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High serum OX40 ligand correlates with severity and mortality in patients with massive cerebral infarction

Lun-Lin Mao, MM[a,b], Wen-Ya Chen, BM[a,b,*], Ai-Jin Ma, BM[a,b], Li-Li Ji, MM[a,b], Ting-Ting Huang, MM[a,b]

Abstract

OX40 ligand (OX40L) is a member of tumor necrosis factors (TNF)/TNFR superfamily and is mainly expressed in activated T cells and participates in various inflammatory reactions. However, it remains unclear about the role of serum OX40L as a biomarker of cerebral infarction (CI). This study aimed to explore the possibility of serum OX40L as a meaningful predictor in mortality of CI. Severe CI patients were included to collect clinicopathological and laboratory data and measure serum OX40L level. Patients were followed up after discharge and 60-day survival rate was used as the study endpoint. The results showed that of all 294 patients, 123 (41.8%) died within 60 days after admission. Serum OX40L levels were significantly higher in patients with severe CI compared to healthy controls, and were significantly higher in nonsurvivors compared to survivors ($P < .05$). The levels of OX40L were correlated with Glasgow Coma Scale score, serum creatinine and high-sensitive C-reactive protein. Multivariate logistic regression analysis showed that serum OX40L level was an independent prognostic factor for 60-day mortality, after control of pulmonary infection, glasgow coma scale score and high-sensitive C-reactive protein (odds ratio = 1.089; 95% confidence interval = 1.053–1.126; $P < .001$). The receiver operating characteristic (ROC) curve was used to predict the best cut-off of serum OX40L for 60-day survival as 35.5 ng/mL. Patients with high serum OX40L levels (>35.5 ng/mL) had a significantly higher mortality within 60 days (hazard ratio = 2.885; 95% confidence interval = 1.901–4.378). In conclusion, OX40L is a serum biomarker of patients with CI and associated with severity and mortality of this disease.

Abbreviations: ACI = atherosclerotic cerebral infarction, CI = cerebral infarction, hs-CRP = high-sensitive C-reactive protein, OX40L = OX40 ligand, TNF = tumor necrosis factors, WBC = white blood cells.

Keywords: biomarker, cerebral infarction, ischemic stroke, OX40 ligand

1. Introduction

Cerebral infarction (CI) is 1 common ischemic stroke associated with severe health burden, disability and mortality.[1] In CI, blood clots cause cerebral blood flow disruption and blood vessel obstruction, resulting in local brain tissue ischemia and cell death. In addition, CI is often accompanied by secondary lesions such as inflammation, apoptosis, oxidative stress, increased vascular permeability, and cerebral edema, which further promote neural cell death.[2] A key pathophysiological process of ischemic stroke is inflammatory response, especially in the acute phase after the onset of CI, accompanied by higher concentration of proinflammatory cytokines, such as C-reactive protein (CRP).[3,4] Then the blood-brain barrier is damaged, which in turn activates peripheral immune cells such as neutrophils and T cells to infiltrate and accumulate in ischemic brain area.[5] Inflammation may play a dual role in ischemic brain tissue. It may promote inflammation of the brain through inflammatory mediators and increase tissue damage. It may also facilitate the repair process by accelerating the removal of necrotic debris.[6] Increasing evidence has confirmed that smaller infarct size and better clinical outcomes can be achieved by reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines, and suggests that the prognosis is determined by the balance between inflammatory and anti-inflammatory cytokines.[7] Therefore, biomarkers of proinflammatory or anti-inflammatory cytokines may be an early diagnostic and prognostic indicator of ischemic stroke.

OX40 ligand (OX40L, CD252) and its receptor OX40 (CD134) are members of TNF superfamily.[8] OX40L is mainly expressed by immune cells, such as B cells, macrophages and dendritic cells.[9] Rosuvastatin is an effective drug for controlling atherosclerosis. Recent studies have reported that rosuvastatin significantly reduced OX40L expression in peripheral blood lymphocyte and plasma soluble OX40L in patients with atherosclerotic CI (ACI).[10] This suggests that OX40/OX40L may promote atherosclerosis in ACI

Editor: Leyi Wang.

This research was approved by the ethics committee of Wujin Hospital Affiliated to Jiangsu University. All participants provided written informed consent.

This study was supported by: (1) Major scientific and technological projects of Changzhou health Commission (ZD201820); (2) Science and technology support plan of Changzhou Wujin District: social development (WS201916).

The authors have no conflicts of interest to disclose.

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

[a] Department of Neurology, Wujin Hospital Affiliated to Jiangsu University, [b] The Wujin Clinical College of Xuzhou Medical University, Changzhou, Jiangsu, P.R. China.

[*] Correspondence: Wen-Ya Chen, Department of Neurology, Wujin Hospital Affiliated to Jiangsu University, No.2 North YongNing Road, Changzhou 213002, Jiangsu Province, China (e-mail: chenwenyajs@163.com).

How to cite this article: Mao LL, Chen WY, Ma AJ, Ji LL, Huang TT. High serum OX40 ligand correlates with severity and mortality in patients with massive cerebral infarction. Medicine 2020;99:29(e20883).

Received: 27 June 2019 / Received in final form: 22 April 2020 / Accepted: 19 May 2020

http://dx.doi.org/10.1097/MD.0000000000020883

patients. However, the clinical significance of serum OX40L in patients with CI is unclear.

In this study, we measured serum soluble OX40L concentration and analyzed its relationship with clinical severity and mortality in patients with CI. Our study will identify OX40L as a serum biomarker for predicting prognosis in patients with CI.

2. Materials and methods

2.1. Subjects

A prospective study was conducted in 294 patients with acute CI. They were admitted to the Department of Neurology in Wujin Hospital Affiliated to Jiangsu University, from January 2014 to December 2017. The diagnosis of massive CI was confirmed by computed tomography or magnetic resonance imaging. The severity of CI was evaluated according to Glasgow Coma Scale (GCS), and the severe CI was defined as when GCS$\leq$9.[11] Exclusion criteria included previous ischemic stroke, intracerebral hemorrhage or subarachnoid hemorrhage, brain tumor, infectious brain disease, and previous brain trauma. The clinical data, medical history and laboratory indicators were recorded for patient. Serum of 120 gender and age-matched healthy donors were selected as controls. All patients were regularly followed-up for at least 60 months. The study was approved by the ethics committee of Wujin Hospital Affiliated to Jiangsu University and conducted in accordance with the Declaration of Helsinki. The patient or family member signed the informed consent.

2.2. Measurement of clinical and laboratory variables

We recorded the following clinical variables for each patient: gender, age, atrial fibrillation, hypertension, pulmonary infection, cardiac insufficiency, diabetes, and hyperlipidemia. The acute physiology and immunological chronic health assessment II score was used to estimate systemic organ damage. The patient's laboratory variables were measured: white blood cells, platelets, lactic acid, glucose, creatinine, and high-sensitive C-reactive protein (hs-CRP). The end point study was a 60-day mortality rate.

2.3. ELISA detection of serum OX40L

Blood samples were collected within 24 hours of hospital admission to separate serum, and stored at -80°C. Serum OX40L levels were measured by ELISA using Human Soluble OX40L kit (Abebio; cat. no. AE13973HU), and absorbance at 450 nm was measured with a microplate reader. OX40L concentrations were calculated according to the standard curve established by different concentrations of recombinant human OX40L, and expressed as pg/mL for each case.

2.4. Statistical analysis

SPSS19.0 statistical software was used to analyze the data. Continuous variables were presented as median (interquartile range) and analyzed using the Wilcoxon-Mann-Whitney test. Categorical variables were presented as frequency (percentage) and analyzed using the chi-square test. The correlation between OX40L and continuous variables was analyzed using the Spearman's rank correlation test. Multivariate logistic regression analysis determine the independent contribution of OX40L on mortality, and expressed as odds ratio and the 95% confidence interval. The receiver operating characteristic curve was plotted to determine the cut-off point of serum OX40L between the survivors and the nonsurvivors. Kaplan-Meier curves were used to analyze the effect of high serum OX40L levels ($\geqq$35.5 pg/mL) on 60-day mortality in patients with CI. $P < .05$ was considered as a significant criterion for the difference.

3. Results

3.1. Baseline characteristics of study samples

Of the 294 patients with CI, the median age was 79 years old, with 121 males and 173 females. The clinical pathological

Table 1

Characteristics of the study population.

Characteristics	Cerebral infarction n = 294	Survivors n = 171	Nonsurvivors n = 123	*P* value
Male sex[†]	121 (41.2%)	72 (42.1%)	49 (39.8%)	.697
Age (yr)[*]	79 (73–84)	79 (72–84)	80 (73–85)	.576
Atrial fibrillation[†]	213 (72.4%)	118 (69.0%)	95 (77.2%)	.119
Hypertension[†]	219 (74.5%)	124 (72.5%)	95 (77.2%)	.360
Pulmonary infection[†]	152 (51.7%)	77 (45.0%)	75 (61.0%)	.007
Cardiac insufficiency[†]	105 (35.7%)	54 (31.6%)	51 (41.5%)	.081
Diabetes mellitus[†]	44 (15.0%)	29 (17.0%)	15 (12.2%)	.259
Hyperlipidemia[†]	31 (10.5%)	17 (9.9%)	14 (11.4%)	.692
GCS score	6 (5–8)	7 (6–8)	6 (4–7)	<.001
APACHE II score[*]	22 (19–23)	21 (19–23)	22 (19–24)	.195
WBC (10^3 cells/μL)[*]	7 (6.4–7.8)	6.9 (6.3–7.8)	7.4 (6.4–8.3)	.037
Platelets (10^3 cells/μL)[*]	147 (128–164)	148 (130–168)	143 (124–158)	.010
Lactic acid (mmol/L)[*]	2.65 (2.33–3.1)	2.66 (2.36–3.09)	2.64 (2.29–3.1)	.751
Glucose (mmol/L)	6.2 (5.4–7.1)	6.2 (5.5–7.1)	6.1 (5.1–7)	.186
Creatinine (μmol/L)[*]	92 (74–109)	87 (69–107)	95 (77–111)	.025
hs-CRP (pg/mL)[*]	2.6 (2.3–2.9)	2.6 (2.2–2.8)	2.7 (2.3–3.1)	<.001
OX40L (ng/mL)[*]	37 (32–43)	35 (29–41)	41 (36–46)	<.001

APACHE = Acute Physiology and Chronic Health Evaluation, GSC = Glasgow Coma Scale, hs-CRP = high sensitive C-reactive protein, WBC = white blood cell count.

[*] Continuous variable are expressed as median (25th to 75th percentiles) and analyzed by Mann-Whitney *U* test.

[†] Categorical Variable are expressed as frequency (%) and analyzed by Chi-squared test.

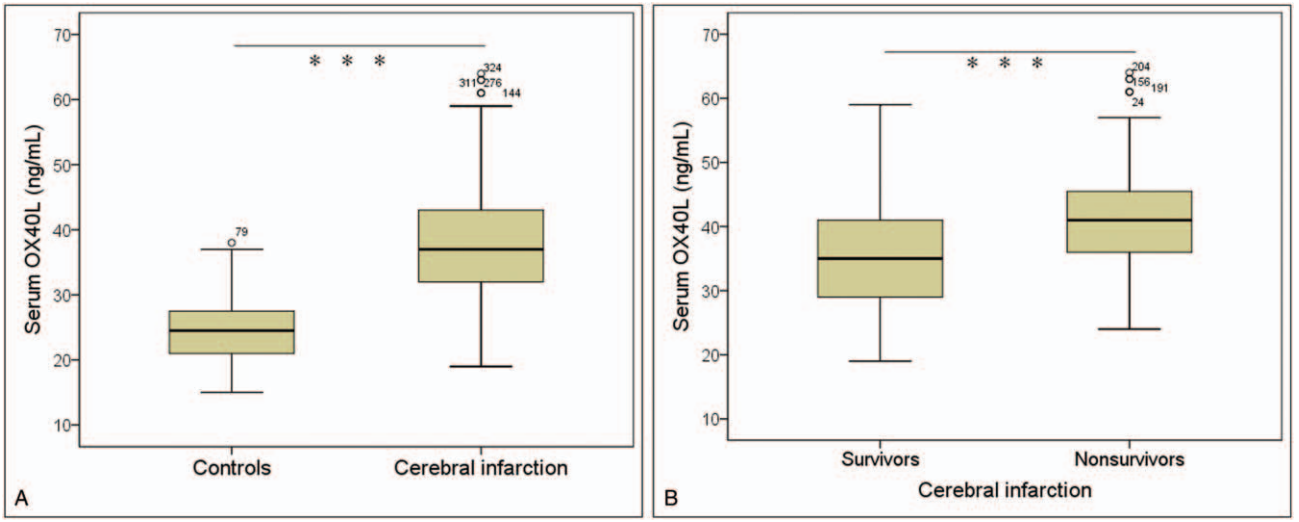

Figure 1. Serum OX40L levels in healthy controls and patients with cerebral infarction. (A) Serum OX40L levels were higher in patients with cerebral infarction (n = 294) than in healthy controls (n = 120) ($P < .001$). (B) Serum OX40L levels were higher in the nonsurvivors (n = 123) than in the survivors (n = 171). $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. OX40L = OX40 ligand.

features of CI admission are shown in Table 1. Within 60 days after onset, 123 patients died and the mortality rate was 41.8%. These nonsurvivors had significantly higher white blood cells, serum creatinine and hs-CRP levels, and significantly lower GCS scores and platelets compared to survivors (all $P < .05$). At the same time, nonsurvivors had a higher frequency of pulmonary infection than survivors (all $P < .05$).

3.2. Serum OX40L levels were elevated in CI patients

We measured serum OX40L concentrations by ELISA assay. Patients with CI (median 37 ng/mL) had significantly elevated serum OX40L levels than the control group (median 24.5 ng/mL) ($P < .001$) (Fig. 1A). In patients with CI, serum OX40L levels were significantly higher in nonsurvivors (median 41 ng/mL) than in survivors (median 35 ng/mL) ($P < .001$) (Fig. 1B).

3.3. Correlations of serum OX40L with clinical variables of CI

We performed Spearman rank correlation test to determine the associations of OX40L with clinical severity of CI. Serum OX40L correlated negatively to GCS score ($r = 0.161$, $P = .006$) (Fig. 2A), and correlated positively to serum creatinine ($r = 0.198$, $P = .001$) (Fig. 2B) and hs-CRP ($r = 0.167$, $P = 0.004$) (Fig. 2C).

3.4. Serum OX40L predicted 60-day mortally of CI

Multivariate logistic regression analysis demonstrated that serum OX40L level is an independent contributor of 60-day mortality after controlling for pulmonary infection, GCS score and hs-CRP (odds ratio = 1.089; 95% confidence interval = 1.053–1.126; $P < .001$) (Table 2). Receiver operating characteristic (ROC) curve was plotted to determine the cut-off point of serum OX40L was 35.5 ng/mL (sensitivity = 76.4%, specificity = 56.1%), so as to differentiate survivors and nonsurvivors (Fig. 3A). It was found that serum OX40L levels predicted a 60-day mortality area (AUC) of 0.701% (95% confidence interval = 0.642–0.760; $P < .001$). Using the Kaplan-Meier curve for survival analysis, patients with serum OX40L levels above 35.5 ng/mL showed a significantly higher 60-day mortality rate (hazard ratio = 2.885; 95% confidence interval = 1.901–4.378; Log Rank = 19.569; $P < .001$) (Fig. 3B).

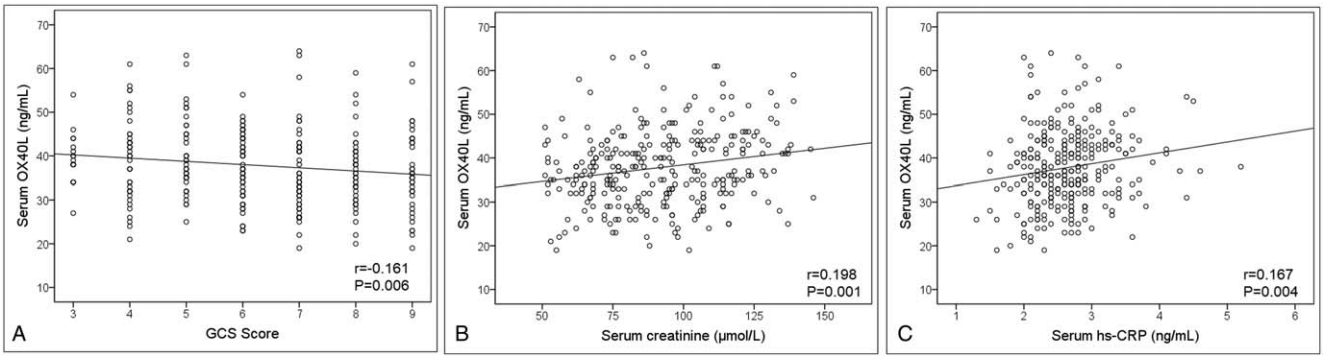

Figure 2. Correlation of serum OX40L to disease severity in cerebral infarction patients. Serum OX40L levels are negatively correlated with (A) GCS score ($r = 0.163$, $P = .005$), are positively correlated with (B) serum creatinine ($r = 0.198$, $P = .001$) and (C) hs-CRP ($r = 0.167$, $P = .004$). Spearman rank correlation test was performed. OX40L = OX40 ligand.

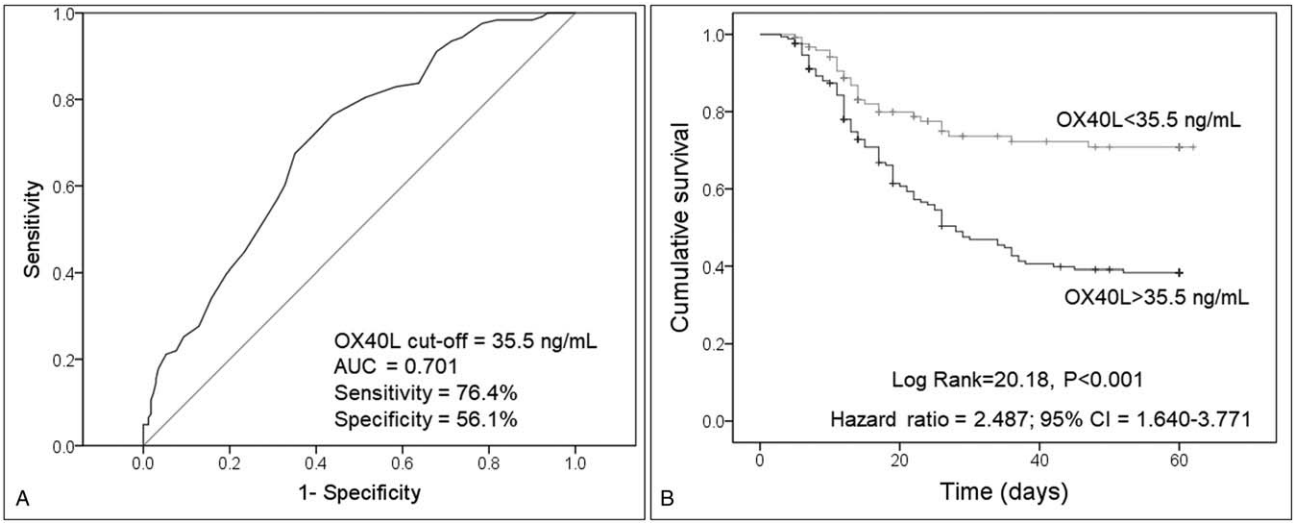

Figure 3. High serum OX40L is associated with high mortality in patients with cerebral infarction. (A) The ROC curve was used to determine the cut-off point for serum OX40L that distinguishes the survivors and nonsurvivors. (B) Kaplan-Meier survival curves show significantly higher 60-d mortality in patients with high serum OX40L (≧35.5 ng/mL) compared to patients with low serum OX40L (<35.5 ng/mL). OX40L = OX40 ligand.

4. Discussion

This study investigated serum OX40L levels in 294 patients with CI. We found that serum OX40L levels were elevated in patients with CI compared to age- and sex-matched healthy controls, and were also higher in nonsurvivors than in survivors. Serum OX40L showed negative correlation with GCS score, and showed positive correlation with serum creatinine and hs-CRP in CI patients. Serum OX40L, as well as pulmonary infection, GCS score and hs-CRP, contributed independently to 60-day mortality of patients with CI. Patients with higher serum OX40L levels (≧35.5 ng/mL) have a higher mortality rate at 60 days, so OX40L may be a good serum biomarker in patients with CI.

This study is the first report about the elevation of serum OX40L in patients with CI. Previous studies have supported our results and showed OX40L in peripheral blood lymphocytes and plasma can be reduced by rosuvastatin and simvastatin in patients with ACI.[10,12] In fact, statins seem to has a common effect on OX40L, as pitavastatin or simvastatin could also repressed the expressions of OX40L Dendritic cells.[13] Statins control atherosclerosis by inhibiting the inflammatory response and release of inflammatory factors.[14] It can be speculated that OX40L may be an inflammatory factor induced by CI. However, this study reported a new finding about the correlation between high serum OX40L and mortally of patients with CI, which is consistent with previous studies. For example, serum OX40L was associated with the severity and persistence of asthma in children, and associated with the prognosis of patients with acute coronary syndrome.[15,16] After middle cerebral artery occlusion (MCAO), rats had significantly higher OX40 expression in the ischemic brain tissue and peripheral blood.[17] OX40 is a receptor for OX40L, suggesting that occlusion of the middle cerebral artery may activate the OX40L-OX40 signaling pathway. This article shows higher serum OX40L levels in patients with CI compared to the control group, thus confirming this hypothesis.

We reported that serum OX40L correlated negatively to GCS score, and correlated positively to serum creatinine and hs-CRP in CI patients. GCS score is a coma index and was routinely used to assess the conscious state of patients. It measures blink reaction, language reaction and limb movement, with lower GCS score indicating higher extent of unconsciousness and disease severity. This indicates that OX40L might be a contributor to the progression of CI. In our study, serum OX40L showed positive correlation with serum creatinine, an indicator of renal function and prognosis of ischemic stroke, which was also reported by other scholars in patients with systemic lupus erythematosus.[18,19] We also found that serum OX40L positively correlated with a proinflammatory cytokine hs-CRP. OX40L also demonstrated positive correlation with hs-CRP in acute coronary syndrome patients, and both these 2 proteins involve the pathogenesis of atherosclerosis, and associated with disease severity and progression.[20] Moreover, serum OX40L and hs-CRP can both be reduced by rosuvastatin treatment in acute ACI patients.[10] This suggests that there might be a regulatory connection between OX40L and hs-CRP, which needs further investigation.

Our study showed that patients with higher serum OX40L had worse clinical outcomes within 60 days, suggesting that OX40L may be an inflammatory factor and could predict the prognosis of CI. Therefore, we speculate that OX40L signaling might play an key role in pathophysiological mechanisms of CI. The association of high serum OX40L with poor prognosis may be ascribed to following pathways: First, regulatory T cells can inhibit the activation of immune responses during ischemic stroke and reduce inflammation-mediated brain injury [21]. For example, in rats with transient middle cerebral artery occlusion, atorvastatin

Table 2

Logistic multivariate regression predicts 30-d mortality.

Characteristics	Odds ratio	95% confidence interval	*P* value
Pulmonary infection	1.767	1.049–2.976	.032
GCS score	0.791	0.681–0.919	.002
Hs-CRP (pg/mL)	2.216	1.347–3.643	.002
OX40L (ng/mL)	1.089	1.053–1.126	<.001

GCS = Glasgow Coma Scale, hs-CRP = high sensitive C-reactive protein.

increases the number and proportion of regulatory T cells in brain tissue and thus exerts a neuroprotective effect.[22] OX40L-OX40 can inhibit the differentiation and activity of regulatory T cells.[23] Second, ischemic stroke triggers sustained and stable changes in the systemic immune system, including specific lymphopenia, excessive production of IL-10, and prolonged Th2 biased immunity, all of which lead to severe immunosuppression in stroke patients.[24] The OX40L-OX40 pathway could enhance Th2 responses, and this indicates that patients with high serum OX40L have high likelihood to develop low immune function and are prone to various infections.[25] In this article, non-survivors of CI patients showed significantly higher rate of pulmonary infection than survivors. Our results are also supported by a previous report that subjects with higher OX40L expression on bronchiolar progenitors had increased susceptibility to influenza infection and pneumonia.[26] However, the contribution of OX40L to pulmonary infection is still unclear and deserves further investigation.

The limitations of this study are as follows. First, the source of serum OX40L in patients with CI is still unclear. Further study is required to explore whether it is derived from peripheral blood lymphocytes. Second, in this study, only serum OX40L levels in patients with CI at the beginning of admission were measured, and detailed time series of serum OX40L levels after admission was lacking. Third, an animal model is needed to elucidate the possible pathological mechanisms of OX40L on ischemic brain tissue.

In conclusion, serum OX40L levels are elevated in patients with CI, and elevated in nonsurvivors than in survivors. There was a correlation between serum OX40L levels and mortality in patients with CI.

Author contributions

Lun-Lin Mao performed the experiments and wrote the manuscript; Wen-Ya Chen designed the study and revised the manuscript; Ai-Jin Ma performed the experiments; Li-Li Ji collected and analyzed clinical data; Ting-Ting Huang collected laboratory variables of patients and performed statistical analysis.

Conceptualization: Wen-Ya Chen.
Data curation: Li-Li Ji, Ting-Ting Huang.
Investigation: Lun-Lin Mao, Ai-Jin Ma.
Project administration: Wen-Ya Chen.
Software: Li-Li Ji, Ting-Ting Huang.
Writing – original draft: Lun-Lin Mao.
Writing – review & editing: Wen-Ya Chen.

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