial frequency algorithm. No intravenous contrast was administered. Two experienced pulmonologist (TK and ST) independently evaluated all HRCTs that were obtained 1–4 weeks before BAL. The observers scored ground glass opacity (GGO score) and reticular opacity (fibrosis score) on a scale of 0–5. These scores were also summed into a total CT score. For the purpose of analysis, each lobe was scored by the interpreters, and the mean of all lobes was incorporated into a GGO, fibrosis, and total score for each patient.

**Statistical analysis.** All data were expressed as the mean  $\pm$  SE. Among the patient groups with different underlying diseases, differences in the sRAGE levels were compared by the Kruskal–Wallis test using SPSS Windows 15.0 statistical analysis software (SPSS Inc.). The relationships between variables were analyzed by the Spearman rank-order correlation test, and Mann–Whitney *U* test was used for the group comparison. A value of  $P < 0.05$  was considered to be statistically significant.

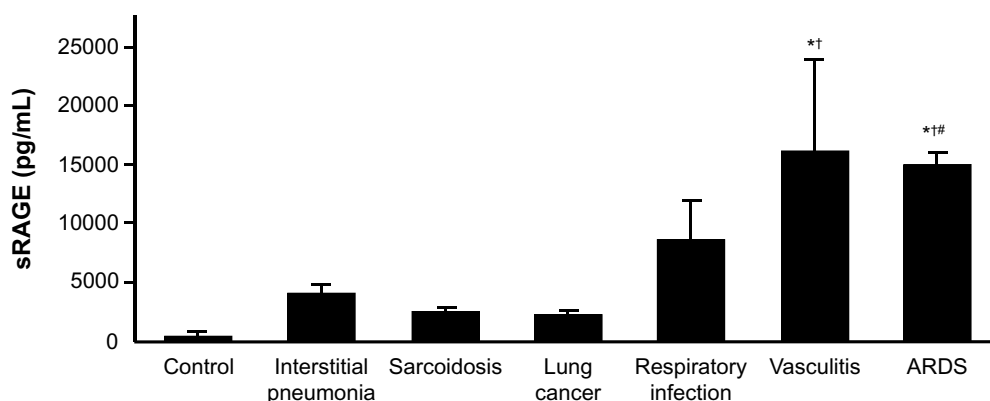
## Results

**sRAGE levels in BALF.** The levels of sRAGE were detected in BALF of 73 patients (94%). The levels of sRAGE and other parameters examined are summarized in Table 1. As shown in Figure 1, the sRAGE levels in BALF were significantly higher in patients with ARDS ( $P = 0.020$ ) and vasculitis ( $P = 0.019$ ) when compared with the control subjects. In patients with ARDS, the sRAGE levels in BALF were significantly elevated when compared to those with interstitial pneumonia ( $P = 0.010$ ) and sarcoidosis ( $P = 0.014$ ). In patients with vasculitis, the sRAGE concentrations were also increased when compared to those with interstitial pneumonia ( $P = 0.016$ ).

**Table 1.** sRAGE levels and other parameters.

sRAGE (pg/mL)	4646.8 $\pm$ 579.9
BAL cell	
Total cell count ( $\times 10^5$ /mL)	7.7 $\pm$ 1.0
Differentials	
Macrophage (%)	63.4 $\pm$ 2.6
Lymphocyte (%)	18.6 $\pm$ 2.1
Neutrophil (%)	12.4 $\pm$ 1.8
Serum markers	
CRP (mg/dL)	3.4 $\pm$ 0.5
LDH (IU/L)	251.6 $\pm$ 11.2
KL-6 (U/mL)	934.0 $\pm$ 88.2
SP-D (ng/mL)	278.0 $\pm$ 29.6
PaO <sub>2</sub> /FIO <sub>2</sub> (Torr)	395.0 $\pm$ 5.8
CT scores	
Fibrosis score	6.4 $\pm$ 0.4
GGO score	2.5 $\pm$ 0.5

**Note:** Data expressed as mean  $\pm$  SE.



**Figure 1.** Levels of sRAGE in bronchoalveolar lavage fluid. In patients with ARDS and vasculitis, the sRAGE levels were significantly higher than in the control subjects and those with interstitial pneumonia.

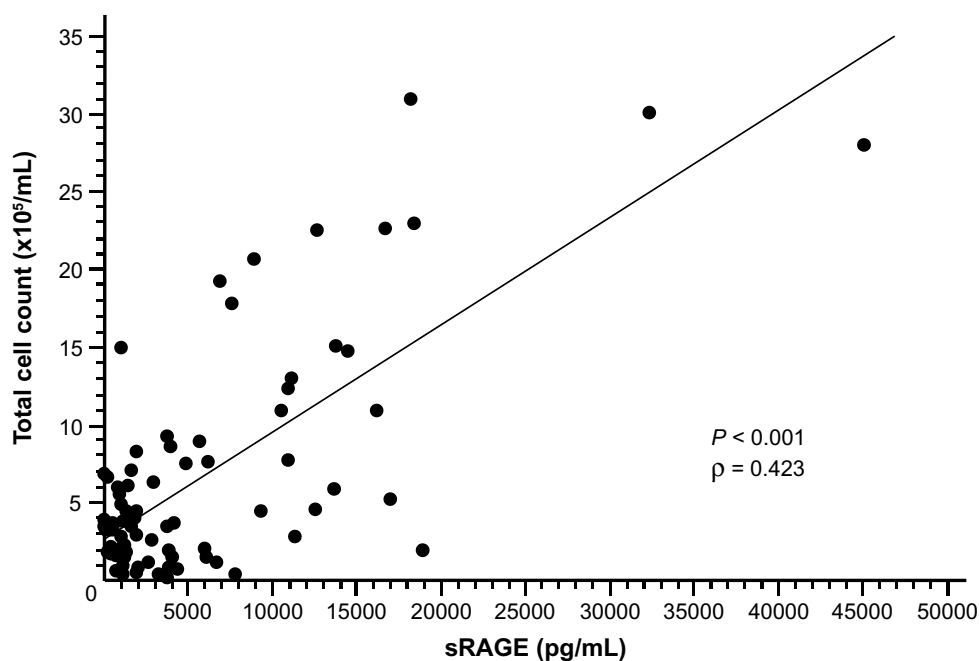
**Notes:** \* $P < 0.05$  versus control. † $P < 0.05$  versus interstitial pneumonia. # $P < 0.05$  versus sarcoidosis.

No significant increases in the sRAGE levels in BALF were observed in patients with interstitial pneumonia, sarcoidosis, respiratory infection, and lung cancer when compared with the control subjects.

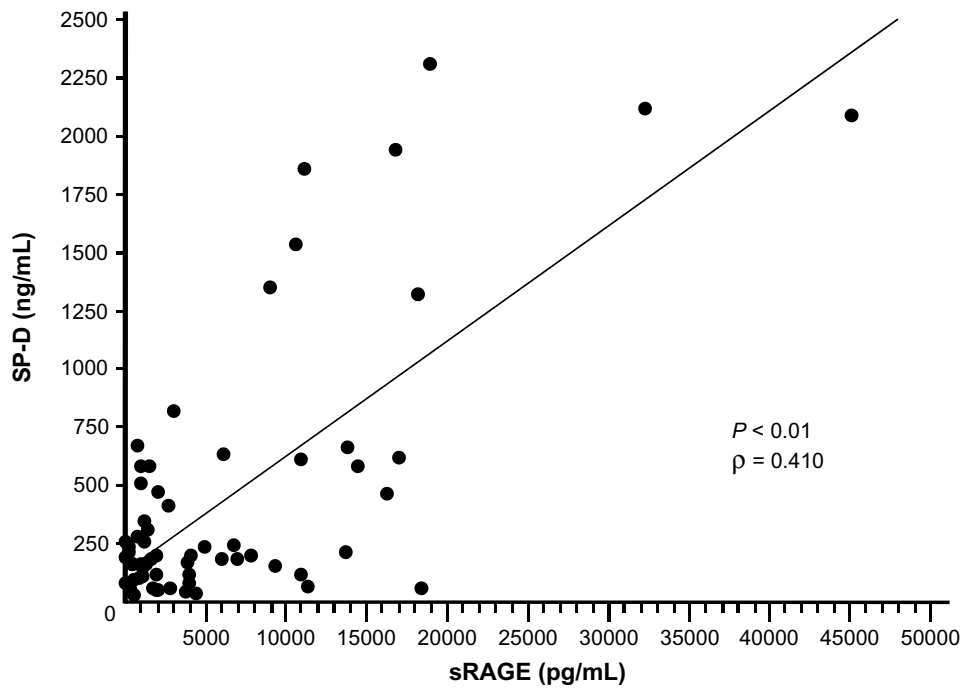
**Correlation between sRAGE and other clinical parameters.** We evaluated the correlation between the sRAGE levels and cell counts in BALF. The sRAGE levels were positively correlated with total cell counts in BALF ( $P < 0.001$ ,  $\rho = 0.423$ ; Fig. 2). The levels of sRAGE were correlated with total cell counts in patients with IIP ( $P < 0.05$ ,  $\rho = 0.337$ ) and vasculitis ( $P < 0.05$ ,  $\rho = 0.468$ ). In contrast, there were no significant correlation between sRAGE level and total cell counts in those with sarcoidosis, lung cancer, respiratory infection, and ARDS. No significant correlation

was observed between the sRAGE levels and differential cell counts in BALF (data not shown).

The correlation between the levels of serum markers and the sRAGE levels in BALF was also examined. The sRAGE levels in BALF were positively correlated with the serum levels of SP-D ( $P < 0.01$ ,  $\rho = 0.410$ ; Fig. 3). The sRAGE levels in BALF were also correlated with the serum levels of LDH ( $P < 0.0001$ ,  $\rho = 0.475$ ; Fig. 4) and CRP ( $P < 0.0001$ ,  $\rho = 0.452$ ; Fig. 5). There was no significant correlation between serum KL-6 levels and sRAGE concentrations in BALF (Fig. 6). The oxygenation index, which was determined from the arterial oxygen tension and inspiratory oxygen concentration values, was inversely correlated with the sRAGE levels in BALF ( $P < 0.001$ ,  $\rho = -0.488$ ; Fig. 7).



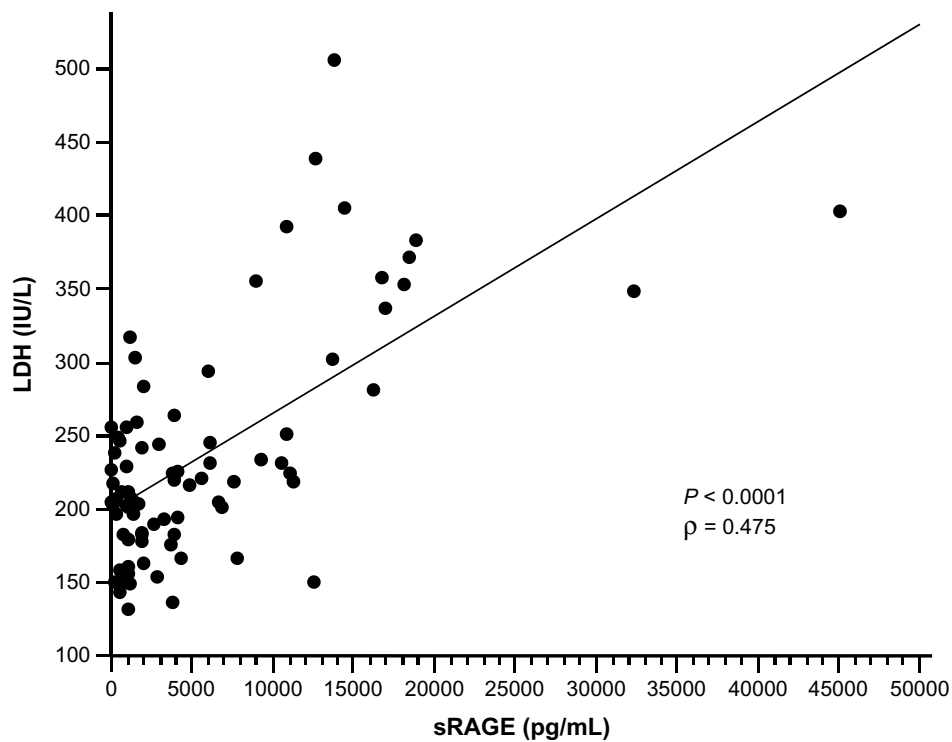
**Figure 2.** Correlation between sRAGE levels and total cell counts in bronchoalveolar lavage fluid. The sRAGE levels were positively correlated with total cell counts in BALF ( $P < 0.001$ ,  $\rho = 0.423$ ).



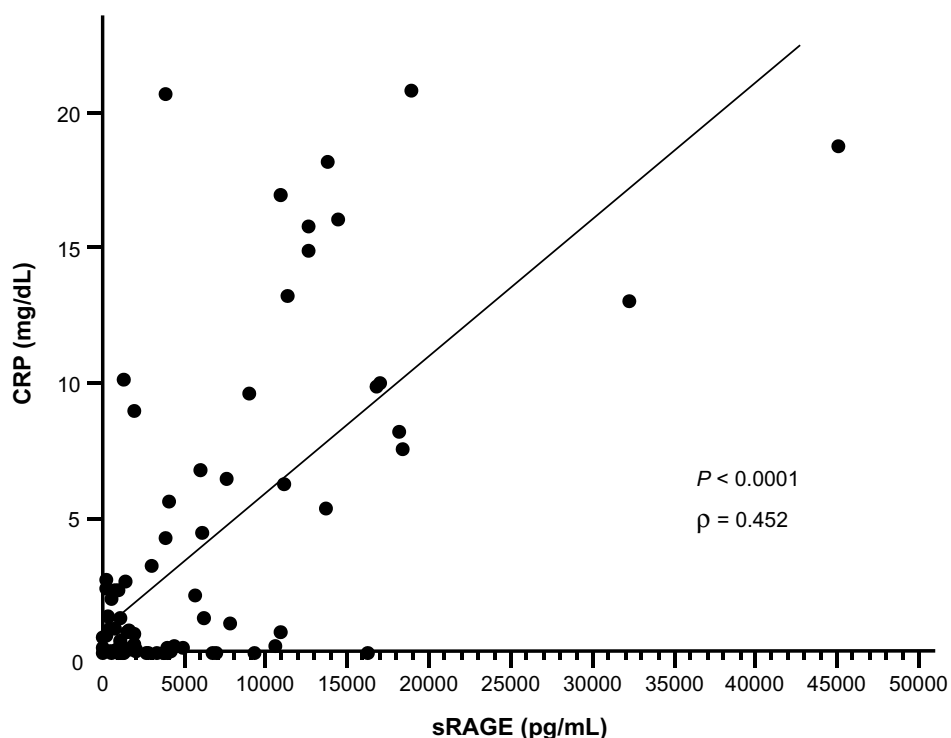
**Figure 3.** Correlation between sRAGE levels and serum concentration of SP-D. The sRAGE levels in BALF were positively correlated with the serum levels of SP-D ( $P < 0.01$ ,  $\rho = 0.410$ ).

The sRAGE levels in BALF were positively correlated with the GGO scores of HRCT ( $P < 0.0001$ ,  $\rho = 0.523$ ; Fig. 8), whereas no significant correlation was observed between the fibrosis scores and sRAGE levels.

Although the sRAGE levels were correlated with serum LDH levels in patients with IIP ( $P < 0.05$ ,  $\rho = 0.348$ ) and vasculitis ( $P < 0.05$ ,  $\rho = 0.539$ ), there were no significant correlation between sRAGE and the clinical parameters in other patient groups.



**Figure 4.** Correlation between sRAGE levels and serum concentration of LDH. The sRAGE levels in BALF were positively correlated with the serum LDH levels ( $P < 0.0001$ ,  $\rho = 0.475$ ).

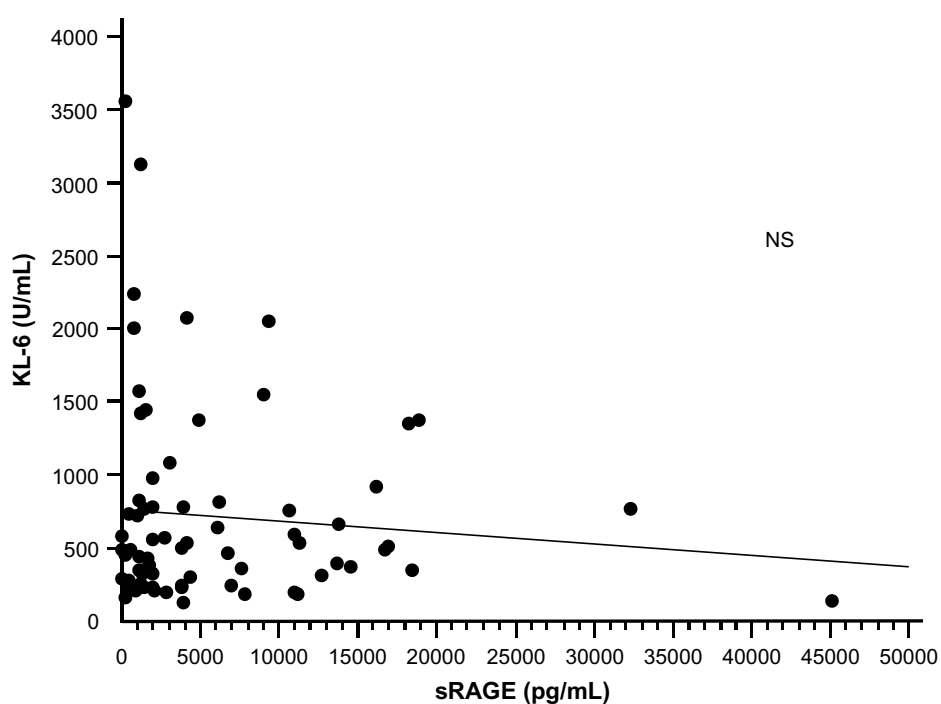


**Figure 5.** Correlation between sRAGE levels and serum concentration of CRP. The sRAGE levels in BALF were positively correlated with the serum CRP levels ( $P < 0.0001$ ,  $\rho = 0.452$ ).

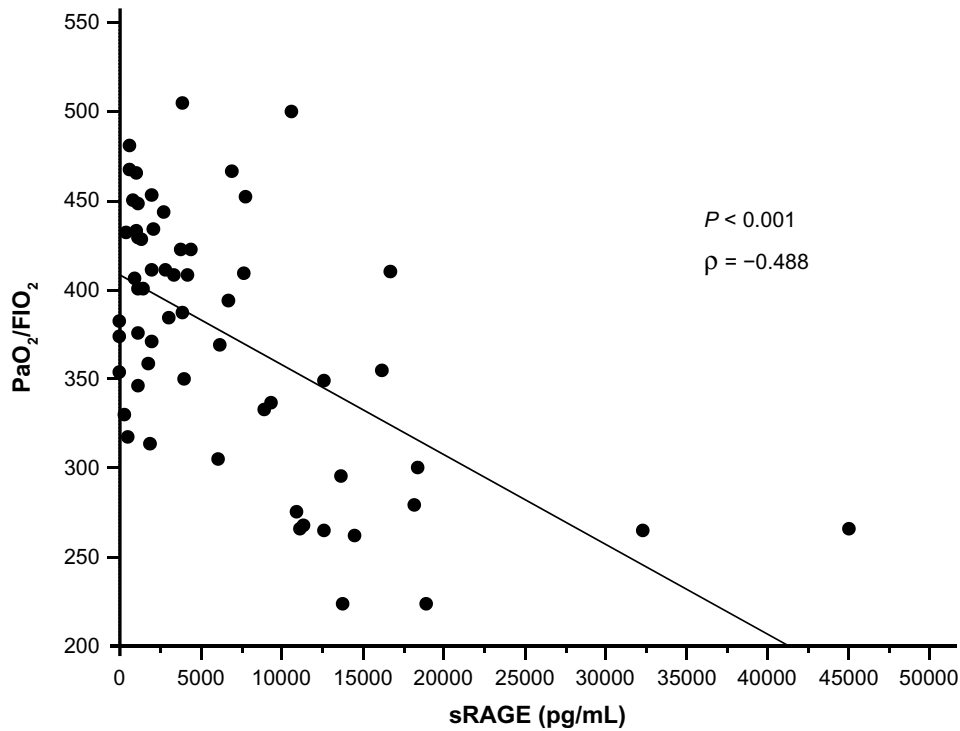
### Discussion

The results of this study have revealed that sRAGE levels are elevated in the alveolar space in patients with ARDS and vasculitis, both of which are characterized with increased permeability of pulmonary vasculature. The levels of sRAGE

in BALF were associated with oxygenation impairment and serum markers of lung tissue damage. Although elevated sRAGE levels in injured lungs have been reported, to our knowledge, this is the first study describing the differences in sRAGE levels between the patient groups with various



**Figure 6.** Correlation between sRAGE levels and serum concentration of KL-6. The sRAGE levels in BALF were not significantly correlated with the serum KL-6 levels.

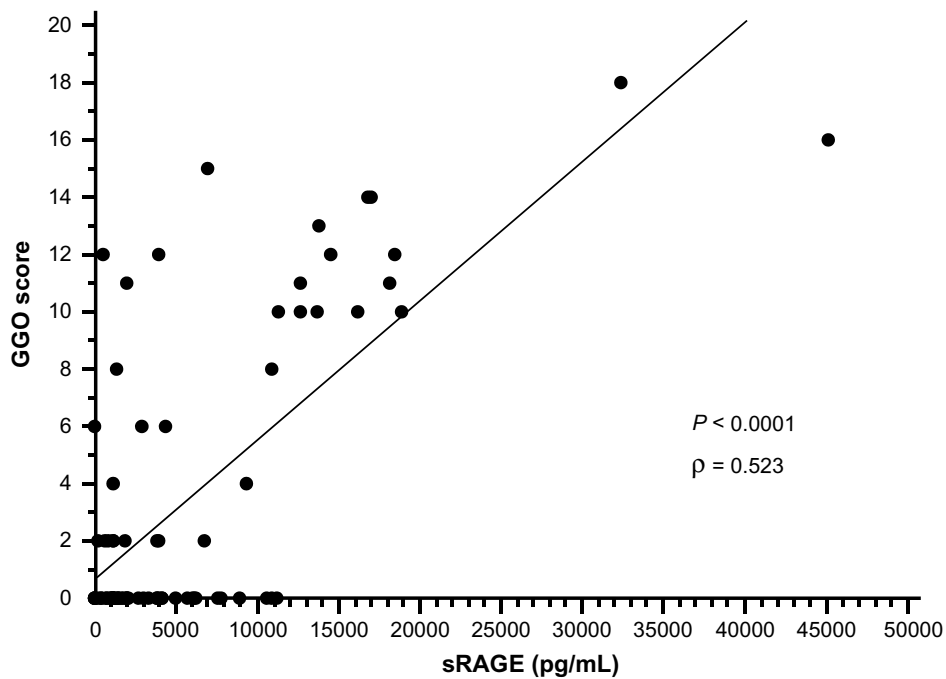


**Figure 7.** Correlation between sRAGE levels and oxygenation index. The oxygenation index ( $\text{PaO}_2/\text{FIO}_2$ ) was inversely correlated with the sRAGE levels in BALF ( $P < 0.001$ ,  $r = -0.582$ ).

underlying diseases and the association between sRAGE levels and other clinical parameters such as oxygenation index and serum markers.

In this study, the sRAGE levels were correlated with the cell counts in BALF. Besides the role of receptor for

AGEs and HMGB-1, RAGE also acts as an endothelial adhesion receptor that mediates interactions with the leukocyte integrin Mac-1 (CD11b/CD18).<sup>14</sup> We speculated that sRAGE levels might reflect the expression of RAGE on pulmonary microvascular endothelium,



**Figure 8.** Correlation between sRAGE levels and GGO scores of HRCT. The sRAGE levels in BALF were positively correlated with the GGO scores of HRCT ( $P < 0.001$ ,  $r = 0.705$ ).





leading to the inflammatory cell accumulation into the alveolar space.

In patients with interstitial pneumonia, the sRAGE levels in BALF were not significantly elevated when compared with those in the control subjects. Kyung et al determined the expression of AGEs and RAGE by the immunofluorescence assay of lung tissues and reported that lungs with idiopathic pulmonary fibrosis (IPF) showed strong expression for both AGEs and RAGE when compared to that in nonspecific interstitial pneumonia and controls.<sup>15</sup> Because none of our subjects underwent surgical lung biopsy, no patient had pathologically proven usual interstitial pneumonia (UIP). Among 41 patients with interstitial pneumonia, only 5 showed a UIP pattern on HRCT. The lack of significant elevation of sRAGE levels in those with interstitial pneumonia might be due to the smaller number of patients with IPF.

We observed significant correlation between the sRAGE levels in BALF and SP-D in serum, whereas serum KL-6 levels were not associated with sRAGE levels. Both KL-6 and SP-D are lung-specific proteins secreted primarily by alveolar type II cells, and elevated levels of these markers indicate activation of type II cells in the injured lung.<sup>16</sup> It was previously reported that serum levels of KL-6 reflect the overall extent of interstitial lesions on HRCT images, whereas the levels of SP-D mainly reflect the extent of inflammatory lesions.<sup>17</sup> In this study, the sRAGE levels were correlated with the GGO score of HRCT, which could reflect the extent of inflammatory lesions. Taken together, sRAGE levels in the alveolar space might be associated with rather inflammatory than fibrotic changes of the lungs.

In this study, we observed that the oxygenation index ( $P_aO_2/F_iO_2$ ) was inversely correlated with the sRAGE levels in BALF (Fig. 4). Calfee et al reported that, in patients with ARDS, higher plasma levels of sRAGE were associated with severity of hypoxemia and increased lung injury scores.<sup>18</sup> In experimental lung injury, sRAGE levels in BALF was shown to be much higher than those in plasma, suggesting that the primary source of plasma sRAGE is the alveolar type I cell.<sup>12,18</sup> Although we did not measure the plasma sRAGE levels, sRAGE levels in BALF might be a better indicator of alveolar epithelial damage.

RAGE plays a pivotal role, regulating inflammation and epithelial survival in the setting of stress.<sup>19</sup> Decreased levels of circulating sRAGE are associated with severity of COPD,<sup>20</sup> which might be contradictory to this study. In contrast, there have been several reports describing that higher levels of RAGE are associated with increased severity or poor outcome of lung injury, which is compatible with our findings.<sup>12,18</sup> This discrepancy may be owing to the difference in the roles of RAGE in the pathogenesis of various lung disorders.

The major limitation of this study is that sRAGE levels in BALF were measured only at one time point. Although sRAGE levels were correlated with other clinical parameters, its clinical significance remains to be determined

in serial measurements. Another limitation is the lack of measurement of sRAGE levels in plasma. Because sRAGE levels were greater in patients with ARDS and vasculitis, both of which are associated with systemic inflammation, it will be a subject of future investigation whether sRAGE levels in BALF correlate with those in plasma. In addition, as the data came from a relatively small number of patients with a variety of underlying diseases, the results could be influenced by possible confounders, such as the age and smoking status of patients.

In summary, the results of the present study indicate that sRAGE levels in BALF were elevated in patients with ARDS and vasculitis and associated with other clinical parameters of inflammatory damage of the lungs. Although further investigation is necessary, sRAGE in BALF might be considered as a biomarker of lung inflammatory disorders, especially ARDS and vasculitis.

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### Author Contributions

Conceived and designed the experiments: TK, ST. Analyzed the data: TK, ST. Wrote the first draft of the manuscript: TK. Contributed to the writing of the manuscript: ST, YT, SS, TA, KY, HN, MI, NH, TB. Agree with manuscript results and conclusions: TK, ST, YT, SS, TA, KY, HN, MI, NH, TB. Jointly developed the structure and arguments for the paper: TK, ST, YT, SS, TA, KY, HN, MI, NH, TB. Made critical revisions and approved final version: TK, ST, YT, SS, TA, KY, HN, MI, NH, TB. All authors reviewed and approved of the final manuscript.

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