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Original Article

## Serum Soluble Triggering Receptor Expressed on Myeloid Cells-1 in Acute Respiratory Distress Syndrome: A Prospective Observational Cohort Study

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**Background/Purpose:** Serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), a detector of acute inflammatory response to microbial products and a good marker for diagnosing sepsis and pneumonia, has not yet been described as a predictor for infection or a prognostic factor in patients with acute respiratory distress syndrome (ARDS).

**Methods:** This prospective observational cohort study enrolled 63 ventilated adult patients with ARDS; 50 as septic and 13 as non-septic, and followed them for 28 days in intensive care units at a university hospital in Taiwan. Serial serum sTREM-1 levels and cytokines, such as interleukin (IL)-1, IL-8, and tumor necrosis factor- $\alpha$ , on days 1, 3, 5, 7 and 14 were measured by an enzyme-linked immunosorbent assay. The association between biomarkers and clinical infectious diagnosis/outcome in ARDS was explored.

**Results:** Serum sTREM-1 and cytokine levels could not differentiate septic from non-septic ARDS. Serum log sTREM-1 and inflammatory cytokine levels were correlated positively ( $r=0.325$  for IL-1 $\beta$ ;  $r=0.247$  for IL-8;  $r=0.480$  for tumor necrosis factor- $\alpha$ ). As prognostic factors, higher serum sTREM-1 level on day 1 and increasing levels over time, especially in the first 5 days, were independent predictors of mortality on day 28, using a multivariate Cox regression model. Serum sTREM-1 levels remained stable or even increased in the non-surviving patients, but decreased in the survivors.

**Conclusion:** Serum sTREM-1 level might not be a reliable marker for infection in ARDS patients. However, as an inflammatory marker, initial serum sTREM-1 level and its trend over time, especially in the first 5 days, could be predictive of short-term mortality. A progressive decline in serum sTREM-1 levels during follow-up indicates a favorable outcome, whereas persistently elevated sTREM-1 indicates a poor prognosis and should lead to a re-evaluation of therapy.

**Key Words:** acute respiratory distress syndrome, cytokines, infection, prognosis, soluble triggering receptor expressed on myeloid cells-1

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Acute respiratory distress syndrome (ARDS) is a devastating clinical condition with high morbidity and mortality, and can have a septic or non-septic etiology.<sup>1</sup> Sepsis is the most common cause and has a worse prognosis compared to other risk factors.<sup>2,3</sup> The discrimination between septic and non-septic causes of ARDS is important, because it can prompt physicians to start multimodal treatment of severe sepsis, including the use of recombinant human activated protein C (drotrecogin- $\alpha$ ), as early as possible.<sup>4,5</sup> It can also encourage them to feel free to use corticosteroid therapy in the fibroproliferative phase of ARDS without an ongoing infectious process.<sup>6</sup> However, prompt and correct diagnosis of septic ARDS is difficult because many infectious clinical features, such as changes in body temperature, leukocytosis, or tachycardia, are non-specific. A serum biological marker that indicates severe bacterial infection would be useful in this situation. Many inflammatory biomarkers have been studied to differentiate septic from non-septic ARDS, but only a few fulfill the requirements.<sup>7-10</sup>

Trigger receptor expressed on myeloid cells-1 (TREM-1) has recently been identified as an infectious marker.<sup>11,12</sup> TREM-1 is a transmembrane glycoprotein that consists of a single extracellular immunoglobulin-like domain, a transmembrane region, and a short cytoplasmic tail.<sup>11,13</sup> TREM-1 is a receptor that is expressed on neutrophils and macrophages/monocytes, which are the main effector cells in innate responses.<sup>11,13</sup> TREM-1 can trigger and amplify the inflammatory response. In the presence of Gram-positive and Gram-negative bacteria, as well as fungi, the expression of TREM-1 is greatly upregulated on neutrophils and monocytes, but TREM-1 is hardly expressed at all in non-infectious inflammatory diseases, such as psoriasis, ulcerative colitis, vasculitis, and granulomatous disorders.<sup>14</sup> Soluble TREM-1 (sTREM-1) does not have the transmembrane and intracellular domains that are released from activated phagocytes, and can be found in body fluids.<sup>15-18</sup> In previous studies, the presence of sTREM-1 in the bronchoalveolar fluid has been shown to be a good indicator of lung infection.<sup>16,18</sup> In addition,

serum sTREM-1 has been shown to be able to distinguish survivors from non-survivors of sepsis.<sup>17</sup> However, information on the diagnostic role of sTREM-1 as an infectious marker in ARDS patients has been lacking until now.

Therefore, we designed a clinical observational study to investigate whether this new inflammatory marker, sTREM-1, can differentiate septic from non-septic ARDS. In addition, we investigated the serial changes of sTREM-1, as well as serum cytokine levels such as IL (interleukin)-1, IL-8, and tumor necrosis factor (TNF)- $\alpha$  in ARDS patients and their association with clinical outcomes.

## Materials and Methods

### Study subjects

All ventilated patients admitted to the intensive care units (ICUs) of the National Taiwan University Hospital between October 2007 and March 2008 were surveyed. We enrolled patients who fulfilled the clinical diagnosis for ARDS, as defined by the established recommendations of the American-European Consensus Conference Committee in 1994<sup>19</sup> (i.e. acute onset; bilateral infiltrates on chest radiography; PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq$  200; pulmonary-arterial wedge pressure  $\leq$  18 mmHg or absence of clinical evidence of left-atrial hypertension; and predisposing conditions associated with the development of ARDS).

Patients were excluded if they were  $<$  18 years of age, pregnant, treated with corticosteroids  $>$  1 mg/kg equivalent prednisolone, or bone marrow/organ transplant recipients; or if neutropenia (absolute neutrophil count  $<$  500/ $\mu$ L) or acquired immune deficiency syndrome were noted. The study was approved by the National Taiwan University Hospital institutional review board, and informed consent from all of the patients or their relatives was obtained before enrollment.

### Study design

Upon enrollment, demographic and laboratory characteristics were collected and are presented in Table 1. All patients were followed until discharge

**Table 1.** Demographic and laboratory characteristics on enrollment of acute respiratory distress syndrome patients

Characteristics*	Septic (n = 50)	Pathogen-confirmed septic (n = 34)	Non-septic (n = 13)
Age (yr)	75 (57–83)	76 (55–83)	62 (48–67) <sup>†‡</sup>
Sex, male	30 (60)	22 (65)	8 (62)
History of gouty arthritis	4 (8)	2 (6)	2 (15)
Recent abdominal surgery	6 (12)	5 (15)	0 (0)
Malignancy	17 (34)	10 (29)	7 (54)
Shock	32 (64)	23 (68)	8 (62)
Positive blood cultures	12 (24)	12 (35)	0 (0) <sup>†‡</sup>
Duration of SIRS before enrollment (d)	2 (1–6.5)	2 (1–5)	3 (1–5)
Etiology of ARDS			
Infectious focus	50	34	
Pneumonia	44	28	
Urosepsis	2	2	
Liver abscess	1	1	
Biliary tract infection	1	1	
Endocarditis	1	1	
Necrotizing fasciitis	1	1	
Drug-related acute lung injury			3
TRALI			2
Lymphoma with lung involvement			2
Catastrophic APS			1
Vasculitic pulmonary hemorrhage			1
Pancreatitis			1
Chest contusion			1
Blood aspiration <sup>§</sup>			1
Inhalation injury			1
Laboratory data			
Body temperature (°C)	37.8 (36.9–38.2)	37.8 (37.0–38.3)	37.9 (36.4–38.8)
WBC (/μL)	10,990 (4095–15,535)	8515 (2363–13,663)	13,270 (6045–21,730)
ANC (/μL)	8711 (2419–12,566)	6398 (1478–12,212)	11,153 (5514–15,221)
CRP (mg/dL)	12.2 (6.87–19.68)	12.2 (7.35–19.47)	6.88 (1.95–16.66) <sup>†</sup>
Biomarker			
Log (serum sTREM-1, pg/mL)	1.29 (0–2.31)	0.87 (0–2.22)	2.01 (0–2.87)
Log (serum IL-1β, pg/mL)	0.33 (0–1.23)	0.61 (0–1.38)	0.52 (0.04–1.05)
Log (serum IL-8, pg/mL)	2.43 (2.27–2.97)	2.67 (2.28–2.98)	2.33 (2.07–2.58)
Log (serum TNF-α, pg/mL)	0.82 (0–1.70)	1.03 (0–1.76)	0.90 (0.18–1.26)

\*Data presented as medians (interquartile range) or n (%); <sup>†</sup>p ≤ 0.05 between septic and non-septic groups; <sup>‡</sup>p ≤ 0.05 between pathogen-confirmed septic and non-septic groups; <sup>§</sup>aspiration of blood into the lung tissue secondary to upper airway bleeding. ARDS = acute respiratory distress syndrome; SIRS = systemic inflammatory response syndrome; TRALI = transfusion-related acute lung injury; APS = antiphospholipid syndrome; WBC = white blood cell count; ANC = absolute neutrophil count; CRP = C-reactive protein; sTREM-1 = soluble triggering receptor expressed on myeloid cells-1; IL = interleukin; TNF = tumor necrosis factor.

or death. The length of ICU stay and outcome of the 28-day period were also recorded.

Septic or non-septic etiology was retrospectively determined according to the decisions of the clinical attending physicians and the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.<sup>20</sup> The septic group was based on a presumed or identified source of infection, in combination with signs of systemic inflammatory response syndrome (SIRS). Within the septic group, patients with causative microbial pathogens were defined as the pathogen-confirmed septic group. Patients in the non-septic group only had SIRS without a searchable infectious focus. All patients were managed according to the Surviving Sepsis Campaign Guidelines.<sup>21</sup> The symptoms of SIRS were as defined previously<sup>20</sup> and the duration of SIRS before enrollment was recorded. Causative pathogens were defined as: organisms cultured or grown in a normally sterile body fluid or tissue; intracellular organisms phagocytosed by the polymorphonuclear cells, as seen by microscopic examination of sputum specimens; or urine *Streptococcus pneumoniae* antigen or virus (using the polymerase chain reaction for detection of herpes simplex virus DNA) by serological analysis.

### *Measurement of sTREM-1 and inflammatory cytokines*

The levels of sTREM-1 were measured using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA). IL-1 $\beta$ , IL-8 and TNF- $\alpha$  in the serum were determined using cytokine-specific ELISAs according to the manufacturer's protocol (R&D Systems). All measurements were performed in duplicate, as in our previous study.<sup>22</sup> Serum levels of high-sensitivity C-reactive protein (CRP) were measured with a latex-particle-enhanced immunoturbidimetric assay.

Serum sTREM-1 and cytokine levels on days 1, 3, 5, 7 and 14 were measured. "ARDS Day 1" was defined as the day that the patient fulfilled the ARDS criteria: the day of enrollment. The clinical

attending physicians or members of the primary care team were blinded to these data. For non-surviving patients, serum sTREM-1 and cytokines levels were followed until death.

### *Statistical analysis*

Descriptive results of continuous variables were expressed as medians (interquartile ranges). sTREM-1 and cytokines levels were transformed to log values. Variables were tested for comparison between the different groups using the Pearson  $\chi^2$  test/Fisher's exact test for categorical data and the non-parametric test, the Mann-Whitney *U* test, for numerical data. Statistical correlations were calculated with Spearman's non-parametric coefficient (*r*). To adjust for baseline differences, we used a univariate general linear model and set age and lung injury score (LIS) as covariates. Possible confounding factors on elevation of serum sTREM-1 were analyzed with multivariate logistic regression to clarify the effect of the septic etiology. A survival analysis was performed using the Kaplan-Meier method and the log-rank test. Multivariate analyses were performed using the Cox proportional-hazards regression model for 28-day mortality, with a 95% confidence interval (CI). To enter this model, continuous variables were transformed into a categorical binary value using median values, and the trend for sTREM-1 or cytokines over time was represented by the slope of the regression line over multiple time points. All analyses were done with SPSS version 13.0 (SPSS, Chicago, IL, USA). A *p* value < 0.05 for significance and two-tailed tests was used in this study.

## **Results**

### *Characteristics of the study population*

In this prospective study, 1098 patients who were admitted to the medical/burns/surgical ICUs were surveyed over 6 months. Sixty-three ARDS patients who fulfilled the inclusion criteria were enrolled. The etiology was septic in 50 (79%) patients and non-septic in 13 (21%). Infections were microbiologically proven in 34 of 50 (68%) septic

patients. The baseline characteristics of the study groups are shown in Table 1.

Between the septic or pathogen-confirmed septic and non-septic groups, age and LIS scores were significantly different. The CRP level was significantly higher in the septic group ( $p=0.047$ ), but this showed only an increasing trend between the pathogen-confirmed septic and non-septic groups ( $p=0.057$ ).

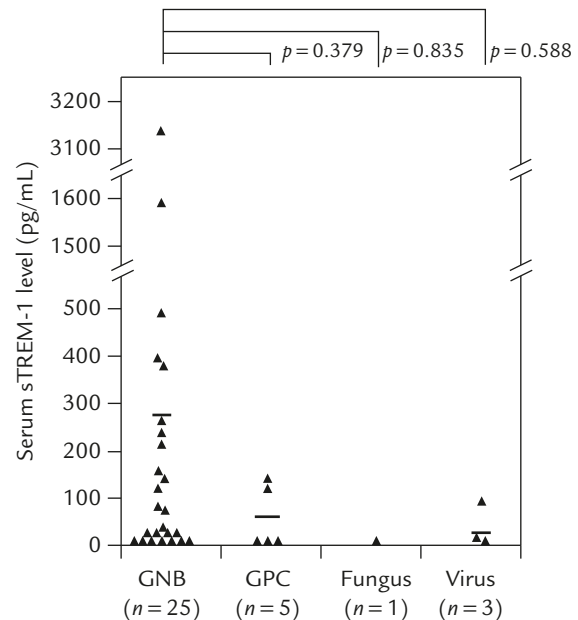
#### **Diagnostic value of baseline sTREM-1 and inflammatory cytokines assay for sepsis**

At enrollment, no difference was observed in the serum log sTREM-1 levels between the septic and non-septic groups ( $p=0.501$ ); the same was true of the serum log cytokine levels (Table 1). After adjusting the baseline for age, LIS, and duration of SIRS before enrollment, there was still no significant difference in serum log sTREM-1 values between the septic and non-septic groups ( $p=0.896$ ). Among patients whose duration of SIRS before enrollment was <48 hours, serum log sTREM-1 level did not differ between the 24 patients in the septic group and the nine in the non-septic group ( $p=0.564$ ). No correlation was noted between serum log sTREM-1 levels at enrollment and the initial  $PAO_2/FiO_2$  ratio, absolute neutrophil count, or CRP level, except for the log IL-1 ( $r=0.343$ ,  $p=0.008$ ) and TNF- $\alpha$  ( $r=0.422$ ,  $p=0.001$ ). In the pathogen-confirmed septic group, sTREM-1 was elevated especially in Gram-negative pathogens (Figure 1), but no statistical significance was observed.

Using multivariate logistic regression models to adjust for possible confounding factors, including history of gouty arthritis, malignancy, abdominal surgery in the past 3 months, presence of pancreatitis, LIS, duration of SIRS before enrollment, and age, septic etiology for ARDS was not found to be an independent factor for elevation of the serum log sTREM-1 value (95% CI = -1.103 to 0.784,  $p=0.736$ ).

#### **Severity of ARDS and outcome**

Overall, 27 patients with ARDS died before day 28 and the mortality rate was 42.9%, which is



**Figure 1.** Serum level of soluble triggering receptor expressed on myeloid cells-1 in the different causative pathogens of septic acute respiratory distress syndrome. GNB = Gram-negative bacilli; GPC = Gram-positive cocci.

concurrent with the predictive risk of death based on the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores (mean  $\pm$  standard deviation:  $25.33 \pm 7.87$  and  $9.87 \pm 3.82$ , respectively).

Clinical and laboratory data of survivors and non-survivors are listed in Table 2. Non-survivors were younger and had longer drinking histories (30%) than the survivors (5%) ( $p=0.01$ ). Survival analysis showed that a younger age, a history of chronic liver disease, and higher baseline severity scores (SOFA and APACHE II) were associated with a higher mortality rate. Sepsis and multiple organ failure were the most common causes of short-term mortality (71%), and only 6% died because of respiratory failure.

#### **Prognostic value of sTREM-1 and inflammatory cytokines assay**

In univariate analysis, serum log sTREM-1 levels on day 1 could not be used as a prognostic factor for mortality on day 28 ( $p=0.394$ ), nor could log cytokine levels be used (Table 2). Higher serum CRP levels, however, were noted in non-survivors ( $p=0.007$ ).



**Table 2.** Clinical and laboratory data according to outcome

Characteristics*†	28-day outcome		
	Survival (n=36)	Non-survival (n=27)	p‡
Sex, male	25 (69)	13 (48)	0.120
Age > 65 yr	25 (69)	9 (41)	0.016§
Chronic liver disease	1 (3)	3 (11)	0.024§
Septic etiology	30 (83)	20 (74)	0.525
APACHE II score	22.5 (18.5–26.8)	28 (23–34)	0.001§
SOFA score at enrollment	9 (7–11)	13 (8–14)	0.004§
LIS	2.75 (2.25–3.25)	3 (2.75–3.75)	0.545
Length of ICU stay (d)	17 (12–22)	8 (4–15)	<0.001§
CRP (mg/dL)	7.33 (2.87–14.37)	13.91 (8.96–19.97)	0.004§
Serum sTREM-1 (pg/mL)			
Log D1	0.47 (0–2.29)	1.99 (0–2.58)	0.388
Log D <sub>first</sub> to Log D <sub>least</sub> slope ≥ 0	15 (42)	20 (74)	0.005§
Serum IL-1β (pg/mL)			
Log D1	0.31 (0–1.20)	0.43 (0–1.12)	0.502
Log D <sub>first</sub> to Log D <sub>least</sub> slope ≥ 0	14 (58)	15 (56)	0.187
Serum IL-8 (pg/mL)			
Log D1	2.34 (2.09–2.85)	2.55 (2.28–2.92)	0.142
Log D <sub>first</sub> to Log D <sub>least</sub> slope ≥ 0	15 (42)	16 (59)	0.179
Serum TNF-α (pg/mL)			
Log D1	0.82 (0–1.58)	0.94 (0–1.61)	0.403
Log D <sub>first</sub> to Log D <sub>least</sub> slope ≥ 0	15 (42)	13 (48)	0.598

\*Data presented as n (%) or medians (interquartile range); †continuous variables were transferred to a categorical binary using the median value; ‡comparison using the Kaplan–Meier product-limit method and the statistical significance was assessed by a log-rank test; §p ≤ 0.05. APACHE=Acute Physiology and Chronic Health Evaluation; SOFA=Sequential Organ Failure Assessment; LIS=Lung Injury Score; ICU=intensive care unit; CRP=C-reactive protein; sTREM-1=soluble triggering receptor expressed on myeloid cells-1; IL=interleukin; TNF=tumor necrosis factor.

Serum log sTREM-1 level was positively correlated with log IL-1β ( $r=0.325$ ,  $p \leq 0.001$ ), log IL-8 ( $r=0.247$ ,  $p \leq 0.001$ ), and log TNF-α levels ( $r=0.480$ ,  $p \leq 0.001$ ). To analyze duration of the course, 95% CI of the mean values for serum log sTREM-1 over time were plotted in Figure 2. In non-survivors, baseline serum log sTREM-1 level was higher and there was a trend to increase over time, especially over the first 5 days. The slope of the regression line for multiple time points confirmed this phenomenon in the serum log sTREM-1 level ( $p=0.005$ , Table 2).

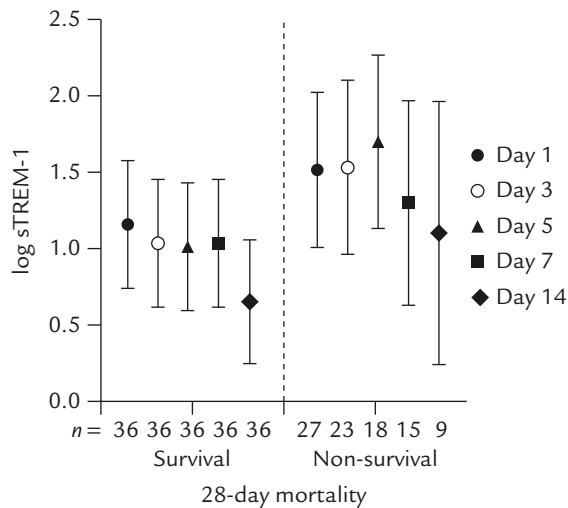
In the multivariate Cox regression model, age ≤ 65 years ( $p=0.003$ ), presence of chronic liver disease ( $p=0.016$ ), higher baseline APACHE II score ( $p < 0.001$ ), and higher initial SOFA score

( $p=0.017$ ) remained independent factors for the prediction of mortality on day 28 (Table 3). With regard to sTREM-1 and cytokines, only day 1 serum log sTREM-1 levels ( $p=0.008$ ), and a progressive increase over time in serum log sTREM-1 levels ( $p=0.040$ ) and log IL-1β levels ( $p=0.004$ ) were independent factors.

## Discussion

Serum sTREM-1 is one of the most promising parameters for differentiating sepsis from other SIRS, according to previous studies.<sup>15,23</sup> However, in our study, serum sTREM-1 levels on day 1 of ARDS could not differentiate septic from non-septic

groups of critically ill patients. Univariate or multivariate analysis, after adjusting for possible confounding factors, such as recent major abdominal surgery,<sup>24</sup> pancreatitis,<sup>25</sup> active malignancy,<sup>22,26</sup> or gouty arthritis,<sup>27</sup> showed that septic etiology of



**Figure 2.** Time course of log value of the serum level of soluble triggering receptor expressed on myeloid cells-1 in surviving and non-surviving patients. Data expressed as means with 95% confidence interval. The number of available cases is listed below and decreases over time for non-survival. CI = confidence interval.

ARDS was not associated with elevation of serum log sTREM-1 level. Moreover, considering the duration of SIRS in septic or non-septic groups before the onset of ARDS, it did not seem to affect the serum log sTREM-1 levels according to the univariate, multivariate, or subgroup analyses for patients whose duration of SIRS before enrollment was < 48 hours. These results depart from the findings for sepsis reported by Gibot et al.<sup>15,17,23</sup> This could be explained as follows. First, ARDS induced by direct lung injury might have a higher sTREM-1 concentration in the lungs than in the serum.<sup>18,28</sup> Pulmonary infection or aspiration-related ARDS might have lower sTREM-1 levels in the serum, although they are classified as septic ARDS. Second, recent clinical studies investigating the role of sTREM-1 in an infectious diagnosis have shown that sTREM-1 is not a good marker for infection in sepsis<sup>29</sup> or ventilator-associated pneumonia<sup>30,31</sup> in critically ill patients. To explain these discrepancies, some have proposed the following: different sensitivities of the sTREM-1 assays (ELISA or immunoblotting),<sup>31</sup> exposure to antibiotics or lack thereof,<sup>18,31</sup> inadequate controls in the absence of suspected infection,<sup>30</sup> and differences

**Table 3.** Cox regression analysis of baseline and sequential variables in acute respiratory distress syndrome patients for 28-day mortality

Variable*	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age > 65 yr	0.404 (0.187–0.872) <sup>†</sup>	0.132 (0.035–0.495) <sup>†</sup>
Presence of chronic liver disease	3.655 (1.089–12.270) <sup>†</sup>	0.116 (0.02–0.665) <sup>†</sup>
LIS	1.265 (0.586–2.727)	1.085 (0.338–3.490)
SOFA score	2.958 (1.348–6.487) <sup>†</sup>	7.700 (1.444–41.047) <sup>†</sup>
APACHE II score	3.632 (1.654–7.977) <sup>†</sup>	18.986 (4.088–88.185) <sup>†</sup>
CRP, day 1	3.173 (1.372–7.336) <sup>†</sup>	2.316 (0.652–8.226)
Log sTREM-1, day 1	1.392 (0.651–2.975)	6.338 (1.607–24.998) <sup>†</sup>
Log IL-1 $\beta$ , day 1	1.299 (0.600–2.811)	1.355 (0.357–5.140)
Log IL-8, day 1	1.788 (0.810–3.945)	0.935 (0.280–3.114)
Log TNF- $\alpha$ , day 1	1.385 (0.640–2.995)	3.691 (0.668–20.998)
Log sTREM-1 trend (slope $\geq$ 0)	3.160 (1.333–7.490) <sup>†</sup>	3.893 (1.062–14.269) <sup>†</sup>
Log IL-1 $\beta$ trend (slope $\geq$ 0)	1.652 (0.773–3.532)	7.076 (1.877–26.679) <sup>†</sup>
Log IL-8 trend (slope $\geq$ 0)	1.677 (0.778–3.617)	1.586 (0.451–5.574)
Log TNF- $\alpha$ trend (slope $\geq$ 0)	1.223 (0.575–2.602)	2.723 (0.444–16.710)

\*Continuous variables were transferred to a categorical binary using the median value; <sup>†</sup> $p \leq 0.05$ . HR = hazard ratio; CI = confidence interval; LIS = Lung Injury Score; SOFA = Sequential Organ Failure Assessment; APACHE = Acute Physiology and Chronic Health Evaluation; CRP = C-reactive protein; sTREM-1 = soluble triggering receptor expressed on myeloid cells-1; IL = interleukin; TNF = tumor necrosis factor.



among patient groups in various studies.<sup>31</sup> Third, limited case numbers and a retrospective definition of non-septic ARDS might compromise the diagnostic value of sTREM-1 for infection.

Although serum sTREM-1 might not be suitable as an infectious marker in ARDS, we still noted that, in pathogen-confirmed septic ARDS patients, serum sTREM-1 was higher when cultures grew Gram-negative bacilli such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. In patients with Gram-positive coccal, fungal, or viral infections, serum sTREM-1 levels were lower. However, there was no significant difference between them.

Instead of serum sTREM-1 levels as an infectious marker, our findings suggest that sTREM-1 is a prognostic factor. In multivariate analysis, a higher serum log sTREM-1 level at day 1 and an increased trend of serum log sTREM-1 levels over time, especially in the first 5 days, were associated with an unfavorable outcome. In comparison to sTREM-1 levels in septic patients, our findings are in line with those of Gibot et al<sup>32</sup> and Determann et al,<sup>18</sup> which showed a progressive decline of serum sTREM-1 in surviving patients, especially in the first 5 days.

Furthermore, our results showed a significant positive correlation between serum log sTREM-1 and inflammatory cytokine levels (IL-1 $\beta$ , IL-8 and TNF- $\alpha$ ). From the above-mentioned results, elevated serum sTREM-1 levels in ARDS patients indicated severe inflammation, which was what induced the higher mortality rate, and not the infection. The first 5 days of serum sTREM-1 elevation in ARDS is compatible with the acute exudative phase when alveolar macrophages and neutrophils are recruited in the alveolar space, and most cytokines are released.<sup>33</sup> Our prognostic findings in ARDS patients were similar to those in the sepsis study of Gibot et al.<sup>32</sup> Further intervention was needed for the elevation of serum log sTREM-1 levels, especially during the first 5 days of follow-up, which indicated the progression of a systemic inflammatory response. Such data clarified that sTREM-1 was an inflammatory marker, albeit not a good infectious one.

Our findings confirmed that higher SOFA and APACHE II scores were associated with poor prognosis, as did the results of previous studies.<sup>34</sup> However, age < 65 years in our study was another prognostic factor with unfavorable outcomes. This might have been due to a longer drinking history in our younger patients; alcohol abuse is thought to be associated with high mortality in ARDS patients, according to the study of Wakabayashi et al.<sup>35</sup> In addition, a persistent or elevated trend of serum IL-1 $\beta$  might have predicted poor prognosis in our multivariate analysis (Table 3), which was also found in the previous ARDS study of Goodman et al.<sup>7</sup>

With regard to serum CRP level in our study, it might be used to differentiate septic and non-septic ARDS patients, even better than serum sTREM-1. Barati et al reported the same phenomenon as we have: CRP performs better than sTREM-1 in diagnosing infection.<sup>36</sup> Barati et al, however, noted that the diagnostic accuracy of sepsis markers is highly dependent on the setting in which they are tested. Their study was conducted in a heterogeneous group of ICU patients, which was similar to our ARDS group, that consisted of various causative etiologies. The heterogeneous population and small number of patients might be the reasons for the different diagnostic value of CRP and sTREM-1. In the analysis of prognostic value, although higher serum CRP level was observed in the non-survivors in univariate analysis, this effect was not seen in multivariate analysis (Table 3). It could be because the short-term mortality correlates better with other inflammatory variables, such as the level of serum cytokines or sTREM-1, than with the serum CRP level.

There were several limitations in the present study. First, the number of patients was small. In the non-septic group, only 13 patients were enrolled. Based on our data for *post hoc* power analysis, a clinical trial to clarify the diagnostic value of serum sTREM-1 levels for infection is estimated to require 545 patients in each group under a statistical power of 80% and a significance criterion of 5%. Second, we did not analyze other inflammatory markers, such as procalcitonin

or IL-6. We checked the CRP at day 1, but we did not follow it up during the course of ARDS. Third, we did not investigate the presence of peptic ulcer disease by using pan-endoscopy due to ethical sensitivities for the critical patients who did not present with active gastrointestinal bleeding. Peptic ulcer disease could potentially elevate sTREM-1 levels.<sup>37,38</sup> Finally, but not least, the non-septic ARDS group in our study was defined by a retrospective review, which could have compromised our conclusion about the diagnostic value of sTREM-1 for sepsis, because of possible occult infections in the group that could not be ruled out. Clinically, precise prospective identification of non-septic ARDS is very difficult, because sepsis is always considered to be the causative differential diagnosis that is lethal if no adequate treatment is taken. Large studies, including the detection of other inflammatory markers, are warranted to confirm our results.

In summary, the serum sTREM-1 level might not be a reliable marker to differentiate septic from non-septic ARDS patients but, as an inflammatory marker, it could provide a useful predictor of short-term mortality, especially when follow-up levels have increased in the first 5 days. A decline in serum sTREM-1 levels during treatment indicates improvement. On the contrary, persistent elevation of serum levels should lead to a re-evaluation of treatment management.

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