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Soluble Endothelium-selectin (sE-selectin) in Critically Ill Patients

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Systemic inflammatory response syndrome (SIRS) is caused by proinflammatory cytokines, such as TNF-α. SIRS that is mild soon remit naturally but some SIRS are severe and may change into multiple organ failure (MOF) associated with serious infections and tissue damage. If early differential diagnosis were possible, early measures could be taken to prevent poor outcomes. Endothelial selectin (E-selectin) is a single-chain glycoprotein that belongs to the selectin family. It is distributed in vascular endothelial cells, and is one of the cell adhesion molecules that contribute to the adhesion between endothelial cells and neutrophils and monocytes. E-selectin is induced by proinflammatory cytokines, and it appears in the blood of inflammatory disease and cancer patients.

In this study, we investigated the correlations between soluble E(sE)-selectin with severity, outcome, and functional failure of individual organs, and we assessed the usefulness of sE-selectin for judging outcome in severe cases.

The subjects were 50 emergency patients brought to our center, diagnosed with SIRS and had a Sequential Organ Failure Assessment (SOFA) score of 3 or more. The method consisted of measuring sE-selectin on arrival at the hospital (day 0) and on hospital days 1, 3, 5, and 7, and then testing for correlations with organ failure and survival.

The results showed patients who died within 28th hospital day either had significantly higher sE-selectin levels on arrival or continued to have high levels within 7 days of admission than those who survived. This finding made it possible to predict the outcome of the patients. MOF group showed significantly higher levels than the non-MOF group. The number of failing organs increased as the sE-selectin values rose, and there was a positive correlation between the changes in SOFA scores and sE-selectin values. Testing for correlations between the sE-selectin values and each organ failure showed that the serum sE-selectin levels were most significantly correlated with the PaO_2/F_IO_2 ratio (P/F ratio), which reflects the degree of failure to the respiratory system. In addition, comparison of the acute lung injury (ALI)/adult respiratory distress syndrome (ARDS) group and the non-ALI/non-ARDS group showed that the sE-selectin levels were significantly higher in the ALI group. A significant correlation was also found between the sE-selectin values and DIC score. Furthermore, the sE-selectin levels also significantly increased in the DIC than in non-DIC group. Based on the above findings, sE-selectin measurements correlated with DIC scores, SOFA scores, functional failure of the respiratory system, coagulation, and kidney. Since the sE-selectin level also correlated with patient survival, it may be a useful blood marker for predicting severity outcome and survival in critically-ill patients.

Key words: soluble endothelial selectin (sE-selectin), systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), disseminated intravascular coagulation (DIC)

Introduction

Endothelial selectin (E-selectin) is a single-chain glycoprotein having a molecular mass of 115 Kda. It belongs to the selectin family called endothelial leu-

kocyte adhesion molecule-1 (ELAM-1), and is distributed in vascular endothelial cells. E-selectin is a cell adhesion molecule between endothelial cells and neutrophils, monocytes, and other elements[1)2)]. Other members of the selectin family besides the E-selectin expressed in vascular endothelial cells are platelet selectin (P-selectin) which is expressed in activated blood platelets, and leukocyte selectin (L-selectin) which is expressed in leukocytes[3)]. E-selectin is not expressed in vascular endothelial cells under ordinary conditions. It is only expressed when induced by proinflammatory cytokines, such as TNF-α and IL-1β, and it promotes the adhesion of neutrophils, monocytes, or cancer cells to the vascular endothelium[4)].

When the amount of E-selectin increases, as expressed in response to induction by proinflammatory cytokines, the extracellular domain is cleaved at the membrane binding site of the molecule. It then becomes soluble E-selectin (sE-selectin), and appears in blood. Large amounts of sE-selectin generally appear in the blood of patients with inflammatory diseases, such as bacterial infections and collagen diseases, or in the blood of cancer patients[5)-9)].

Systemic inflammatory response syndrome (SIRS) is a pathological condition caused by an increased production of proinflammatory cytokines[10)11)]. Some cases of SIRS are mild and remit naturally, while others become severe and progress to multiple organ failure (MOF). Early diagnosis of the condition and determination of treatment policy are linked to improved patient outcome[12)]. Currently, there is not a consensus method to predict the outcome of SIRS patients. In our study, we measured sE-selectin levels in the blood of SIRS patients when patients arrived at the emergency center of our hospital and analyzed the associations of sE-selectin with disease severity and disease outcome.

Methods

We included 50 patients brought to our emergency center between January and May, 2003, who were diagnosed with SIRS at the time of the initial examination.

Severity was rated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score[13)], the Sequential Organ Failure Assessment (SOFA) score[14)], and the Disseminated Intravascular Coagulation (DIC) score[15)]. DIC was diagnosed when the DIC score was 4 or more, and MOF was diagnosed when the SOFA score was 2 or more for at least 2 items (organs). Acute Lung Imjury (ALI) was diagnosed when the PaO_2/F_IO_2 ratio (P/F ratio) was <300, in accordance with the American-European Consensus Conference (AECC) definition[16)].

Patients' blood sE-selectin levels were measured on arrival and on hospital days 1, 3, 5, and 7. The patients were divided into (1) survived group or non-survival group, (2) MOF group or non-MOF group, (3) acute lung injury (ALI)/adult respiratory distress syndrome (ARDS) group or non-ALI / non-ARDS group, and (4) DIC group or non-DIC group. We investigated whether there were significant differences in blood sE-selectin levels between each pair of groups and whether sE-selectin levels correlated with (1) SOFA scores, (2) number of organ failure, and (3) each organ failure.

Arterial blood specimen was collected at room temperature. Five ml of whole blood was immediately transferred to a test tube containing citrate and was centrifuged at 3000 rpm for 15 min. The reagent was then added to 1 ml of the supernatant (citrated plasma) and measured with sE-selectin assay reagent (I-sES) by a fully automated immune serum testing apparatus (LPIA-S500) that uses latex immunonephelometry based on the latex agglutination[17)], developed by Mitsubishi Kagaku Iatron Inc. (Tokyo, Japan).

This clinical study (No. 499) was performed with the approval of Ethics Committee of Tokyo Women's Medical University.

Statistical analysis

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. All numerical data was expressed as median. The Mann-Whitney U test was used to analyze difference between two groups because of not distribute normally. The Kruskal-Wallis test was used for multiple-group comparisons. The chi-square test and Fisher's exact probability test were used for

Table Characteristics of patient

	Total	Survive	Non-survive	p
Number of patients (%)	50	43 (86)	7 (14)	NA
Age (y)	58 (15-86)	56 (15-86)	67 (49-86)	0.037
Male/Female	37/13	33/10	4/3	0.357
APACHE II score (admission)	17.5 (6-37)	17 (6-32)	27 (9-37)	0.126
SOFA score (admission)	4 (0-16)	4 (0-16)	7 (4-12)	0.015
DIC (admission) (%)	5 (10)	3 (7)	2 (29)	0.138
MOF (admission) (%)	17 (34.0)	13 (30.2)	4 (57.1)	0.210
sE-selectin (admission) (ng/ml)	24.76 (0-188.44)	22.25 (0-188.44)	75.90 (49.32-187.17)	< 0.001
PRIMARY ADMISSION DIAGNOSIS				
Trauma	23	23	0	
Sepsis	11	6	5	
Coma	3	3	0	
Acute respiratory failure	3	3	0	
Diabetic keto acidosis	2	1	1	
Celebral injury	2	1	1	
Gastrointestinal bleeding	2	2	0	
Other	4	4	0	

the other categorized data. Spearman's rank-correlation coefficient was used to test for correlations.

A statistically significant difference was considered when p value was less than 0.05.

Results

The background of all 50 subjects is shown in Table. Their mean age was 53.6 ± 20.1 years (range: 15 to 86 years), and there were 37 males and 13 females. There were 23 trauma patients and 27 non-trauma patients, and the diagnosis on arrival in the non-trauma patients was sepsis/septic shock in 11 cases, consciousness disorder in 3 cases, diabetic ketoacidosis in 2 cases, acute respiratory failure in 3 cases, cerebral hemorrhage in 2 cases, hemorrhagic shock secondary to gastrointestinal bleeding in 2 cases, and hyperthyroidism, electrical shock, acute drug toxicity, and acute heart failure in 1 case each.

On hospital day 28 there were 43 survivors, and 7 had died (mortality rate: 14%). The APACHE II score on arrival at the hospital was 17 in the survivor group and 27 in the group that died, but the difference was not statistically significant ($p = 0.126$). The SOFA score, however, was 4 in the survivor group and 7 in the group that died, and the difference was statistically significant ($p < 0.05$).

DIC was already present on arrival at the hospital in 3 patients (7%) in the survivor group and 2 patients (29%) in the group that died, and there were 13 patients (30.2%) with MOF in the survivor group and 4 (57.1%) in the group that died, but the differences between the group that survived and the group that died were not significant. The sE-selectin values were 22.3 ng/ml in survivors and 75.9 ng/ml in non-survivors, and the difference was statistically significant between survivors and non-survivors ($p < 0.05$).

Changes in sE-selectin

The changes in blood sE-selectin values of all patients between the time they were admitted and hospital days 1, 3, 5, and 7 are shown in Fig. 1. Many patients who survived had either a lower sE-selectin level on arrival or the level decreased over time even if the patients had a high level on arrival. In contrast, the sE-selectin levels of the non-survival patients were higher on arrival or did not decrease during the 7-day course.

Comparison of sE-selectin values on admission and hospital days 1, 3, 5, and 7 in the group that survived and the group that died revealed significant differences on each day: 22.3 vs 75.9, 25.1 vs 75.3, 25.3 vs 118.1, 29.2 vs 88.9, 29.1 vs 95.1, respectively, all $p < 0.05$).

sE-selectin and MOF

The blood sE-selectin values were compared between the MOF group and non-MOF group during

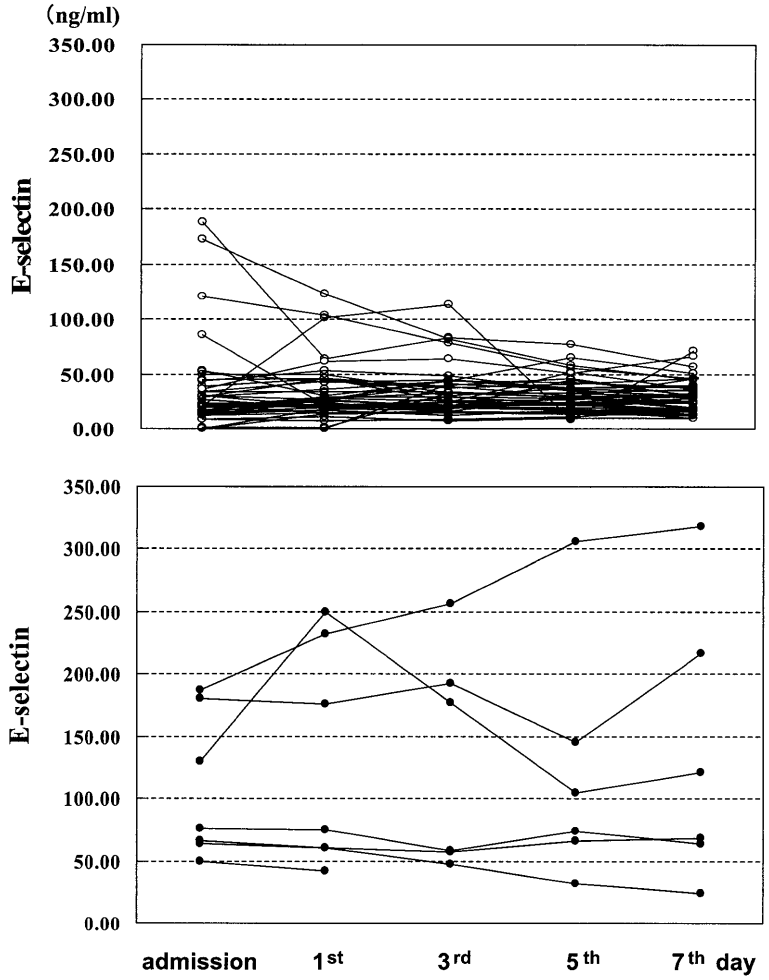

Fig. 1 Daily changes of serum level of sE-selectin
Upper panel is survive: ○ (n = 43), lower panel is non-survive: ● (n = 7).

the entire course of all patients (Fig. 2). The sE-selectin value was 46.08 ng/ml in the MOF group (n = 152) and 22.24 ng/ml in the non-MOF group (n = 89), and the difference was significant ($p < 0.05$). Comparison of the number of organ failure and the sE-selectin values revealed that the sE-selectin values increased with the number of organ failure, and a significant difference was observed at each number of organ failure. The sE-selectin value was 19.64 ng/ml in no organ failure at all; 26.31 ng/ml in one organ failure; 38.7 ng/ml in two organ failures; 54.19 ng/ml in three organ failures; 54.19 ng/ml in four organ failures; 180.77 ng/ml in five organ failures ($p < 0.05$) (Fig. 3). The statistically significant difference between 4 organs failures and 5 organs failures, however, did not reached.

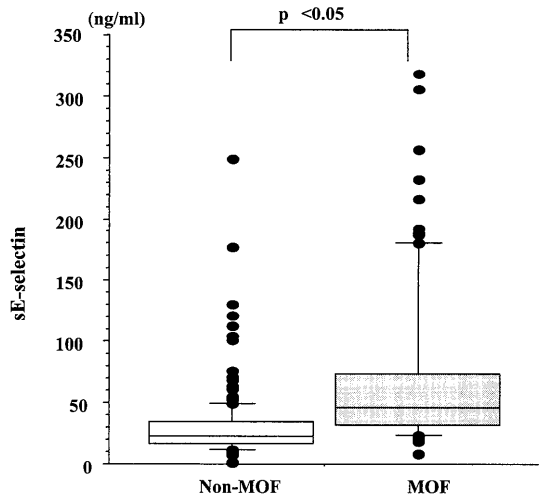

Fig. 2 Serum level of sE-selectin with (open square: n = 152) and without (gray square: n = 89) MOF
* $p < 0.05$.

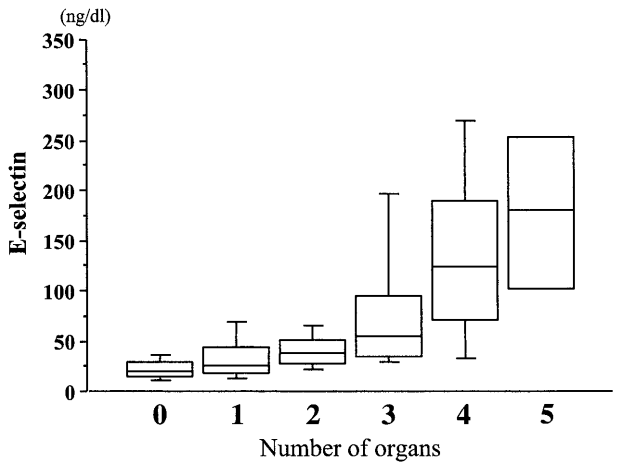

Fig. 3 Serum level of sE-selectin and number of organs
Number of organs '0' means no organ failure. There were statistically significantly change between all groups except for only between 4 and 5.

Correlations between sE-selectin values and failures of individual organs (Fig. 4)

A correlation was found between the SOFA scores throughout the entire course of all patients and the blood sE-selectin values ($r=0.590$, $p<0.05$). There was a weak correlation between the Glasgow Coma Scale (GCS) and the blood sE-selectin values ($r=-0.235$, $p<0.05$). A significant association was found between the P/F ratios and sE-selectin values ($r=-0.560$, $p<0.05$). No association was observed between mean arterial blood pressure (MAP) and the sE-selectin values ($r=-0.110$, $p=0.086$). There was a significant correlation between the serum creatinine concentrations and sE-selectin values on arrival at the hospital ($r=0.401$, $p<0.05$). A weak correlation was found between the blood platelet counts and the sE-selectin values ($r=-0.307$, $p<0.05$). No association with the sE-selectin values was found in the blood total bilirubin levels ($r=0.044$, $p=0.490$).

sE-selectin and ALI

Comparison between the sE-selectin values over the entire course in the ALI/ARDS group ($n=83$) and non-ALI/non-ARDS group ($n=162$) revealed a significant difference between the two groups. The sE-selectin value was 44.56 ng/ml in the ALI/ARDS group and 22.35 ng/ml in the non-ALI/non-ARDS group, and it was significantly higher in the non-ALI/non-ARDS group ($p<0.05$) (Fig. 5).

sE-selectin and DIC

Comparison between the blood sE-selectin values in the DIC group ($n=32$) and non-DIC group ($n=204$) showed that the sE-selectin value was 63.85 ng/ml in the DIC group was significantly higher than the value of 27.37 ng/ml in the non-DIC group ($p<0.05$) (Fig. 6). In addition, the results of the assessment with the DIC scores showed that the blood sE-selectin values increased as the DIC scores rose, but the correlation was weak ($r=0.369$, $p<0.05$) (Fig. 7).

Discussion

Large amounts of sE-selectin are expressed in the serum as a result of vascular endothelial cell injury in patients with infections and chronic inflammatory diseases, such as collagen diseases, and in cancer patients[5)-9)]. Moss et al[18)] reported that sE-selectin and sICAM-1 levels are not high in all ARDS cases and the levels depended on the pathogenetic mechanism of diseases. Newman et al[5)] reported a higher serum sE-selectin level in septic shock patients with unstable hemodynamics than in sepsis patients.

sE-selectin expression begins as a leukocyte-vascular endothelium adhesion molecule in the early stage of the inflammatory response. We think the degree of neutrophil activity among vascular endothelial cells is correlated with endothelial cell injury; thus, we selected serum sE-selectin as an index of neutrophil activation to rate disease severity. In our study, we performed a series of serum sE-selectin measurements in 50 acute SIRS patients of a wide variety of pathogenetic mechanisms, and we investigated the associations between sE-selectin and survival, severity of disease, indicated by failure of individual organs, such as the brain (consciousness), lungs (respiration), heart (circulation), coagulation (platelet count), kidney and liver, and DIC.

Our results showed that although there was no significant difference in APACHE II scores on arrival at the hospital, the blood sE-selectin level on ad-

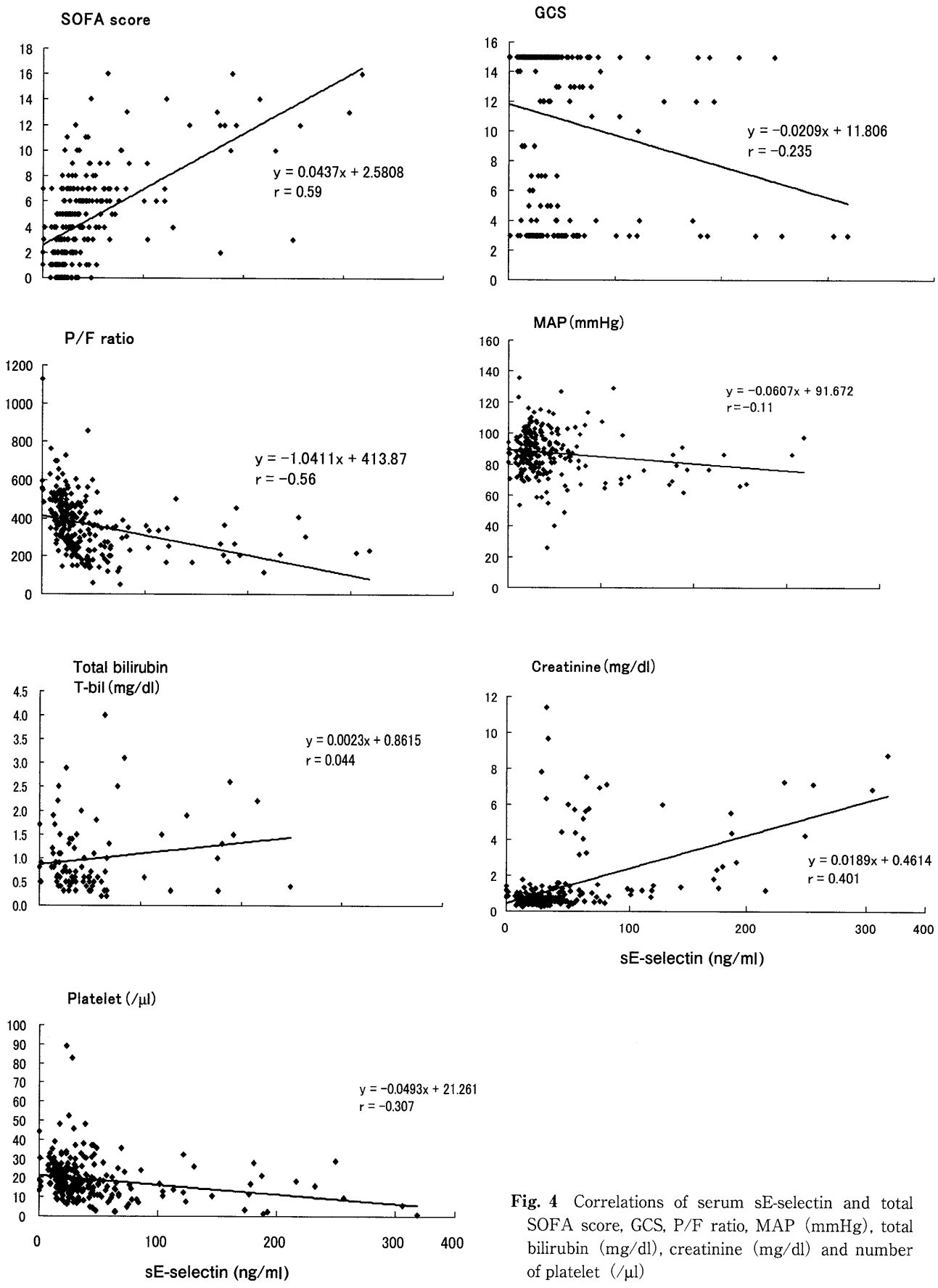

Fig. 4 Correlations of serum sE-selectin and total SOFA score, GCS, P/F ratio, MAP (mmHg), total bilirubin (mg/dl), creatinine (mg/dl) and number of platelet (/μl)

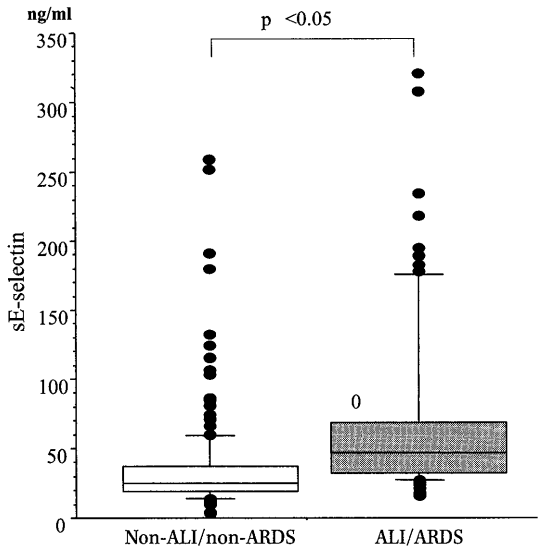

Fig. 5 Serum level of sE-selectin between ALI/ARDS and non-ALI/non-ARDS
□: P/F ratio >300, ▨: P/F ratio <300, ＊: p < 0.05.

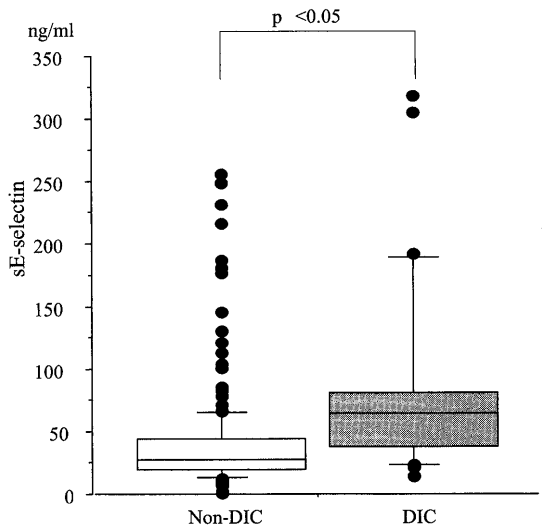

Fig. 6 Serum level of sE-selectin between DIC and non-DIC
□: P/F ratio >300, ▨: P/F ratio <300, ＊: p < 0.05.

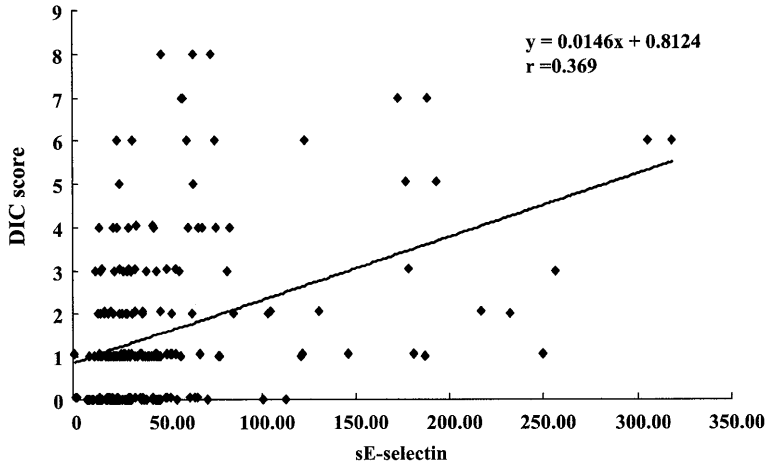

Fig. 7 Correlation of serum level of sE-selectin and DIC score

mission and until 7th hospital day was significantly higher in patients who survived than those who died on the 28th hospital day. Cummings et al[19] reported that the blood sE-selectin values of patients admitted to the intensive care unit on day 1 were significantly higher in the group that died than in the group that survived.

In our verification, comparison of the sE-selectin values on arrival at the hospital and on each hospital day, days 1, 3, 5, and 7, over the entire admission process showed a significant difference every time between the group that survived and the group that died. When the sE-selectin value on admission was high, or remained high during the subsequent week, the patients either had poor outcome or died. Our findings suggested that serum sE-selectin levels may be useful for predicting patients' outcome or survival among critically-ill patients.

Evaluation of the severity of SIRS is essential to further treat SIRS patients, and since mortality increases if patients develop MOF, we correlated MOF and sE-selectin levels. We found that sE-selectin levels increased significantly with MOF. The number of failing organs increased as the blood

sE-selectin levels rose in SIRS patients with organ failure, and that there was a significant difference in the number of failing organs between groups. Moreover, SOFA scores, which were used to rate severity and the number of failing organs, also revealed that serum sE-selectin levels increased whenever the SOFA scores rose.

Hugh et al[20] showed that when compared with the healthy subjects, SIRS patients had significantly higher blood E-selectin concentrations, particularly in those associated with organ failure. According to Simons et al[21], trauma patients who had a higher serum sE-selectin concentration had a high probability of developing infection or organ failure.

Because the proinflammatory cytokines that are released when the body is exposed to an excessive insult trigger the liberation of sE-selectin into the blood by vascular endothelial cells, a strong correlation has been found with the magnitude of the insult and sE-selectin is considered an indicator of the severity of the organ failure that is induced. Moreover, when we investigated correlations between the sE-selectin values and the severity of the organ failure according to individual failing organs, the most significant correlation was found between the P/F ratio, which reflects the severity of disease in the respiratory system, and the blood sE-selectin values, and there were also correlations with the serum creatinine concentration, which reflects kidney function, and the platelet count, which reflects damage to the blood coagulation system. The fact that no correlations were found in relation to the central nervous system, heart, vascular system, or liver function, on the other hand, suggests that the blood sE-selectin values may be organ-specific.

All of the cases were divided into an ALI/ARDS group and a non-ALI/non-ARDS group according to whether they had a P/F ratio of less than 300 or of 300 or more, when the patients with impaired respiratory systems were compared for serum sE-selectin levels, the ALI/ARDS group had higher sE-selectin levels, and the P/F ratio was found to be the strongest factor among all the organ failure indicators that correlated with sE-selectin. Burnham et al[22] detected significantly higher sE-selectin values in the alveolar lavage fluid of ARDS patients who had been exposed to alcohol for long periods. The fact that the serum sE-selectin level, which is an indicator of endothelial cell injury, was measured elsewhere besides the blood also suggested its usefulness. Furthermore, Kayal et al[23], reported that sE-selectin is useful for predicting the outcome of ALI. Gando et al[24], reported that the increase in sE-selectin in ARDS patients shows that the systemic inflammation spreads out from the vascular endothelial injury, and it predicts the outcome of ARDS. With these studies, sE-selectin appears to reflect disease severity even in patients with respiratory failure.

Serum sE-selectin levels also correlated with platelet counts. Our results showed that the serum sE-selectin levels were significantly higher in the DIC group, and that there was a positive correlation between the DIC scores and the serum sE-selectin values. Gando et al[25], reported that among septicemia patients, neutrophil elastase, E-selectin, and other molecular markers were significantly higher in the DIC group than in the non-DIC group. DIC is one of the factors that induces organ failure. Because the DIC score reflects the severity of inflammatory vascular endothelial injury at the capillary level, and because there is a positive correlation between the DIC score and sE-selectin, sE-selectin correlated positively with vascular endothelial injury and it reflected the transition of a disease state to MOF in SIRS patients.

Blood sE-selectin values were previously measured by ELISA, which was inconvenient and time-consuming. The method we used is a device that uses latex agglutination and does not require any special technical skills. The results can be obtained in approximately 20 min.

The Abbreviated Injury Scale[26], degree of injury by the ISS[27], the TRISS method[28], the Trauma Score[29], etc., have been devised to predict the outcomes of critically-ill patients but a common consensus on their accuracies has not been established[21]. Thus, there is a need for a new blood marker to be developed that will serve as an indicator for managing ciritcally-ill patients.

In summary, serum sE-selectin levels of SIRS patients reflected disease severity and outcome. In particular, the strongest correlations among the indicators and markers were found for impaired respiratory systems indicators and DIC. A high serum sE-selectin level on arrival at the hospital indicated a poor outcome. Since sE-selectin reflects vascular endothelial injury and neutrophil activation, sE-selectin in critically-ill patients may be a useful marker for predicting survival. Because the test can be performed with a compact test device and the method is convenient and fast, it is a suitable measuring device.

Conclusion

Our results suggest that serum sE-selectin levels obtained by latex agglutination may serve as an important marker for rating disease severity and outcome in the emergency center.

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重症患者における血中可溶性 E-selectin 濃度測定の臨床的意義

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全身性炎症反応性症候群（SIRS）は侵襲に対する生体反応として TNF-α などの炎症性サイトカインにより引き起こされる．この中には，一過性で自然軽快に向かう SIRS と，重篤な感染症・組織障害を伴い多臓器障害（MOF）へと重症化する SIRS があり，両者を早期に鑑別診断できれば重篤化を防ぐことができ臨床上の利点が大きい．E-selectin はセレクチンファミリーに属する単鎖糖蛋白で，血管内皮細胞に分布し内皮と好中球・単球等の接着に関与する細胞接着分子の一つであり，炎症性サイトカインにより誘導され，炎症性疾患や癌患者の血中に出現することが知られている．我々は血中 soluble E-selectin に着目し，SIRS 患者の重症度，予後，各臓器の機能不全との相関と重症患者の予後判定に有用か検討した．

SIRS と診断され SOFA スコアーで 3 点以上を呈した症例 50 例を対象とし，第 0, 1, 3, 5, 7 病日に sE-selectin を測定し検討した．結果，来院時の血中 sE-selectin 値は第 28 病日の死亡群が生存群に比べ有意に高値を示し，その後の変動も死亡群で有意に高値が続き，患者の予後を推測できた．MOF 群と非 MOF 群間の比較では，MOF 群が有意に高値を示した．また，sE-selectin が上昇すると共に不全臓器数も増加しさらに SOFA score と sE-selectin 値の変動は正の相関を認めた．また sE-selectin 値と各臓器障害の相関をみると，呼吸器系の重症度を反映する PaO_2/F_IO_2 比（P/F ratio）で sE-selectin 値が最も有意に相関し，急性肺障害（ALI/ARDS）群と non-ALI/non-ARDS 群では ALI 群で sE-selectin 値が有意に上昇した．播種性血管内血液凝固症候群（DIC）群と non-DIC 群の間では DIC 群で sE-selectin が有意に高値を示し，DIC score と sE-selectin 値の間でも正の相関を認めた．

以上より sE-selectin は DIC score・SOFA score・呼吸・凝固・腎臓の機能不全のみならず患者の生命予後とも相関することから，重症化や生命予後の有用な血中マーカーになると考えられた．