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Original Article

Elevated serum soluble ICAM-1 is correlated with severity and mortality of patients with severe sepsis

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Abstract: Intercellular adhesion molecule 1 (ICAM-1) and its soluble counterpart (sICAM-1) are proteins that play roles in endothelial dysfunction. Increased sICAM-1 level is correlated with sepsis; however, there are rarely data on the association between sICAM-1 levels and mortality of septic patients. This study aimed to determine whether serum sICAM-1 levels could be a marker for adverse outcome of severe sepstic patients. A total of 182 severe septic patients were included and their serum sICAM-1 levels were measured by enzyme-linked immunosorbent assay (ELISA). Serum sICAM-1 was also measured in 60 gender and age-matched healthy controls. Patients were followed for at least 30 days. Our results showed that serum sICAM-1 levels were significantly higher in septic patients compared with healthy controls (P<0.001), and in nonsurvivors (n = 67) compared with survivors (n = 115) (P<0.001). The levels of sICAM-1 were closely correlated with APACHE II score, SOFA score, serum creatinine, and inflammtory mediators such as C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor-α (TNF-α), as well as associated with the presence of septic shock, diabetes mellitus and chronic obstructive pulmonary disease (COPD) (All P<0.05). High sICAM-1 level (≥256 ng/mL) were associated with higher mortality at 30 days (odds ratio = 2.295; 95% confidence interval = 1.057 to 4.983; P = 0.036). In conclusions, serum sICAM-1 levels are increased in septic patients and are associated with severity of disease. sICAM-1 could potentially serve as a prognostic biomarker in severe septic patients.

Keywords: Severe sepsis, septic shock, intercellular adhesion molecule 1 (ICAM-1), systemic inflammatory response syndrome (SIRS), mortality, biomarker

Introduction

Sepsis is a global health problem caused by infection with high morbidity and mortality, and is the most common cause of death in critically ill patients of intensive care unit (ICU) [1]. Severe sepsis is characterized by systemic inflammatory response syndrome (SIRS) [2], and is often complicated with septic shock (refractory hypotension) [3] and multiple organ dysfunction syndrome (MODS) [4], thereby determining the outcome of severe sepsis. Both pro-inflammatory and anti-inflammatory pathways are activated in severe sepsis [5], and their imbalance can determine the probability of septic shock and MODS [6]. Therefore, new biomarkers are highly needed in the early phase of sepsis to aid diagnosis and stratification of severe sepsis patients [7].

Intercellular adhesion molecule 1 (ICAM-1) is a glycoprotein member of the immunoglobulin superfamily, and acts as one adhesion molecule that stimulates leukocyte adhesion and transmigration across the endothelium. ICAM-1 is constitutively expressed on endothelium and its expression can be significantly up-regulated by a variety of mediators, such as proinflammatory cytokines, cellular stresses, hormones and virus infection [8]. Circulating soluble ICAM-1 (sICAM-1) is cleaved and released from membrane-bound ICAM-1, and measurement of blood sICAM-1 levels can estimate ICAM-1 expression in the tissue [9]. Circulating sICAM-1 levels are increased in many diseases, such as coronary heart disease, systemic lupus erythematosus, obstructive sleep apnea syndrome, atherosclerosis, idiopathic pulmonary fibrosis, colorectal and lung cancers [10-16].

Circulating sICAM-1 is up-regulated in neonatal sepsis and associated with disease severity and systemic inflammation [17, 18]. However,

the relationship between circulating sICAM-1 and adult sepsis is complex and in whether sICAM-1 concentration is associated with severity and mortality of severe sepsis is not well established. Therefore, this study we investigated serum sICAM-1 concentrations in severe sepsis patients at ICU admission. This study aimed to determine the association between serum sICAM-1 and clinical severity, mortality and inflammatory response of severe sepsis. We also explored whether serum sICAM-1 levels can serve as a prognostic biomarker for severe sepsis patients.

Materials and methods

Subjects

A total of 182 consecutive patients (116 male, 66 female; median age 59.5 years, range 26-81 years) were included between July 2014 and December 2015 in the general Internal Medicine intensive care unit (ICU) of Zhejiang Taizhou Hospital. The sepsis was diagnosed based on the criteria proposed by the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference Committee for sepsis [19]. Sepsis was defined as documented or suspected infection induced by a microorganism (positive blood cultures) and at least two of the following parameters: ① temperature >38°C or <36°C; ② heart rate >90 beats/min; ③ respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg; ④ white blood cell (WBC) count >12,000 or <4,000 cells/mm^3, or >10% immature forms. Severe sepsis was defined as sepsis complicated with organ dysfunction. Septic shock was defined as severe sepsis complicated with refractory arterial hypotension (SBP<90 mmHg, or MAP< 65 mmHg) and fluid replacement and vasopressors were needed. Patient clinical data and laboratory parameters were collected, and follow-up was performed in each patient for at least 30 days by directly contacting the patients or their relatives. A total of 60 gender and age-matched healthy blood donors were collected as control subjects. This study was approved by the ethics committee of Zhejiang Taizhou Hospital and was conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from the patients or their relatives.

Determination of clinical data and laboratory parameters

The following variables were recorded for each severe septic patient: gender, age, body mass index (BMI), site of infection, Acute Physiology and Chronic Health Evaluation II (APACHE II) score [20], Sepsis-related Organ Failure Assessment (SOFA) score [21], mechanical ventilation, ICU days, septic shock, serum creatinine, white blood cell (WBC) count, diabetes mellitus, chronic obstructive pulmonary disease (COPD), C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor-α (TNF-α). Survival at 30 days was used as the endpoint. Blood samples were collected from 182 patients with severe sepsis at admission to the ICU before therapeutic intervention and from 60 gender and age-matched controls. All samples were immediately placed on ice, followed by centrifugation at 1000 g for 10 min, and stored at -80°C. Enzyme-linked immunosorbent assay (ELISA) was performed to determine the level of CRP, IL-6 and TNF-α.

Serum levels of sICAM-1

Venous blood samples were collected from severe septic patients at admission to the ICU, or from healthy controls, and underwent centrifugation within 30 min at 1000 g for 15 min. The serum was separated and stored in aliquots at -70°C until measurement. The serum sICAM-1 was measured by ELISA kit (R&D Systems, Minneapolis, MN; cat. no. DY720), according to the manufacturer's protocol. An ELISA plate reader (Ricso RK201, Shenzhen Ricso Technology Co., Ltd, Shenzhen, Guangdong, China) was used to measure absorbance at OD450 wavelength. The serum concentrations sICAM-1 were determined by the standard curves constructed from recombinant human sICAM-1 (Range: 0~1000 ng/mL).

Statistical analysis

The statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are displayed as medians and interquartile ranges. Categorical variables are displayed as frequencies and percentages. Differences between two groups were determined by Wilcoxon-Mann-Whitney test in comparing continuous variables, or by Chi-squared test or a Fisher's exact test in comparing cate-

Table 1. Characteristics of the study population

Parameter	Sepsis patients n = 182	Survivors n = 115	Nonsurvivors n = 67	*P* value
Male sex*	116 (63.7%)	72 (62.6%)	44 (65.7%)	0.678
Age (years)†	59.5 (51 to 67)	57 (49 to 66)	62 (54 to 71)	0.023
BMI†	22.9 (21.2 to 24.5)	22.9 (20.8 to 24.5)	23.2 (21.3 to 24.7)	0.646
Site of infection*				0.309
Pulmonary	113 (62.1%)	71 (61.7%)	42 (62.7%)	
Abdominal	44 (24.2%)	31 (27.0%)	13 (19.4%)	
Other	25 (13.7%)	13 (11.3%)	12 (17.9%)	
APACHE II score†	22 (19 to 24)	21 (18 to 23)	23 (21 to 25)	<0.001
SOFA score†	12 (10 to 13)	11 (10 to 13)	13 (11 to 14)	<0.001
Mechanical ventilation*	104 (57.1%)	59 (51.3%)	45 (67.2%)	0.037
ICU days†	7 (5 to 10)	7 (5 to 9)	7 (5 to 10)	0.235
Septic shock*	103 (56.6%)	55 (47.8%)	48 (71.6%)	0.002
Creatinine (μmol/L)†	111 (82 to 137)	106 (77 to 133)	121 (95 to 152)	0.005
WBC (10^3/μL)†	15 (13 to 17)	14 (13 to 16)	15 (13 to 17)	0.258
Diabetes mellitus*	52 (28.6%)	26 (22.6%)	26 (38.8%)	0.020
COPD*	33 (18.1%)	22 (19.1%)	11 (16.4%)	0.647
CRP (mg/dL)†	196 (173 to 225)	189 (167 to 223)	205 (183 to 231)	0.016
IL-6 (pg/mL)†	412 (355 to 483)	395 (333 to 462)	445 (383 to 542)	<0.001
TNF-α (pg/mL)†	41 (36 to 47)	39 (35 to 45)	44 (38 to 49)	0.002

*Categorical Variable are expressed as frequency (%) and analyzed by Chi-squared test; †Continuous variable are expressed as median (25th to 75th percentiles) and analyzed by Mann-Whitney U test. BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; ICU, intensive care unit; WBC, white blood cell count; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein, IL-6, Interleukin 6; TNF-α, Tumour necrosis factor-α.

Table 2. Comparison between healthy controls and sepsis patients

Parameter	Controls n = 60	Sepsis patients n = 182	Survivors n = 103	Nonsurvivors n = 79
Male sex	38 (63.3%)	116 (63.7%)	72 (62.6%)	44 (65.7%)
Age (years)	62 (52 to 65)	59.5 (51 to 67)	57 (49 to 66)	62 (54 to 71)
BMI	22.6 (21.2 to 24.5)	22.9 (21.2 to 24.5)	22.9 (20.8 to 24.5)	23.2 (21.3 to 24.7)
sICAM-1 (ng/mL)	116 (102 to 129)	234 (208 to 268)	224 (193 to 249)	259 (226 to 294)

BMI, body mass index; sICAM-1, soluble intercellular adhesion molecule-1.

gorical variables. Correlations between sICAM-1 and other variables were analysed using the Spearman's rank correlation tests. Receiver operating characteristic (ROC) analysis was performed to determine the goodness-of-fit of serum sICAM-1 levels to predict 30-day mortality, and determin 256 ng/mL as the cut-off point for high and low levels of serum sICAM-1. Multivariate logistic regression analysis was applied to determine the independent contribution of age, APACHE II score, mechanical ventilation, septic shock, serum IL-6, serum sICAM-1 (≥256 ng/mL) to the prediction of the mortality during the 30-day period. The prognostic impact of these variables was expressed as odds ratio and its 95% confidence intervals (CI). Kaplan-Meier curves and log-rank test calculations were used to analyze the impact of serum sICAM-1 level on survival of severe septic patients. A probability value of $P<0.05$ was considered as statistically significant difference.

Results

Serum sICAM-1 concentrations are elevated in severe septic patients and higher in nonsurvivors than in survivors

Baseline characteristics of 182 patients with severe sepsis at the time of ICU admission are shown in **Table 1**. Among all 182 patients, there are 115 cases of survivors and 67 cases of nonsurvivors. As expected, nonsurvivors had

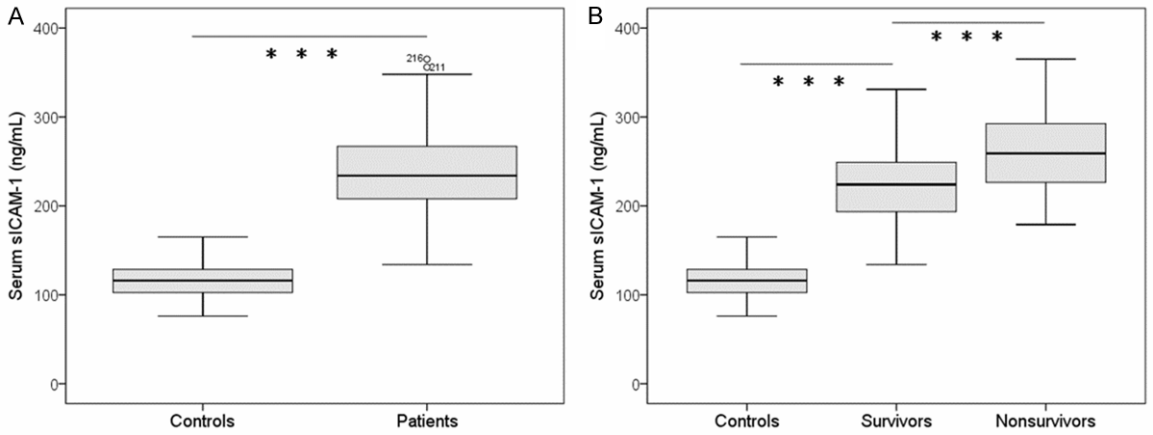

Figure 1. Serum sICAM-1 concentrations in severe septic patients. A: Serum sICAM-1 levels are significantly higher in severe septic patients (n = 182) as compared with healthy controls (n = 60) (P<0.001). B: Serum sICAM-1 levels are significantly higher in nonsurvivors (n = 67) as compared with nonsurvivors (n = 115) patients. Box plots are displayed, where the bold black line indicates the median per group, the box represents 50% of the values, and horizontal lines show minimum and maximum values of the calculated non-outlier values; open circles indicate outlier values. Wilcoxon-Mann-Whitney test was performed. *P<0.05, **P<0.01, ***P<0.001.

Table 3. Serum levels of sICAM-1 according to clinical variables

Clinical variables	Yes patient number and sICAM-1 levels	Non patient number and sICAM-1 levels	*P* value
Mechanical ventilation	(n = 104)	(n = 78)	0.914
	234 (207 to 274)	236 (210 to 261)	
Septic shock	(n =103)	(n = 79)	0.029
	237 (213 to 274)	226 (194 to 258)	
Diabetes mellitus	(n = 52)	(n = 130)	0.013
	247 (221 to 286)	228 (198 to 261)	
COPD	(n = 33)	(n = 149)	0.026
	247 (223 to 284)	231 (203 to 262)	

sICAM-1, soluble intercellular adhesion molecule-1; COPD, chronic obstructive pulmonary disease.

Table 4. Correlations with serum sICAM-1 levels

	Sepsis patients (n = 182)		Survivors (n = 115)		Nonsurvivors (n = 67)	
	r	P	R	P	r	P
APACHE II	0.321	<0.001	0.198	0.034	0.277	0.023
SOFA	0.345	<0.001	0.217	0.020	0.318	0.009
ICU days	-0.080	0.284	-0.108	0.251	0.082	0.511
Creatinine (μmol/L)	0.435	<0.001	0.459	<0.001	0.327	0.007
WBC (10^3/μL)	0.060	0.419	-0.010	0.916	0.111	0.373
CRP (mg/dL)	0.224	<0.001	0.246	0.008	0.412	0.001
IL-6 (pg/mL)	0.447	<0.001	0.301	0.001	0.434	<0.001
TNF-α (pg/mL)	0.392	<0.001	0.325	<0.001	0.348	0.004

r = correlation coefficient; r and *P* values by Spearman's rank correlation.

older age, greater APACHE II and SOFA scores, higher rates of mechanical ventilation, septic shock, diabetes mellitus, higher serum creatinine, CRP, IL-6 and TNF-α levels (All P<0.05). Higher serum sICAM-1 levels were observed in the severe septic patients (median 234 ng/mL) compared with healthy controls (median 116 ng/mL) (P<0.001), and in nonsurvivors (median 259 ng/mL) compared with survivors (median 224 ng/mL) (P<0.001) after the 30-day follow-up (**Table 2**; **Figure 1**).

sICAM-1 is associated with septic shock, diabetes mellitus and COPD

To evaluate the associations of sICAM-1 with mechanical ventilation, septic shock, diabetes mellitus and COPD, we examined and compared serum sICAM-1 levels in subgroups of patients. Serum sICAM-1 levels were significant higher in patients with septic shock (P = 0.029), diabetes mellitus (P = 0.013) and COPD (P = 0.026) compared with their counterparts (**Table 3**). No significant

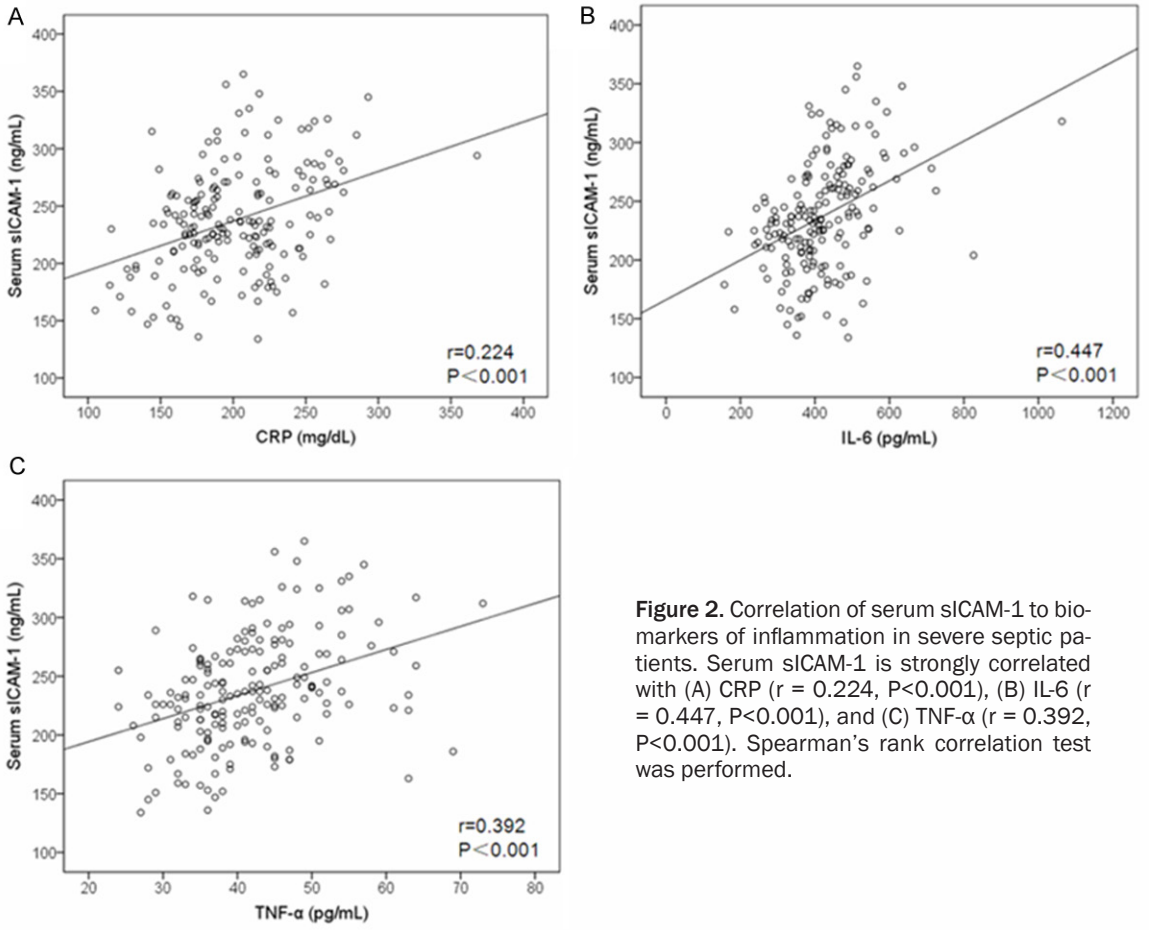

Figure 2. Correlation of serum sICAM-1 to biomarkers of inflammation in severe septic patients. Serum sICAM-1 is strongly correlated with (A) CRP (r = 0.224, P<0.001), (B) IL-6 (r = 0.447, P<0.001), and (C) TNF-α (r = 0.392, P<0.001). Spearman's rank correlation test was performed.

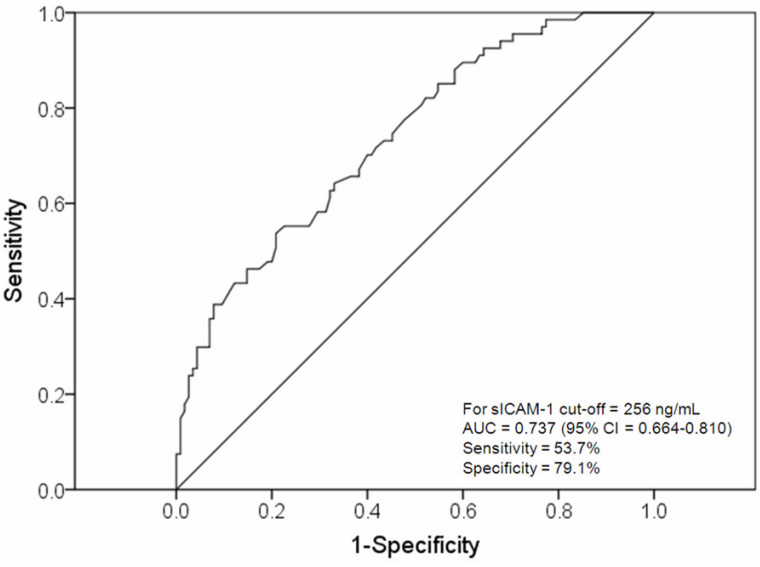

Figure 3. Receiver operating characteristic (ROC) analysis using sICAM-1 levels ≥256 ng/mL as 30-days mortality predictors.

association was observed between mechanical ventilation and serum sICAM-1.

sICAM-1 correlates with inflammatory mediators and renal function

In all severe septic patients, sICAM-1 was found to correlate with markers of renal function, and inflammation. Serum sICAM-1 correlated positively to creatinine (r = 0.435, P<0.001), CRP (r = 0.224, P<0.001), IL-6 (r = 0.447, P<0.001) and TNF-α (r = 0.392, P<0.001) (**Table 4**; **Figure 2**). Similar results were also found in the subgroups of survivors and nonsurvivors.

sICAM-1 may be a prognostic factor for survival in severe septic patients

To determine the goodness-of-fit for serum sICAM-1, receiver operating characteristic (ROC)

Table 5. Multiple logistic regression analysis of variables to predict 30-day mortality

Variable	Odds Ratio	95% Confidence Interval	*P* value
APACHE II	1.166	1.043 to 1.303	0.007
Mechanical ventilation	2.212	1.097 to 4.459	0.026
IL-6 (pg/mL)	1.004	1.001 to 1.008	0.023
sICAM-1 (≥256 ng/mL)	2.295	1.057 to 4.983	0.036

analysis was performed to predict 30-day mortality. The area under the curve (AUC) of sICAM-1 was 0.737 (95% CI = 0.664-0.810; P<0.001) (**Figure 3**). Diagnostic cut-off point for serum sICAM-1 level was 256 ng/mL (sensitivity = 53.7%, specificity = 79.1%).

To evaluate whether serum sICAM-1 is an independent prognostic factor of severe septic patients, we performed multivariate logistic regression analysis and showed that APACHE II score, mechanical ventilation, IL-6 (pg/mL) and serum sICAM-1 levels ≥256 ng/mL were significantly associated with death at Day 30 (**Table 5**). To evaluate the association between sICAM-1 and disease severity, we performed Spearman's rank correlation tests and found that in patients of severe sepsis, serum sICAM-1 was correlated with the APACHE II score (r = 0.321, P<0.001) and SOFA score (r = 0.345, P<0.001) on admission (**Figure 4A**, **4B**). To further investigate the effect of serum sICAM-1 on moatality of sepsis patients, we performed Kaplan-Meier survival analysis. We selected serum sICAM-1 256 ng/mL as a cutoff point, and patients with sICAM-1 ≥256 ng/mL demonstrated significantly poor survival and higher mortality compared to patients with sICAM-1 level <256 ng/mL (Log Rank = 19.569, P< 0.001, **Figure 4C**).

Discussion

This study investigated the role of sICAM-1 as a serum biomarker protein in severe sepsis. Compared with healthy controls, severe septic patients showed elevated sICAM-1 levels. Serum sICAM-1 Levels were also higher in non-survivors compared with survivors, and higher in the presence of septic shock, diabetes mellitus and COPD. The levels of sICAM-1 were closely correlated with clinical severity and inflammatory mediators. Serum sICAM-1 levels ≥256 ng/mL were associated with higher mortality at 30 days by the multiple logistic re-gression analysis. Increased sICAM-1 was previously reported in neonatal and adult septic patients [17, 18]; however, our study firstly reported the association between serum sICAM-1 and mortality of severe septic patients.

It was previously reported that sICAM-1 levels are elevated in diseases other than sepsis [10-16]. The role of sICAM-1 in sepsis remains unclear; but it may share common mechanisms with other diseases whose sICAM-1 levels are elevated. ICAM-1 is constitutively expressed on the surface of endothelial cells and expression level increased in response to tissue damage, inflammation, cellular stresses, virus infection, and environmental factors [8, 22-24]. ICAM-1 participates in the adhesion and transmigration of leukocyte into the subendothelial space [25, 26]. Elevated serum sICAM-1 was found in neonatal infections, SIRS, sepsis-induced multiple organ failure and injured trauma-induced organ failure [27-30]. The serum sICAM-1 is released from endothelial cell surface and acts as a good indicator of tissue ICAM-1 concentrations, which was supported by the significant positive correlation between supernatant sICAM-1 and surface-bound ICAM-1 in cultured human umbilical vein endothelial cells (HUVEC) [31]. sICAM-1 is a biomarker of endothelial activation and its high level can predict higher risk of development of sepsis [32, 33]. In severe sepsis, infection induces microvascular endothelial activation and permeability, thereby leading to multiple organ injury [34]. Endothelial activation and dysfunction facilitate the development of multiple organ failure and death in severe sepsis [35, 36].

For the subgroups analysis of sepsis patients, we found serum sICAM-1 was increased in the presence of septic shock, diabetes mellitus and COPD compared with their counterparts. Our results are in accordance with previous report that increased serum sICAM-1 was present in septic shock than in sepsis patients without hypotension or hypoperfusion [37]. Septic shock is characterized by hypotension and disseminated intravascular coagulation (DIC), thereby contributing to multiple organ failure and a high mortality rate [38]. The endothelial barrier function is almost impaired in septic

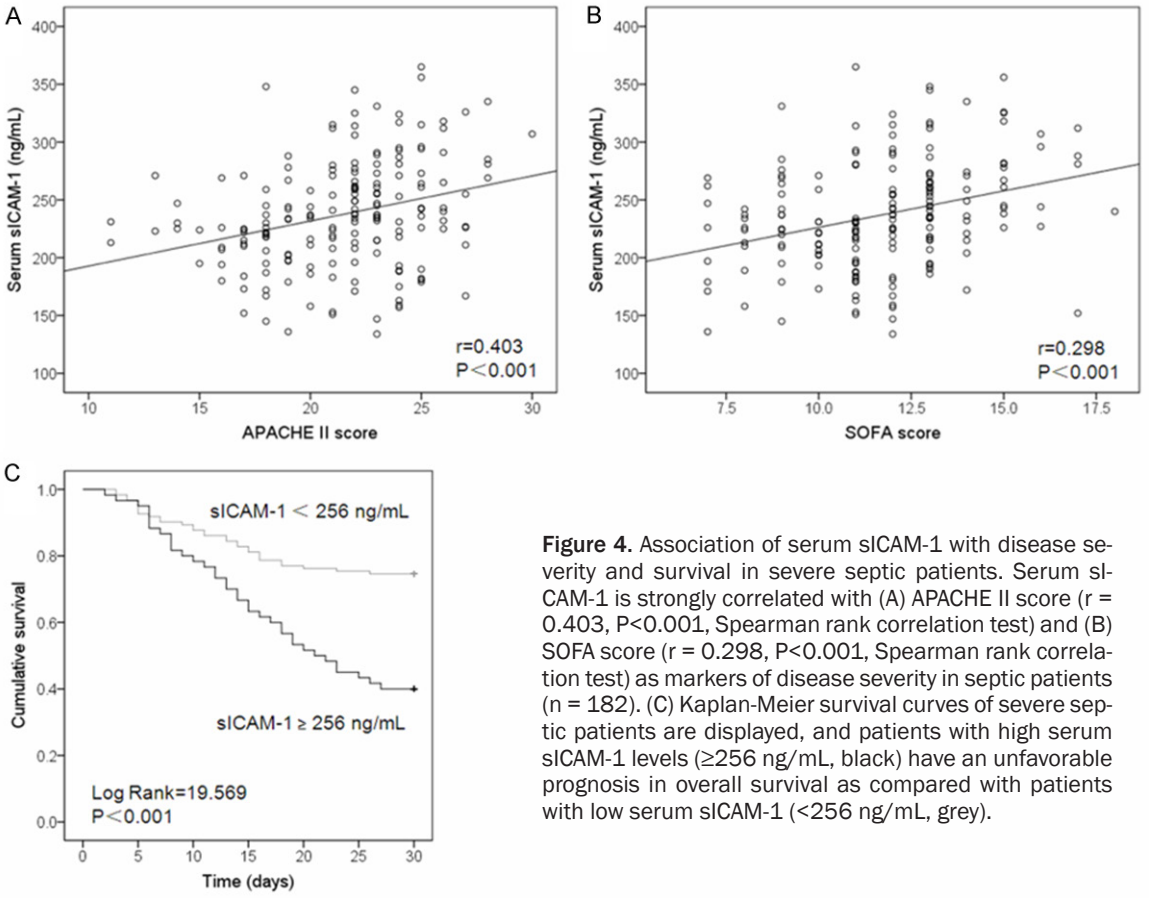

Figure 4. Association of serum sICAM-1 with disease severity and survival in severe septic patients. Serum sICAM-1 is strongly correlated with (A) APACHE II score (r = 0.403, P<0.001, Spearman rank correlation test) and (B) SOFA score (r = 0.298, P<0.001, Spearman rank correlation test) as markers of disease severity in septic patients (n = 182). (C) Kaplan-Meier survival curves of severe septic patients are displayed, and patients with high serum sICAM-1 levels (≥256 ng/mL, black) have an unfavorable prognosis in overall survival as compared with patients with low serum sICAM-1 (<256 ng/mL, grey).

shock, and it is an important contributor to adverse outcomes [39]. Diabetes mellitus is a risk factor of sepsis, and sepsis-induced inflammation is exacerbated in Type 2 diabetic rats, and diabetes mellitus increased plasma proinflammatory cytokines levels and organs injury of septic rats [40, 41]. So our results showed that nonsurvivors had significantly higher rate of diabetes mellitus compared with survivors. Furthermore, compared with healthy subjects, diabetes patients have increased circulating sICAM-1 levels, which are caused by genetic polymorphisms or activation of leptin synthesis [42, 43]. In pulmonary tissues of COPD patients and rats, ICAM-1 gene expressions was increased [44, 45], thereby making elevated serum sICAM-1 as a biomarker of COPD [46]. Therefore, the increased serum sICAM-1 of sepsis patients with COPD might come from pulmonary tissues as well as endothelium.

We reported positive correlation between serum sICAM-1 and inflammatory mediators, such as CRP, IL-6 and TNF-α. There are serum biomarker of sepsis and associated with SIRS and multiple organ failure [47-49]. Furthermore, these pro-inflammatory cytokines could determine ICAM-1 expression and concentration [50, 51]. Currently, rapid early diagnostic and therapeutic management is a major challenge for ICU sepsis patients, and it is important for the prognosis of sepsis [52]. Therefore, searching for novel biomarkers may significantly improve the early intervention and prognosis of sepsis patients [53]. Our results showed that serum sICAM-1 of severe sepsis patients was correlated with the disease severity, namely APACHE II score and SOFA score on admission. Patients with sICAM-1 ≥256 ng/mL showed significantly higher mortality rate at 30 day compared to patients with sICAM-1 level <256 ng/mL. Furthermore, multivariate logistic regression analysis showed that serum sICAM-1 is an independent prognostic factor of severe sepsis, and this indicates more unknown mechanisms, other than inflammatory response and endothelial activation, might be involved in develop and progression of severe sepsis.

In conclusion, this study demonstrates the potential role of sICAM-1 as a biomarker in sepsis patients and its correlation to inflammatory response and organ damage. sICAM-1 serum levels are elevated in sepsis patients compared to healthy controls, and in nonsurvivors compared to survivors at ICU admission. Future studies with larger sample size and more detailed mechanisms are required to make sICAM-1 serve as a novel prognostic biomarker of ICU severe sepsis patients.

Disclosure of conflict of interest

None.

Authors' contribution

Wei Sun analyzed the data and wrote the manuscript; Ren-Fei Shan designed the study and revised the manuscript; Yan-An Zhu and Jie Qin performed all the experiments and collected all the data; Jian-Ping Chen analyzed the data.

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References

[1] Mayr FB, Yende S and Angus DC. Epidemiology of severe sepsis. Virulence 2014; 5: 4-11.

[2] Kaukonen KM, Bailey M, Pilcher D, Cooper DJ amd Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015; 372: 1629-1638.

[3] Cawcutt KA and Peters SG. Severe sepsis and septic shock: clinical overview and update on management. Mayo Clin Proc 2014; 89: 1572-1578.

[4] Guirgis FW, Khadpe JD, Kuntz GM, Wears RL, Kalynych CJ and Jones AE. Persistent organ dysfunction after severe sepsis: a systematic review. J Crit Care 2014; 29: 320-326.

[5] Angus DC and van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369: 840-851.

[6] Zhang H. Immune-imbalance in sepsis. Minerva Anestesiol 2000; 66: 435-437; discussion 438.

[7] Liu X, Ren H and Peng D. Sepsis biomarkers: an omics perspective. Front Med 2014; 8: 58-67.

[8] Roebuck KA and Finnegan A. Regulation of intercellular adhesion molecule-1 (CD54) gene expression. J Leukoc Biol 1999; 66: 876-888.

[9] Witkowska AM and Borawska MH. Soluble intercellular adhesion molecule-1 (sICAM-1): an overview. Eur Cytokine Netw 2004; 15: 91-98.

[10] Luc G, Arveiler D, Evans A, Amouyel P, Ferrieres J, Bard JM, Elkhalil L, Fruchart JC, Ducimetiere P; PRIME Study Group. Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and incident coronary heart disease: the PRIME Study. Atherosclerosis 2003; 170: 169-176.

[11] Tso TK and Huang WN. Elevated soluble intercellular adhesion molecule-1 levels in patients with systemic lupus erythematosus: relation to insulin resistance. J Rheumatol 2007; 34: 726-730.

[12] Ursavaş A, Karadağ M, Rodoplu E, Yilmaztepe A, Oral HB and Gözü RO. Circulating ICAM-1 and VCAM-1 levels in patients with obstructive sleep apnea syndrome. Respiration 2007; 74: 525-532.

[13] Gross MD, Bielinski SJ, Suarez-Lopez JR, Reiner AP, Bailey K, Thyagarajan B, Carr JJ, Duprez DA and Jacobs DR Jr. Circulating soluble intercellular adhesion molecule 1 and subclinical atherosclerosis: the Coronary Artery Risk Development in Young Adults Study. Clin Chem 2012; 58: 411-420.

[14] Okuda R, Matsushima H, Aoshiba K, Oba T, Kawabe R, Honda K and Amano M. Soluble intercellular adhesion molecule-1 for stable and acute phases of idiopathic pulmonary fibrosis. Springerplus 2015; 4: 657.

[15] Toiyama Y, Miki C, Inoue Y, Okugawa Y, Koike Y, Yokoe T, Tanaka K and Kusunoki M. Soluble intercellular adhesion molecule-1 as a prognostic marker for stage II colorectal cancer patients. Ann Surg Oncol 2008; 15: 1617-1624.

[16] Gu X, Ma C, Yuan D and Song Y. Circulating soluble intercellular adhesion molecule-1 in lung cancer: a systematic review. Transl Lung Cancer Res 2012; 1: 36-44.

[17] Figueras-Aloy J, Gómez-López L, Rodríguez-Miguélez JM, Salvia-Roiges MD, Jordán-García I, Ferrer-Codina I, Carbonell-Estrany X and Jiménez-González R. Serum soluble ICAM-1, VCAM-1, L-selectin, and P-selectin levels as markers of infection and their relation to clinical severity in neonatal sepsis. Am J Perinatol 2007; 24: 331-338.

[18] Sugitharini V, Prema A and Berla Thangam E. Inflammatory mediators of systemic inflammation in neonatal sepsis. Inflamm Res 2013; 62: 1025-1034.

[19] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J,

Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296-327.

[20] Knaus WA, Draper EA, Wagner DP and Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13: 818-829.

[21] Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F and Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998; 26: 1793-1800.

[22] Springer TA. Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. Annu Rev Physiol 1995; 57: 827-872.

[23] Sjögren P, Cederholm T, Heimbürger M, Stenvinkel P, Vedin I, Palmblad J and Hellenius ML. Simple advice on lifestyle habits and long-term changes in biomarkers of inflammation and vascular adhesion in healthy middle-aged men. Eur J Clin Nutr 2010; 64: 1450-1456.

[24] Monagas M, Khan N, Andres-Lacueva C, Casas R, Urpí-Sardà M, Llorach R, Lamuela-Raventós RM and Estruch R. Effect of cocoa powder on the modulation of inflammatory biomarkers in patients at high risk of cardiovascular disease. Am J Clin Nutr 2009; 90: 1144-1150.

[25] Ley K, Laudanna C, Cybulsky MI and Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat Rev Immunol 2007; 7: 678-689.

[26] Laudanna C and Alon R. Right on the spot: chemokine triggering of integrin-mediated arrest of rolling leukocytes. Thromb Haemost 2006; 95: 5-11.

[27] Mahmoud S, Maklad S, Abo Elmagd EK. Soluble intercellular adhesion molecule-1 (sICAM-1) for early diagnosis of neonatal infections. Egypt J Immunol 2009; 16: 83-94.

[28] de Pablo R, Monserrat J, Reyes E, Díaz D, Rodríguez-Zapata M, de la Hera A, Prieto A and Álvarez-Mon M. Circulating sICAM-1 and sE-Selectin as biomarker of infection and prognosis in patients with systemic inflammatory response syndrome. Eur J Intern Med 2013; 24: 132-138.

[29] Whalen MJ, Doughty LA, Carlos TM, Wisniewski SR, Kochanek PM and Carcillo JA. Intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 are increased in the plasma of children with sepsis-induced multiple organ failure. Crit Care Med 2000; 28: 2600-2607.

[30] Law MM, Cryer HG and Abraham E. Elevated levels of soluble ICAM-1 correlate with the development of multiple organ failure in severely injured trauma patients. J Trauma 1994; 37: 100-109; discussion 109-110.

[31] Kjaergaard AG, Dige A, Krog J, Tønnesen E and Wogensen L. Soluble adhesion molecules correlate with surface expression in an in vitro model of endothelial activation. Basic Clin Pharmacol Toxicol 2013; 113: 273-279.

[32] Page AV and Liles WC. Biomarkers of endothelial activation/dysfunction in infectious diseases. Virulence 2013; 4: 507-516.

[33] Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S and Howard G. Inflammatory and endothelial activation biomarkers and risk of sepsis: a nested case-control study. J Crit Care 2013; 28: 549-555.

[34] Darwish I and Liles WC. Emerging therapeutic strategies to prevent infection-related microvascular endothelial activation and dysfunction. Virulence 2013; 4: 572-582.

[35] Coletta C, Módis K, Oláh G, Brunyánszki A, Herzig DS, Sherwood ER, Ungvári Z and Szabo C. Endothelial dysfunction is a potential contributor to multiple organ failure and mortality in aged mice subjected to septic shock: preclinical studies in a murine model of cecal ligation and puncture. Crit Care 2014; 18: 511.

[36] Johansen ME, Johansson PI, Ostrowski SR, Bestle MH, Hein L, Jensen AL, Søe-Jensen P, Andersen MH, Steensen M, Mohr T, Thormar K, Lundgren B, Cozzi-Lepri A, Lundgren JD and Jensen JU. Profound endothelial damage predicts impending organ failure and death in sepsis. Semin Thromb Hemost 2015; 41: 16-25.

[37] Sessler CN, Windsor AC, Schwartz M, Watson L, Fisher BJ, Sugerman HJ and Fowler AA 3rd. Circulating ICAM-1 is increased in septic shock. Am J Respir Crit Care Med 1995; 151: 1420-1427.

[38] Boisramé-Helms J, Kremer H, Schini-Kerth V, Meziani F. Endothelial dysfunction in sepsis. Curr Vasc Pharmacol 2013; 11: 150-160.

[39] Opal SM and van der Poll T. Endothelial barrier dysfunction in septic shock. J Intern Med 2015; 277: 277-293.
[40] Jacob A, Steinberg ML, Yang J, Dong W, Ji Y and Wang P. Sepsis-induced inflammation is exacerbated in an animal model of type 2 diabetes. Int J Clin Exp Med 2008; 1: 22-31.
[41] Uyanik MH, Albayrak A, Odabasoglu F, Karakus E, Ozden K, Polat B, Yayla M, Karamese M, Albayrak A and Yazgi H. Effects of diabetes on cytokines and oxidative organ injury in a rat model of sepsis. Cell Mol Biol (Noisy-le-grand) 2012; 58 Suppl: OL1623-OL1631.
[42] Gu HF, Ma J, Gu KT and Brismar K. Association of intercellular adhesion molecule 1 (ICAM1) with diabetes and diabetic nephropathy. Front Endocrinol (Lausanne) 2013; 3: 179.
[43] Cha JJ, Hyun YY, Jee YH, Lee MJ, Han KH, Kang YS, Han SY and Cha DR. Plasma concentration of soluble intercellular adhesion molecule-1 (sICAM-1) is elevated in type 2 diabetic patients, and sICAM-1 synthesis is associated with leptin-induced activation of the mitogen-activated protein kinase (MAPK) pathway. Inflammation 2013; 36: 878-887.
[44] Zandvoort A, van der Geld YM, Jonker MR, Noordhoek JA, Vos JT, Wesseling J, Kauffman HF, Timens W and Postma DS. High ICAM-1 gene expression in pulmonary fibroblasts of COPD patients: a reflection of an enhanced immunological function. Eur Respir J 2006; 28: 113-122.
[45] Ji M, Wang Y, Li X and Qian Z. Up-regulation of ICAM-1mRNA and IL-1βmRNA in lung tissues of a rat model of COPD. Int J Clin Exp Med 2015; 8: 21956-21963.
[46] El-Deek SE, Makhlouf HA, Saleem TH, Mandour MA and Mohamed NA. Surfactant protein D, soluble intercellular adhesion molecule-1 and high-sensitivity C-reactive protein as biomarkers of chronic obstructive pulmonary disease. Med Princ Pract 2013; 22: 469-474.
[47] Ohlin A, Björkqvist M, Montgomery SM and Schollin J. Clinical signs and CRP values associated with blood culture results in neonates evaluated for suspected sepsis. Acta Paediatr 2010; 99: 1635-1640.
[48] Ding Y, Lin Y, Zhu T, Huang M and Xu Q. Interleukin 6 increases dysfunction of organs in sepsis rats through sirtuin 1. Int J Clin Exp Med 2014; 7: 2593-2598.
[49] van der Poll T and Lowry SF. Tumor necrosis factor in sepsis: mediator of multiple organ failure or essential part of host defense? Shock 1995; 3: 1-12.
[50] Ponthieux A, Herbeth B, Droesch S, Haddy N, Lambert D and Visvikis S. Biological determinants of serum ICAM-1, E-selectin, P-selectin and L-selectin levels in healthy subjects: the Stanislas study. Atherosclerosis 2004; 172: 299-308.
[51] Fontani F, Domazetovic V, Marcucci T, Vincenzini MT and Iantomasi T. Tumor Necrosis Factor-Alpha Up-Regulates ICAM-1 Expression and Release in Intestinal Myofibroblasts by Redox-Dependent and -Independent Mechanisms. J Cell Biochem 2016; 117: 370-381.
[52] Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS and Goyal M. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010; 38: 1045-1053.
[53] Lin J, Parente JD, Chase JG, Shaw GM, Blakemore AJ, Lecompte AJ, Pretty C, Razak NN, Lee DS, Hann CE and Wang SH. Development of a model-based clinical sepsis biomarker for critically ill patients. Comput Methods Programs Biomed 2011; 102: 149-155.