

# Persistently higher serum sCD40L levels are associated with mortality in septic patients

**Yingjian Liang**

China Medical University Hospital

**Chengrui Zhu**

China Medical University Hospital

**Yini Sun**

China Medical University Hospital

**Zhiliang Li**

China Medical University Hospital

**Liang Wang**

China Medical University Hospital

**Yina Liu**

China Medical University Hospital

**Xin Li**

China Medical University Hospital

**xiaochun ma** (✉ [cmu1hcu2002@sina.com](mailto:cmu1hcu2002@sina.com))

China Medical University Hospital

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## Research article

**Keywords:** Soluble CD40 ligand, Sepsis, Mortality

**Posted Date:** July 6th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-39594/v1>

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**Version of Record:** A version of this preprint was published on January 22nd, 2021. See the published version at <https://doi.org/10.1186/s12871-021-01241-9>.

# Abstract

## Background

Soluble CD40 ligand (sCD40L) exhibits proinflammatory and procoagulant effects. Recent data indicated that sCD40L plays a significant role in septic patients. The aim of the present study was to determine sCD40L changes in surgical patients without sepsis (SWS) and in surgical sepsis patients (SS) during the first three days at Intensive Care Unit (ICU) admission, and to observe the association between sCD40L and mortality.

## Methods

Time changes in sCD40L levels were assessed for 3 days after ICU admission in 49 patients with SS and compared with 19 SWS. Serum sCD40L concentration was detected by ELISA. Survival at 28-days was used as the endpoint.

## Results

SS had significantly higher sCD40L levels than SWS and control patients. Advanced age ( $P = 0.023$ ) was observed in the group of nonsurviving patients compared with surviving SS. We observed an association between sCD40L levels  $\geq 1028.75$  pg/ml at day 2 and 28-days mortality (odds ratio = 7.888; 95% confidence interval = 1.758 to 35.395;  $P = 0.007$ ).

## Conclusions

Septic patients show persistently higher circulating sCD40L levels in the first three days at ICU admission, and it is likely that sCD40L on the day 2 may have a predictive value; thus, serum sCD40L could be used as a reliable biomarker and therapeutic target in sepsis.

## Background

Sepsis is the overwhelming inflammatory host response to the infectious agent causing the over-expression of inflammatory mediators(1). Moreover, sepsis is also almost associated with coagulation abnormalities, present as manifest thromboembolic disease or clinically less apparent microvascular fibrin deposition(2). In sepsis, inflammation and coagulation are extensive cross-talk, which promotes the progress of disease and leads to organ dysfunction(3).

CD40 ligand (CD40L) and the soluble form of CD40L (sCD40L) are members of the tumor necrosis factor (TNF) family, they expressed in a diversity of cell types including B cells, epithelial cells, fibroblasts, endothelial cells (ECs), as well as in platelets. CD40L and sCD40L exhibit proinflammatory and

procoagulant effects(4, 5). Previous studies have found higher sCD40L levels in sepsis patients and that sCD40L levels are associated with mortality(6–8). Lorente's study also showed that persistent higher of sCD40L in sepsis patients at 1, 4 and 7 days predicted poor prognosis(9).

Surgical patients suffer from endothelial cell damage after surgery, postoperative inflammatory and blood coagulation changes will happen. Therefore, the purpose of this study was to determine sCD40L changes in surgical patients without sepsis (SWS)and in surgical sepsis patients (SS) during the first three days at ICU admission, and to observe the relationship between sCD40L and mortality.

## Methods

### Design and subjects

This was a prospective, observational study. 68 patients were enrolled in Intensive Care Unit of the first affiliated hospital, China Medical University from October 1, 2013 to February 28, 2014. These patients included 49 SS and 19 SWS. 6 healthy controls were selected in the meanwhile. The Ethical Committee of the First Affiliated Hospital of China Medical University approved this study and the informed consents were signed by patients' family members.

Sepsis and septic shock were diagnosed according to the Surviving Sepsis Campaign guidelines committee 2012(10). Exclusion criteria were pregnancy, or age  $\geq$  18 years.

### Variables recorded

In all the patients, age, sex, Acute Physiology and Chronic Health Evaluation  $\text{\AA}$  (APACHE  $\text{\AA}$ ) score, Sepsis-related Organ Failure Assessment (SOFA) score, sCD40L, International Society on Thrombosis and Haemostasis (ISTH) score, Japanese Association for Acute Medicine (JAAM) score, platelets, prothrombin time international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT), fibrinogen, D-Dimer, Fibrinogen degradation product (FDP), leukocytes, lactate, site of infection were recorded. Survival at 28 days was used as the endpoint of our study.

### Blood samples

For patients, blood samples were drawn on the day 1, 2 and 3 at ICU admission. For healthy controls fasting blood samples were taken at 8:00 am. Serum blood samples were centrifuged at 1500 g for 15 minutes. Temperature was kept at 4°C in all steps after blood collection. Aliquots were stored at -80°C for further analysis. Samples were thawed only once.

### Soluble CD40L determination

Serum sCD40L concentration was detected by enzyme-linked immunosorbent assays $\text{\AA}$ (ELISA) Usn Life Science Inc, China $\text{\AA}$ . Each sample was measured and made duplicate. The detection limits was 6.1 pg/mL. The intra-test variability among the duplicate items of all samples was less than 10%.

## Statistical analysis

Continuous variables were analyzed as medians and inter-quartiles (IQ) 25% and 75% (Q25-Q75), and categorical variables as frequencies and percentages. Significant differences of continuous variables between groups were analyzed using Mann-Whitney U test, and categorical variables were calculated by chi-square test and Fisher's exact test, as appropriate.

Receiver operating characteristic (ROC) curves were used for analyzing serum sCD40L levels at days 1, 2 and 3 and selecting cut off values. Survival analysis was performed with Kaplan-Meier method curves. Multiple logistic regression analysis was applied to predict 28 days mortality. To determine the association between serum levels of sCD40L and other continuous variables at days 1, 2 and 3, Spearman's rank correlation coefficient was used. All p values  $\leq 0.05$  were considered statistically significant. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

## Results

### Patient characteristics

Baseline characteristics of 49 SS, 19 SWS and 6 age- and sex-matched healthy controls were shown in Table 1. The levels of sCD40L in healthy controls were 469.50 (406.83-547.36) pg/ml, and the sCD40L levels in SWS and SS were significantly increased, and the difference between the two groups was statistically significant (Table 1,  $P = 0.000$  vs healthy controls). In addition, compared with SWS, SS also exhibited a higher incidence of higher APACHE-II ( $P = 0.001$ ), SOFA ( $P \leq 0.001$ ), ISTH ( $P \leq 0.001$ ) and JAAM ( $P \leq 0.001$ ) scores, higher PT-INR ( $P = 0.001$ ), fibrinogen ( $P = 0.022$ ), FDP ( $P \leq 0.001$ ), D-dimer ( $P \leq 0.001$ ), lactate ( $P = 0.006$ ), and 28 days mortality ( $P = 0.001$ ) (Table 1).

Table 1  
Baseline demographic and clinical characteristics of the studied population group

	<b>Healty control</b> <b>n = 6</b>	<b>SS</b> <b>n = 19</b>	<b>SWS</b> <b>n = 49</b>	<b>P</b>
Sex(male/female)	3/3	12/7	34/15	0.586
Age(years)-median(p25-p75)	53.00(42.25-62.00)	76.00(71.00–81.00)	61.00(45.00–73.00)	0.005
sCD40L(pg/ml)-median(p25-p75)	469.50(406.83-547.36)	831.36(526.58-981.72)	1022.68(554.85-2215.13)	0.000
APACHE II score-median(p25-p75)		9.00(7.00–11.00)	14.00(11.00–16.00)	0.001
SOFA score-median(p25-p75)		1.00(0.00–2.00)	8.00(6.00–10.00)	0.000
ISTH score-median(p25-p75)		0.00(0.00–2.00)	3.00(2.50–4.50)	0.000
JAAM score-median(p25-p75)		1.00(0.00–2.00)	4.00(3.00–5.00)	0.000
PT-INR-median(p25-p75)		1.16(1.12–1.34)	1.41(1.21–1.66)	0.001
aPTT(seconds)-median(p25-p75)		41.10(36.10–81.40)	49.40(41.55–60.85)	0.080
fibrinogen(g/L)-median(p25-p75)		3.10(1.96–3.60)	3.94(2.50–5.88)	0.022
FDP(ug/dl)-median(p25-p75)		5.46(3.60-13.42)	21.81(12.24–48.66)	0.000
D-Dimer(ug/ml)-median(p25-p75)		1.71(0.80–3.58)	4.81(3.24–10.11)	0.000
platelet-median*10 <sup>3</sup> /mm <sup>3</sup> (p25-p75)		157.00(136.00-191.00)	136.00(77.00-214.50)	0.305
leukocytes-median*10 <sup>3</sup> /mm <sup>3</sup> (p25-p75)		7.87(5.28–11.90)	10.62(7.50-15.44)	0.030
Lactate(mmol/L)-median(p25-p75)		1.50(0.90–1.80)	2.00(1.30–3.90)	0.006
28 days mortality(%)		0/19(0)	20/49(40.82)	0.000
SWS = surgical patients without sepsis; SS = surgical sepsis patients; P 25–75 = percentile 25th-75th ; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sepsis-related Organ Failure Assessment; ISTH = Thrombosis and Haemostasis, JAAM = Japanese Association for Acute Medicine; PT-INR = prothrombin time international normalized ratio; aPTT = activated partial thromboplastin time; FDP = Fibrinogen degradation product				

## Demographic and clinical characteristics of non-survivor and survivor in surgical sepsis patients

In SS, 20 patients died and 29 patients survived, all of whose demographic and clinical features are shown in Table 2 and supply Table 1. Non-surviving had higher serum sCD40L ( $P = 0.009$ ), aPTT than surviving patients at day 2 ( $P = 0.020$ ) and higher lactate at day 3 ( $P = 0.001$ ). besides, higher age ( $P = 0.023$ ) was observed in the group of non-surviving compared with surviving SS. We couldn't discover any significant differences in gender, presence of septic shock and the site of infection between non-survivor and survivor. In addition, on day1, 2, 3 at ICU admission, there were no statistically significant differences in APACHE II score, SOFA score, ISTH score, JAAM score, PT-INR, fibrinogen, FDP, D-dimer, platelet and leukocytes between the non-surviving and surviving groups of SS.

Table 2  
Biochemical characteristics of survivor and nonsurvivor surgical sepsis patients on day 2 of ICU admission

	Survivor(n = 29)	Non-survivor(n = 20)	P
Gender(male/female)	22/7	12/8	0.236
Age(years)-median(p25-p75)	56.00(31.50–64.00)	71.00(52.25–77.25)	0.023
Septic shock	17(58.6%)	10(50.0%)	0.551
Site of infection			0.508
Abdominal - n (%)	5(17.2%)	5(25.0%)	
Respiratory - n (%)	24(82.8%)	15(75.0%)	
APACHE II score-median(p25-p75)	12.00(8.00-16.50)	14.00(11.25-17.00)	0.156
SOFA score-median(p25-p75)	6.00(5.00–10.00)	8.50(6.00–10.00)	0.216
ISTH score-median(p25-p75)	4.00(2.00–5.00)	3.00(3.00-4.75)	0.901
JAAM score-median(p25-p75)	4.00(2.50-5.00)	4.00(2.50–4.75)	0.835
PT-INR-median(p25-p75)	1.36(1.25–1.72)	138.5(128.25-170.75)	0.760
aPTT(seconds)-median(p25-p75)	51.00(43.60-66.95)	68.65(53.20-113.95)	0.020
fibrinogen(g/L)-median(p25-p75)	3.74(2.55–6.70)	2.83(1.70–4.78)	0.106
FDP(ug/dl)-median(p25-p75)	16.96(10.43–33.01)	20.40(7.37–32.33)	0.823
D-Dimer(ug/ml)-median(p25-p75)	3.96(2.95–7.61)	3.86(2.19–7.86)	0.502
platelet- median*10 <sup>3</sup> /mm <sup>3</sup> (p25-p75)	109.00(47.00-191.00)	124.50(65.25-174.25)	0.903
leukocytes-median*10 <sup>3</sup> /mm <sup>3</sup> (p25-p75)	13.71(6.83–17.93)	13.91(9.06–19.22)	0.376
Lactate(mmol/L)-median(p25-p75)	2.10(1.30–3.15)	2.75(1.65–5.60)	0.203
sCD40L(pg/ml)-median(p25-p75)	747.21(422.46-981.47)	1214.72(696.28-2089.57)	0.009
<p>P 25–75 = percentile 25th-75th ; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sepsis-related Organ Failure Assessment; ISTH = Thrombosis and Haemostasis, JAAM = Japanese Association for Acute Medicine; PT-INR = prothrombin time international normalized ratio; aPTT = activated partial thromboplastin time; FDP = Fibrinogen degradation product</p>			

## Predictive Factors For 28 Days Mortality

The area under the curve (AUC) for serum sCD40L levels at day 2 (95% confidence interval (CI) = 0.570–0.871, P = 0.009) could predict mortality at 28 days, the sensitivity and specificity approached to 60.0% and 79.3%, respectively (Fig. 1). Kaplan-Meier survival analysis showed that patients with higher serum sCD40L levels at day 1 (P = 0.035), day 2 (P = 0.005), day 3 (P = 0.003) had a risk of death at 28 days than patients with lower levels (Fig. 2). In addition, patients age  $\geq$  65 years (odds ratio = 7.929; 95% CI = 1.809 to 34.750; P = 0.006) and serum sCD40L levels at day 2  $\geq$  1028.75 pg/ml (odds ratio = 7.888; 95% CI = 1.758 to 35.395; P = 0.007) were significant predictive factors for 28-days mortality in multiple logistic regression analysis.

### Association between sCD40L levels and other clinical parameters in patients with surgical sepsis

Besides, no relationship was observed between serum sCD40L levels and APACHE II, SOFA, ISTH, JAAM score, PT-INR, fibrinogen, FDP, D-dimer, leukocytes, platelet and lactate in the group of SS on day1, 2, 3 at ICU admission (Table 3).

Table 3

Association between sCD40L levels and other clinical parameters in patients with surgical sepsis

	sCD40L day1		sCD40L day2		sCD40L day3	
	Rho	P	Rho	P	Rho	P
APACHE II score	-0.215	0.138	-0.045	0.761	-0.208	0.151
SOFA score	-0.158	0.279	-0.073	0.617	0.069	0.639
ISTH score	0.016	0.914	-0.051	0.726	0.098	0.501
JAAM score	-0.016	0.916	0.016	0.912	0.216	0.136
PT-INR	0.146	0.318	0.166	0.255	0.055	0.708
aPTT	0.132	0.367	-0.027	0.851	-0.043	0.769
fibrinogen	-0.092	0.529	-0.065	0.655	-0.202	0.163
FDP	0.131	0.370	0.137	0.347	0.085	0.562
D-Dimer	0.171	0.240	0.077	0.600	0.069	0.636
platelet	0.046	0.752	0.122	0.405	-0.003	0.983
leukocytes	0.223	0.124	0.158	0.277	0.061	0.679
lactate	-0.050	0.733	0.194	0.181	0.111	0.447

APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sepsis-related Organ Failure Assessment; ISTH = Thrombosis and Haemostasis, JAAM = Japanese Association for Acute Medicine; PT-INR = prothrombin time international normalized ratio; aPTT = activated partial thromboplastin time; FDP = Fibrinogen degradation product

## Discussion

It can be concluded from this study that serum sCD40L levels of SS persistently increased significantly in the first three days after admission to the intensive care unit, and the circulating sCD40L higher on the second day of admission in non-surviving than in surviving group. A novel finding of this study was that SWS also has a slight increase in sCD40L, but not as much as in SS.

Several studies have reported that sCD40L level can predict the prognosis of patients with sepsis(8, 11). In our study, we found that serum sCD40L levels  $\geq 1028.75$  pg/mL at day 2 were associated with higher death risk during the 28-days period in the multiple logistic regression analysis. Serum sCD40L levels could be used as 28-days mortality biomarker. However, we did not find a relationship between sCD40L levels and sepsis severity criteria such as, APACHE II score, SOFA score. We only observed higher lactatemia in non-surviving than in surviving SS at day 3 admission. The serum blood samples were obtained at admission to ICU, but APACHE II or SOFA was calculated at 24 hours of admission to ICU, we were not sure if this time-gap can affect the association between the two variables.

sCD40L with a dual prothrombotic and proinflammatory role. The sCD40L connects to circulating monocytes through its receptor CD40, promoting their adhesion to vascular endothelium. The sCD40L also binds to CD40 on endothelial cell surfaces. Studies have shown that sCD40L stimulates its own expression by interacting with CD40 on the surface of these cells(12). In sepsis, EC activation induced adhesion receptors, released inflammatory mediators such as interleukin(IL)-1, IL-6 and tumor necrosis factor(13, 14). sCD40L also effect on neutrophil oxidative burst and neutrophil extracellular trap(5, 15). Previous studies and our studies suggested that sCD40L has no correlation with other coagulation factors except tissue factor(TF)(8). The main reason was that activated ECs initiate the exogenous coagulation pathway by up-regulating TF and down-regulating the expression of thrombomodulin(16), favoring a local procoagulant status. In experimental models, sCD40L enhanced platelet activation and aggregation and induced thrombus formation(17). All these effects contribute to the development of organ dysfunction and death(18). After intraoperative operation, the ECs were damaged, and the body produced stress response and inflammatory factors(19). Therefore, sCD40L level was also increased after operation in patients with non-sepsis. In patients with sepsis, EC damage, intravascular microthrombus formation and production of inflammatory factors are more obvious, and sCD40L level is much higher than that in patients with simple surgery.

We have not found an association between serum sCD40L levels and platelet count, although 95% of sCD40L was derived from platelets(20). CD40L is stored in  $\alpha$ -granules in unstimulated platelets, which undergo conformational changes during platelet activation, migrates to the surface of platelets and releases into the blood(21). Soluble CD40L can enhance platelet activation, aggregation, and platelet-leukocyte conjugation. Therefore, sCD40L was shown to be implicated in platelet activated(12). Activated platelets via interaction with ECs play a key role in inflammatory and pro-coagulant response to a pathogen(22).

There were some limitations in our study. First, the sample size was relatively small. Second, the subjects came from a single center. Third, we only determined sCD40L levels admission in ICU for 3 days, but did not observe it for a week or longer, unable to better conclude the time course of serum sCD40L levels in sepsis patients. And finally, there are been reported an association between sCD40L levels and the activation function of platelets; we have not examined markers of platelet activation to analyzed a relationship with sCD40L levels.

## Conclusions

Septic patients exhibit persistently higher circulating sCD40L levels in the first three days at ICU admission, and it is likely that sCD40L on the day 2 may have a predictive value; thus, serum sCD40L could be used as a reliable biomarker and therapeutic target in sepsis.

## Abbreviations

CD40L CD40 ligand

sCD40L soluble CD40 ligand

TNF tumor necrosis factor

ECs endothelial cells

SWS surgical patients without sepsis

SS surgical sepsis patients

APACHE  $\square$  acute physiology and chronic health evaluation  $\square$

SOFA sepsis-related organ failure assessment

ISTH international society on thrombosis and haemostasis

JAAM Japanese association for acute medicine

PT-INR prothrombin time international normalized ratio

aPTT activated partial thromboplastin time

FDP Fibrinogen degradation product

## Declarations

## Ethics approval and consent to participate:

The Ethical Committee of the First Affiliated Hospital of China Medical University approved this study and the informed consents were signed by patients' family members.

**Consent for publication:**

Not applicable.

**Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:**

The authors declare that they have no competing interests.

## **Funding:**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## **Authors' contributions:**

YJL and XM participated in the conception of the idea, conduct of the study, and preparation of the manuscript. CZ, YS, ZL provided data collection and critical revision. LW, YNL, XL participated in data analysis and critical revision. All authors reviewed and approved the submitted form of this manuscript.

## **Acknowledgements:**

Not applicable.

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## Figures

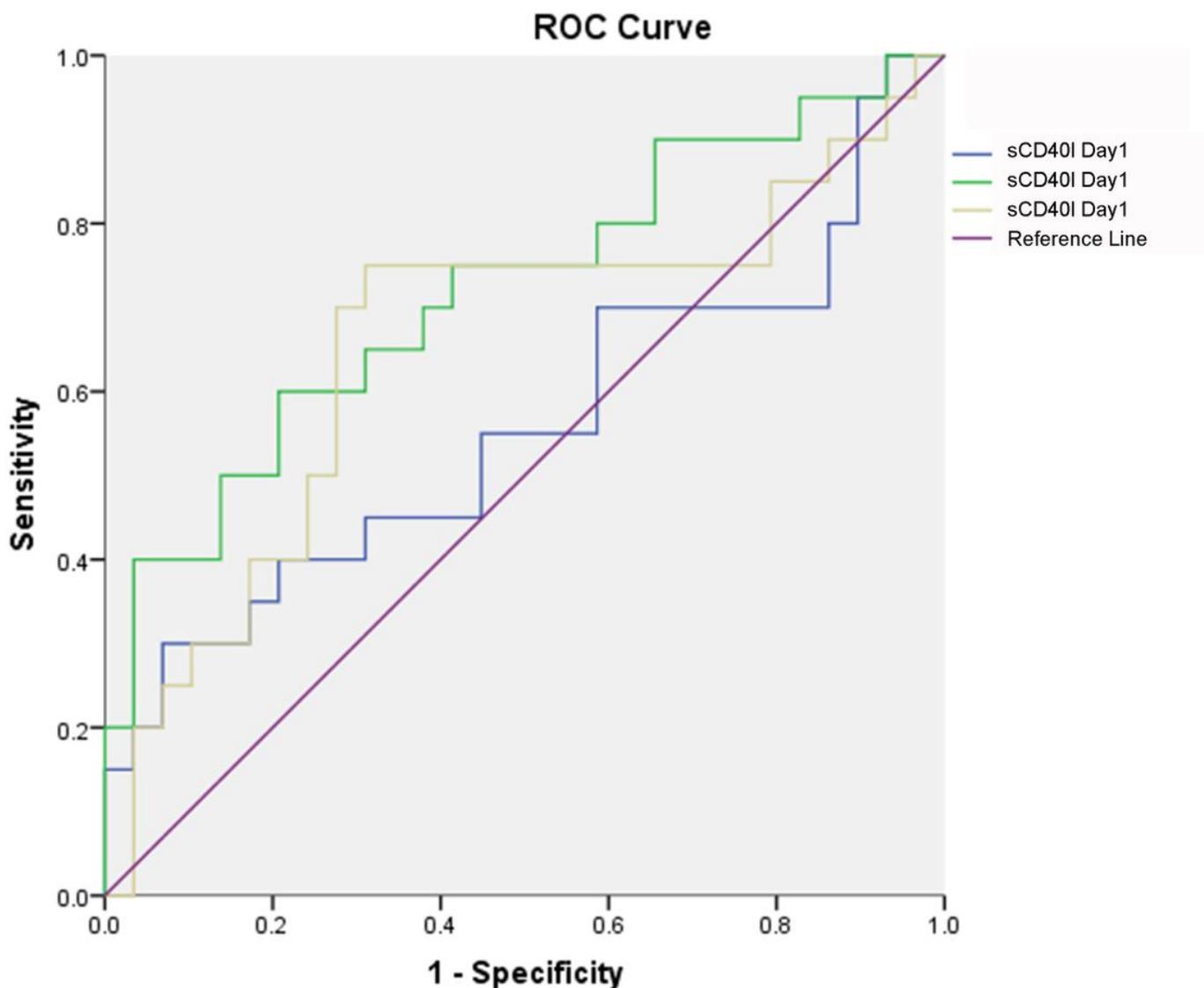
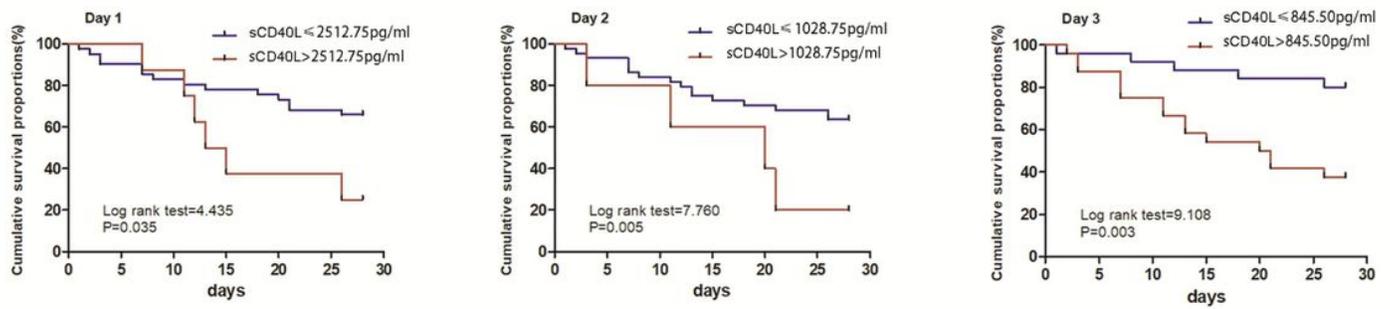


Figure 1

Receiver operation characteristic analysis using sCD40L levels  $\geq 1028.75\text{pg/mL}$  at day 2 as 28-days mortality predictor



**Figure 2**

Curves of survival at 28-days according to serum sCD40L levels at day 1, 2 and 3 of surgical sepsis patients admission to ICU

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaltable1.docx](#)