Original Article

The relationship between soluble CD73 and the incidence of septic shock in severe sepsis patients: a cross-sectional analysis of data from a prospective FINNAKI study

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Background: Sepsis is a leading cause of mortality worldwide. Septic shock is a subtype of sepsis in which the underlying cardiovascular and cellular/metabolic disorders are profound enough to increase mortality significantly. We sought to investigate the association between soluble cluster of differentiation-73 (sCD73) and the incidence of septic shock in severe sepsis patients.

Methods: This cross-sectional study included 588 Finnish patients with severe sepsis or septic shock from the Finnish Acute Kidney Injury (FINNAKI) study. The primary exposure of interest was baseline level of sCD73. The outcome was the incidence of septic shock. Multivariable logistic regression analyses were performed to assess the independent association between sCD73 and the incidence of septic shock.

Results: The average age of 588 participants was 62±16 years, and 65.14% of the patients were male. The average sCD73 was 5.11 (interquartile range, 3.30, 8.25) ng/mL. The incidence of sepsis shock was 429 (72.96%). In the multivariate logistic regression model, sCD73 was negatively associated with septic shock. After multiple adjustments (for age, gender, lactate, the Sequential Organ Failure Assessment score, systolic heart failure, emergency admission, operative admission, and acute kidney injury within 12 h), a 1 ng/mL increment in sCD73 was associated with a 5% lower incidence of septic shock [odds ratio (OR) =0.95; 95% confidence interval (CI): 0.92, 0.98; P<0.001].

Conclusions: We found that sCD73 was negatively correlated with septic shock. Higher sCD73 was associated with a lower incidence of septic shock.

Keywords: Septic shock; severe sepsis; soluble cluster of differentiation-73 (sCD73); inflammation; phosphatidylinositol 3-kinase/Akt signaling (PI3K/Akt signaling)

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Introduction

Sepsis is often seen in emergency departments or intensive care units (ICUs) (1). Conservative estimates indicate that sepsis is a leading cause of mortality and critical illness worldwide (1-3). Septic shock is a subset of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality (1).

Cluster of differentiation-73 (CD73), also called ecto-

5'-nucleotidase, is found in a variety of tissues, including leukocytes derived from peripheral blood, spleen, lymph nodes, thymus, and bone marrow (4). During the process of inflammation, CD73 can inhibit tissue damage (5). The soluble form of CD73 (sCD73), which is released from cell membranes, is thought to has not only increased range of action but also increased anti-inflammatory enzymatic activity (6,7). According to previous study, the circulating level of sCD73 is a predictor for the development and severity of acute pancreatitis (7). Studies showed CD73 promoted the proliferation and migration of breast cancer cells, hepatocellular carcinoma, and human cervical cancer through the activating phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway (8-10). Meanwhile, activation of PI3K/Akt signaling has been reported to be beneficial in sepsis (11-15). In addition, CD73 was identified as a critical mediator of vascular leakage (4) and may involve in development of septic shock.

We performed a secondary data analysis based on open-source data from a previously published paper (16). In the original study, the authors reported sCD73 levels do not associated with the development of acute kidney injury (AKI) or 90-day mortality in patients with severe sepsis or shock (16). In our study, sCD73 was used as an independent variable, while septic shock was used as the outcome. The independently association between sCD73 and the incidence of septic shock was investigated in this cohort. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-371/rc).

Methods

Data source

The original data are freely available online, and had been approved by the authors for use by other investigators (16). A cross-sectional study was conducted using the baseline characteristics of the data set. The baseline variables included in the database file were as follows: age, gender, lactate, diagnosis, and pre-existing comorbidities. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

Vaara *et al.* completed the original study and shared the data. Details of the design and methods of the research can be found in Vaara *et al.*'s paper (16). The methods relevant to the analyses are briefly described below. Vaara *et al.* conducted the original study from September 1, 2011 to February 1, 2012 (16).

Patients were excluded if they met any of the following exclusion criteria: (I) had received regular dialysis to treat end-stage renal disease; (II) were organ donors; (III) had received intermediate care; (IV) had a history of renal replacement therapy; (V) had their data collected repeatedly due to a previous history of ICU stay; and/or (VI) were not permanently living in Finland or were unable to give consent due to insufficient language skills. Ultimately, a total of 588 consecutive patients were recruited and included in the study (16).

Measurement of sCD73

Vaara *et al.* and Maksimow *et al.* used a new method [i.e., the dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA)] modified from a sandwich enzyme-linked immunosorbent assay (7,16). The sCD73 levels obtained by the DELFIAs were correlated with CD73 activity in 42 randomly selected patient samples (16,17).

Septic shock definition

In relation to severe sepsis, the sepsis-1 definition was based on the American College of Chest Physicians/Society of Critical Care Medicine definition (18). The investigators checked the patients for the presence of severe sepsis upon entering the ICU, and daily thereafter until the diagnostic criteria were established (16).

Sepsis-3 was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Organ dysfunction was indicated by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more (1). We assumed a baseline SOFA of zero for all patients (1,19). Patients met the sepsis-3 definition of septic shock if vasopressors (norepinephrine, dopamine, or epinephrine) were initiated and if they had a serum lactate level >2 mmol/L (1). The Kidney Disease Improving Global Outcomes (KDIGO) criteria (20) was used to screen and stage AKI based on both creatinine (measured daily) and urine output (recorded hourly).

Statistical analysis

The distribution of the baseline data of the patients

Table 1 Baseline characteristics of selected participants

Covariates	All	sCD73 (ng/mL)			P value
		Low (0.84–3.78)	Medium (3.81–6.92)	High (6.94–220.59)	
N	588	196	196	196	
Age (years), mean ± SD	62.4±16.4	64.2±17.2	59.9±17.2	62.9±14.3	0.03
Gender (male), n (%)	383 (65.14)	124 (63.27)	126 (64.29)	133 (67.86)	<0.001
Lactate (mmol/L), median (IQR)	1.64 (1.05, 2.94)	1.52 (1.00, 2.50)	1.70 (1.00, 2.60)	1.80 (1.10, 3.60)	0.08
SOFA score, median (IQR)	8.00 (6.00, 10.00)	7.00 (6.00, 10.00)	8.00 (6.00, 10.00)	9.00 (7.00, 11.00)	<0.001
Hypertension, n (%)	296 (50.34)	105 (53.57)	89 (45.41)	102 (50.04)	0.22
Diabetes, n (%)	148 (25.17)	46 (23.47)	41 (20.92)	61 (31.12)	0.05
Universal arteriosclerosis, n (%)	84 (14.29)	29 (14.80)	23 (11.73)	32 (16.33)	0.41
Chronic liver failure, n (%)	31 (5.27)	6 (3.06)	8 (4.08)	17 (8.67)	0.03
Chronic kidney disease, n (%)	41 (6.97)	13 (6.63)	9 (4.59)	19 (9.69)	0.13
Operative admission, n (%)	147 (25.00)	72 (36.73)	40 (20.41)	35 (17.86)	<0.001
Systolic heart failure, n (%)	62 (10.54)	21 (10.71)	18 (9.18)	23 (11.73)	0.70
AKI within 12 h, n (%)	315 (53.57)	90 (45.92)	105 (53.57)	120 (61.22)	0.01
Thrombotic disorder, n (%)	40 (6.80)	16 (8.16)	15 (7.65)	9 (4.59)	0.32
Rheumatoid disease, n (%)	42 (7.14)	16 (8.16)	7 (3.57)	19 (9.69)	0.05
Renal transplantation, n (%)	6 (1.02)	2 (1.02)	1 (0.51)	3 (1.53)	0.61
Malignancy, n (%)	77 (13.10)	30 (15.31)	21 (10.71)	26 (13.27)	0.40
Septic shock*, n (%)	429 (72.96)	152 (77.55)	139 (70.92)	138 (70.41)	0.21
Septic shock**, n (%)	160 (27.21)	49 (25.00)	58 (29.59)	53 (27.04)	0.59

*, septic shock according to the sepsis-1 definition; **, septic shock according to the sepsis-3 definition. sCD73, soluble cluster of differentiation-73; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; SD, standard deviation; IQR, interquartile range.

included in this study is presented for the different sCD73 groups (tertiles). The categorical variables are expressed as percentages (%). The continuous variables are expressed as the mean and standard deviation (SD) when normally distributed, or the median and interquartile range (IQR) when skewed. The q-way analysis of variance (normal distribution), Kruskal-Wallis (skewed distribution) test, and chi-square tests (categorical variables) were used to compare the categorical variables and the normally and non-normally distributed continuous variables, respectively.

Multivariable logistic regression analyses were performed to assess the independent association between sCD73 and the incidence of septic shock. We calculated unadjusted and adjusted estimates using exact methods and asymptotic methods, respectively (21). We adjusted for features that, when added to this model, changed the matched odds ratio (OR) by at least 10% (21). Age and gender were regularly adjusted. Collinearity was assessed before the multivariate analyses. sCD73 was analyzed as a continuous variable in the different adjusted models according to the "Strengthening the Reporting of Observational Studies in Epidemiology" statement (22). We simultaneously showed the results of the unadjusted, minimally adjusted (age, gender), multiply adjusted (age, gender, lactate, SOFA score, systolic heart failure, emergency admission, operative admission, and AKI within 12 h) and fully adjusted (for details of all the covariates, see *Table 1*) analyses. We also performed tests for the linear trends by entering the median value of each category of sCD73 as a continuous variable in the models (23).

Subgroup analyses were performed using stratified linear regression models. The modifications and interactions of subgroups were inspected by likelihood-ratio tests.

Table 2 Relationship between sCD73 and the incidence of septic shock according to the sepsis-1 definition

Exposure	Non-adjusted model		Minimally adjusted model		Multiply adjusted model		Fully adjusted model	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
sCD73 (ng/mL)	0.99 (0.98, 1.00)	0.107	0.99 (0.98, 1.00)	0.101	0.95 (0.92, 0.98)	<0.001	0.94 (0.92, 0.97)	<0.001
sCD73 tertiles (ng/mL)								
Low (0.84–3.78)	Reference		Reference		Reference		Reference	
Medium (3.81–6.92)	0.80 (0.52, 1.24)	0.323	0.84 (0.54, 1.30)	0.432	0.64 (0.34, 1.20)	0.1651	0.64 (0.34, 1.24)	0.186
High (6.94–220.59)	0.79 (0.51, 1.21)	0.274	0.80 (0.52, 1.23)	0.299	0.40 (0.21, 0.75)	0.005	0.38 (0.19, 0.73)	0.004
P for trend		0.360		0.360		0.006		0.004

Non-adjusted: no covariates were adjusted. Minimally adjusted model: adjusted for age and gender. Multiply adjusted model: adjusted for age, gender, lactate, SOFA score, systolic heart failure, emergency admission, operative admission, and AKI within 12 h. Fully adjusted model: adjusted for all the covariates listed in Table 1. sCD73, soluble cluster of differentiation-73; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

All the analyses were performed with the statistical software package R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics (version 1.4). A two-tailed test was performed, and a P value <0.05 was considered statistically significant.

Results

Baseline characteristics of the participants

Data from 588 consecutive patients were analyzed (16). The baseline characteristics of the selected participants, according to tertiles of sCD73, are shown in *Table 1*. In general, the average age of the participants was 62±16 years old, and 65.14% of the patients were male. The sCD73 distribution was 5.11 (IQR, 3.30, 8.25) ng/mL. Participants with the highest sCD73 (high) were mostly male, had higher SOFA scores, and were more likely to have chronic liver failure, AKI within 12 h, and operative admission. The incidence of septic shock was 404 (68.71%) and 155 (26.36%) based on the sepsis-1 and sepsis-3 definitions, respectively. In relation to the incidence of septic shock, there was no signification difference among the tertiles of sCD73 according to the sepsis-1 definition and sepsis-3 definition.

Relationship between sCD73 and septic shock

The results of the univariate and multivariate logistic regression model analyses are shown in *Table 2*. No relationship was found in the non-adjusted and minimally adjusted model (adjusted for age and gender) between sCD73 and septic shock. However, in the multiply adjusted model (adjusted for age, gender, lactate, SOFA score, systolic heart failure, emergency admission, operative admission, and AKI within 12 h) and the fully adjusted model (adjusted for all the covariates as set out in *Table 1*), sCD73 was negatively correlated with septic shock. After multiply adjustment, a 1 ng/mL increment in sCD73 was associated with a 5% lower incidence of septic shock [OR =0.95; 95% confidence interval (CI): 0.92, 0.98; P<0.001; see *Table 2*] based on the sepsis-1 definition and a 7% lower incidence septic shock (OR =0.93; 95% CI: 0.89, 0.97; P<0.001) based on the sepsis-3 definition.

We also considered sCD73 as a categorical variable (tertile) for the sensitivity analysis and discovered the similar trend (P value for the trend was 0.006; see *Table 2*). In the subgroup analysis, the test for the interactions was not statistically significant for age, gender, lactate, SOFA score, systolic heart failure, operative admission, and AKI within 12 h (see *Figure 1*). We did not observe any interactions in the subgroups (all P>0.05).

Discussion

In this study, we examined the relationship between sCD73 and the incidence of septic shock in severe sepsis patients. The multiply adjusted model revealed a negative correlation between sCD73 and the incidence of septic shock. When we treated sCD73 as a categorical variable, an almost linear relationship between sCD73 and the incidence of sepsis was observed.

CD73 plays a significant role in the local production

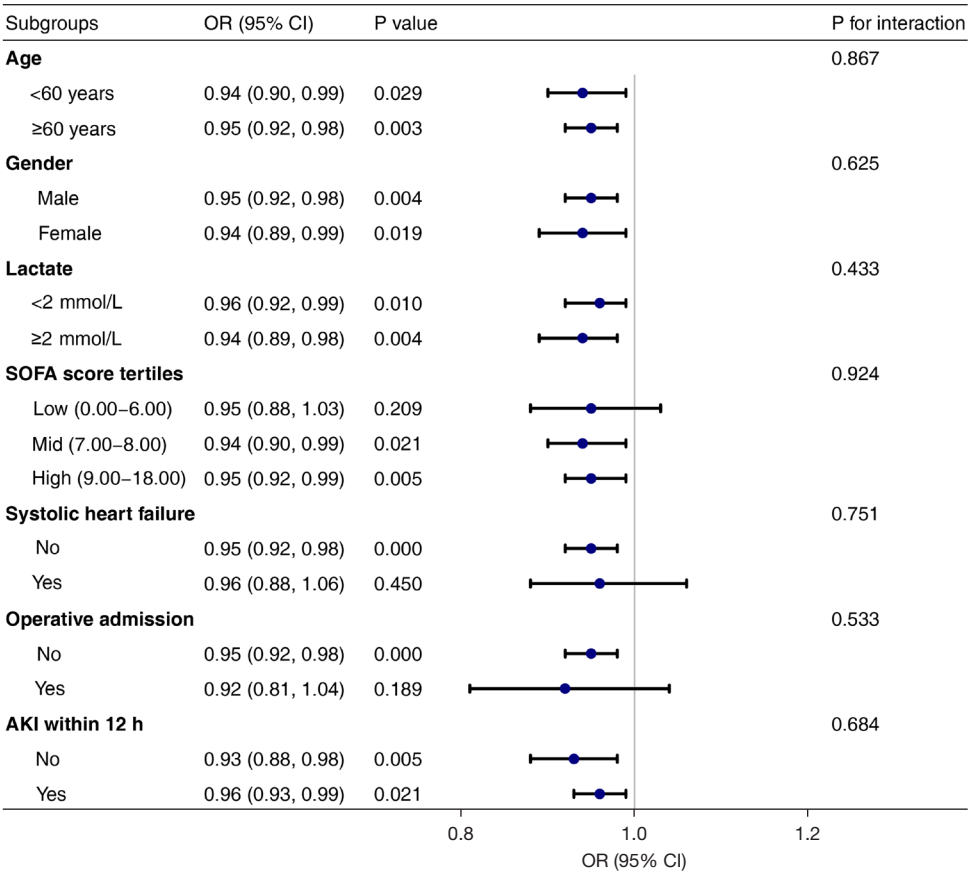

Figure 1 The relationship between sCD73 and the incidence of septic shock in the subgroup analysis based on the sepsis-1 definition. Note 1: adjusted for age, gender, lactate, SOFA score, systolic heart failure, emergency admission, operative admission, and AKI within 12 h. Note 2: in each case, the model was not adjusted for the stratification variable. sCD73, soluble cluster of differentiation-73; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury.

of anti-inflammatory adenosine. Previous research has shown that CD73 is important in the tumor immunoescape process (24). Further research has shown that, compared to that of wild-type sepsis mice, CD73 knock-out sepsis mice had an increased mortality rate, which was associated with increased inflammation (25). SCD73, which is the soluble form of CD73, can be detected in human plasma and exhibit adenosine monophosphatase (AMPase) activity like CD73 (26,27). In the original article, the way of detecting sCD73 protein concentration was reliable, and was correlated with the sCD73 activity in 42 randomly selected patient samples (16).

Sepsis is essentially an inflammation due to infection and organ damage (16). Cecconi *et al.* and Bavunoglu *et al.* reported that the inflammatory response represented by serum interleukin 6, tumor necrosis factor alpha, and oxidized low-density lipoprotein (oxLDL) levels were positively correlated with the severity of sepsis (28,29). In our study, the *in-vivo* anti-inflammatory activity of sCD73 was negatively associated with the incidence of septic shock independent of potential confounders. In 2014, Maksimow *et al.* also found that patients with acute pancreatitis had higher circulating levels of sCD73 than healthy individuals. However, the sCD73 levels at admission to hospital correlated inversely with the severity of acute pancreatitis (7). In the original research, participants were grouped in tertiles according to sCD73 levels. Vaara *et al.* found patients with severe sepsis did not differ from those with septic shock in sCD73 level (16). However, the analyses did not adjust for other covariates, and the independent association between sCD73 and the incidence of septic shock was not evaluated.

SCD73 may have therapeutic potential for sepsis, as a

higher sCD73 level is associated with a lower incidence of sepsis shock. In previous studies, authors found that in cultured endothelial cells and in human lung tissue explants, CD73 was upgraded by interferon-beta and was associated with increased adenosine production, improved endothelial barrier function, and reduced vascular leakage (30-32).

The subgroup analyses showed that our results were stable. As the sepsis-3 definition was published in 2016, we used a new definition if sepsis for sensitivity analysis, and the results were unchanged. Thus, our conclusions could be used in sepsis-3 definition.

The present study had some limitations. First, due to the nature of the cross-sectional study, we only examined the correlation of sCD73 with sepsis shock, and could not establish the cause-effect relationship between them. Second, only Finnish patients were enrolled in this study. In China, sCD73 is not routinely measured in patients with sepsis. Caution should be taken when generalizing the results of this study to other populations. Third, this study was a secondary analysis of data from a previously published study, and it is possible that some eligible patients were excluded in the original study.

Conclusions

SCD73 was negatively correlated with septic shock. Higher sCD73 was associated with a lower incidence of septic shock. This correlation deserves additional investigation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist Available at https://atm.amegroups.com/article/view/10.21037/atm-22-371/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-371/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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