The Diagnostic and Prognostic Value of Soluble ST2 in Sepsis

Xinghua Ye
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Jia Wang
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Le Hu
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Ying Zhang
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Yixuan Li
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Jingchao Xuan
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Silu Han
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Yifan Qu
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Long Yang
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Bing Wei
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Junyu Wang (wangjunyu1007@163.com)
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University
Jun Yang
Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University

Research Article

Keywords: Sepsis, Soluble ST2, SOFA score, APACHE Ⅱ score, Lactic acid, Diagnosis, Prognosis

Posted Date: September 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-914803/v1

Abstract

Objective: To determine the diagnostic and prognostic value of soluble ST2 (sST2) in patients with sepsis.

Methods: A total of 113 critically ill patients were enrolled from the emergency department of the Beijing Chaoyang Hospital Jing Xi Branch. The venous blood levels of sST2 were measured using the AFIAS-6 dry fluorescence immunoassay analyzer. The patients were divided into sepsis group (76 cases) and non-sepsis group (37 cases) based on sepsis 3.0 diagnostic criteria. The sepsis group was further sub-divided into the non-survivor group (38 cases) and survivor group (38 cases) according to the survival outcomes after follow-up for 28 days. The vital signs, blood gas analysis, routine blood tests, liver and kidney function tests, procalcitonin (PCT), C-reactive protein (CRP), sST2, left ventricular ejection fraction (LVEF), and other basic characteristics of the patients were recorded. Further, the SOFA, qSOFA and APACHE Ⅱ scores of each patient were calculated. Statistical software SPSS 25.0 was used for statistical analysis. Independent sample t-test was used for comparisons of measurement data, while chi-square test was used for comparisons of counting data. Logistic regression analysis was used to evaluate the prognostic factors. Further, ROC curves were plotted to determine the predictive ability of sST2, lactic acid levels, SOFA and APACHE Ⅱ scores on survival.

Result: The serum sST2 levels in the sepsis group (125.00±60.32ng/ml) were significantly higher than in the non-sepsis group (58.55±39.03ng/ml) (P<0.05). The SOFA score (8.08±2.88), APACHE Ⅱ score (18.00±4.72), blood sST2 levels (168.06±36.75ng/ml) and lactic acid levels (2.89±3.28) in the non-survivor group were significantly higher than the survivor group (P<0.05). Multiple logistic regression analysis showed that sST2, SOFA score, APACHE Ⅱ score and lactic acid levels were independent risk factors for poor prognosis in patients with sepsis. The ROC curve analysis of the above indexes showed no significant differences between the AUC of sST2 (0.912) and the SOFA score (0.929) (z = 0.389, P = 0.697), or the APACHE Ⅱ score (0.933) (z = 0.484, P = 0.627). However, there was a significant difference between the AUC of sST2 (0.912) and lactic acid levels (0.768) (z = 2.153, P = 0.03).

Conclusion: Blood levels of sST2 shows a clinically diagnostic and prognostic value in sepsis. Further, sST2 shows a similar predictive ability as the SOFA and APACHE Ⅱ scores in determining the prognosis of sepsis patients. However, sST2 has a higher predictive ability than lactic acid levels in determining prognosis in sepsis.

Introduction

Interleukin 1 receptor-like 1, also known as ST2, is a member of the interleukin-1 (IL-1) receptor family. In recent years, ST2 has attracted attention as a new marker in heart failure and inflammation [1]. Several studies have reported that the IL-33 / ST2 signaling pathway plays a crucial role in various inflammatory diseases, cancer, and heart diseases [2–4]. However, only a few studies have investigated the role of ST2

in sepsis. This study analyzed the blood levels of soluble ST2 (sST2) in acute and critically ill patients. Further, the study also explored the diagnostic and prognostic role of sST2 in sepsis patients.

Materials And Methods

Patients A total of 113 acute and critically ill patients were enrolled from the emergency department at the Beijing Chaoyang Hospital Jing Xi Branch between December 2020 and April 2021. The patients included 53 males and 60 females, aged between 33 and 94 years. Sepsis and septic shock (hereinafter referred to as "sepsis 3.0") was diagnosed based on the international consensus on the definition of sepsis published by the European Society of critical care medicine in 2016. The patients were then classified into sepsis group (n = 76) and non-sepsis group (n = 37). Patients in the sepsis group were further subdivided based on the outcome after 28 days into the non-survivor group (38 cases) and the survivor group (38 cases). Routine diagnostic tests were conducted, and treatment was optimized based on the outcomes of the tests. Data on the vital signs, routine blood tests, liver and kidney function tests, blood gas analysis, C-reactive protein (CRP), procalcitonin (PCT), and cardiopulmonary function were recorded. sST2 was measured within 72 hours of admission. Further, patients survival was followed up for 28 days. This study obtained the informed consent of all patients and their families, signed the informed consent form, and was approved by the ethics committee of Beijing Chao Yang Hospital, Capital Medical University.

ST2 Detection by Immunofluorescence

Venous blood was collected within 2 hours of the patients appearing in the emergency department. The samples were collected into purple capped tubes lined with K2-EDTA anticoagulant. ST2 was analyzed using an automated immunofluorescence immunoassay system (AFIAS)immune analyzer (Model: AFIAS-6, Origin: Korea) and AFIAS ST2 Kit (REF: SMFP-70, Origin: Korea). All methods were performed in accordance with the relevant guidelines and regulations in the methods section to this effect.

Statistical Analysis

Statistical analysis was conducted using the statistical software SPSS 25.0. The normal distribution of data was assessed using the nonparametric Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation ($\bar{x} \pm s$) for normally distributed data or median and interquartile range for not normally distributed data. Differences in qualitative parameters between groups were assessed using two independent sample t-test (for normally distributed data). In contrast, the Mann Whitney U test was used for comparisons between groups (for not normally distributed data). On the other hand, one-way ANOVA was used for comparison between multiple groups. Categorical variables were expressed as numbers, and the data were analyzed using the chi-square test. Correlation between variables was conducted using Spearman correlation coefficients. The logistic regression model was used to analyze the prognostic factors. The receiver operating characteristic curve (ROC curve) was plotted to evaluate factors affecting patient prognosis. Statistically significant differences were considered at a $P\text{-}value < 0.05$.

Results

Comparison of the General Information

There were 76 patients in the sepsis group, with an average age of 80.75 years, including 33 males and 43 females. However, there were 37 patients in the non-sepsis group, with an average age of 74.38 years, including 20 males and 17 females. There was no statistically significant difference in gender and age between the sepsis group and the non-sepsis group (all $P > 0.05$) (see Table 1).

Table 1
Comparison of the demographic profile and characteristics between the Sepsis Group and the Non-sepsis Group

Detection Indexes	Sepsis Group	Non-sepsis Group	*P-value*
Age (years)	80.75 ± 8.90	74.38 ± 8.95	0.782
Male/Female	33/43	20/17	0.650
SOFA score	5.71 ± 3.35	2.22 ± 2.32	0.005
APACHE Ⅱ score	14.34 ± 5.46	9.68 ± 4.53	0.282
Lactic acid (mmol/l)	2.03 ± 2.49	1.43 ± 1.14	0.079
PCT (ng/ml)	2.01 ± 4.59	0.90 ± 2.75	0.095
CRP (mg/l)	49.22 ± 44.76	37.22 ± 44.55	0.555
BNP (pg/ml)	584.52 ± 772.13	474.27 ± 741.99	0.520
TnI (ng/ml)	0.15 ± 0.64	1.36 ± 4.87	0.000
LVEF (%)	60.50 ± 11.33	60.24 ± 12.54	0.239
Hospital stay (days)	14.64 ± 9.58	11.97 ± 8.30	0.135
sST2(ng/ml)	125.00 ± 60.32	58.55 ± 39.03	0.000

Comparison of sST2 values between the Sepsis Group and the Non-sepsis Group

sST2 in venous blood of patients in the sepsis group was higher than in the non-sepsis group, with a statistically significant difference (see Table 1). The Spearman correlation analysis showed that sST2 were positively correlated with the SOFA score ($r = 0.539$, $P = 0.000$) and APACHE Ⅱ score ($r = 0.482$, $P = 0.000$). This finding demonstrated that the sST2 levels in the venous blood of patients in the sepsis group were positively correlated with the severity of sepsis.

Prognosis Prediction in Sepsis Patients using sST2 and other Laboratory Parameters

There were no statistically significant differences in age, gender, brain natriuretic peptide (BNP), troponin I (TnI), LVEF and length of hospital stay between the non-survivor group and the survivor group (all $P > 0.05$) (see Table 2). However, the SOFA score, APACHE Ⅱ score, lactic acid, PCT, CRP and sST2 levels in the non-survivor group were significantly higher than the survivor group (all $P < 0.05$).

Multivariate logistic regression analysis of the statistically significant prognostic factors in the univariate analysis showed that sST2, SOFA score, APACHE Ⅱ score and lactic acid levels were independent prognostic factors for sepsis (see Table 3). Analysis of the ROC curve (see Fig. 1 and Table 4), showed that the area under the curve of the sST2 and SOFA score (0.912 vs. 0.929) ($z = 0.389$, $P = 0.697$), and the area under the curve of the sST2 and Apache Ⅱ score were not statistically significant (0.912 vs. 0.933) ($z = 0.484$, $P = 0.627$). However, the area under the curve of sST2 and lactic acid levels was statistically significant (0.912 vs. 0.768) ($z = 2.153$, $P = 0.03$). sST2 showed a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+ LR) and a negative likelihood ratio (-LR) of 97.4%, 76.3%, 80.4%, 96.7%, 4.11, and 0.03, respectively, in predicting the prognosis of sepsis. The SOFA score had a sensitivity, specificity, PPV, NPV, +LR, and −LR of 86.8%, 81.6%, 82.5%, 86.1%, 4.71, and 0.16, respectively, in predicting the prognosis of sepsis. The APACHE Ⅱ score had a sensitivity, specificity, PPV, NPV, +LR, and −LR of 89.5%, 89.5%, 89.5%, 89.5%, 8.5, and 0.12, respectively, in predicting the prognosis of sepsis. The lactic acid levels had a sensitivity, specificity, PPV, NPV, +LR, and −LR of 71.1%, 73.7%, 73.0%, 71.8%, 2.7 and 0.39, respectively, in predicting the prognosis of sepsis.

In conclusion, sST2 has the same prognostic, predictive ability as the SOFA and APACHE Ⅱ scores in sepsis. However, sST2 had a higher predictive ability than lactic acid levels.

Table 2
Comparison of the Detection Indexes between the non-survivor Group and the Survivor Group of Sepsis Patients

Detection Indexes	Non-survivor Group	Survivor Group	*P-value*
Male/Female	13/25	20/18	0.108
Age (years)	81.61 ± 7.93	79.89 ± 9.81	0.406
SOFA score	8.08 ± 2.88	3.34 ± 1.71	0.000
APACHE Ⅱ score	18.00 ± 4.72	10.68 ± 3.26	0.000
Lactic acid (mmol/l)	2.89 ± 3.28	1.16 ± 0.52	0.010
PCT (ng/ml)	3.65 ± 6.07	0.36 ± 0.64	0.001
CRP (mg/l)	66.85 ± 45.38	31.59 ± 36.93	0.000
BNP (pg/ml)	666.78 ± 697.17	502.26 ± 841.74	0.356
TnI (ng/ml)	0.23 ± 0.90	0.08 ± 0.08	0.305
LVEF (%)	60.13 ± 8.74	60.87 ± 13.55	0.779
Hospital stay (days)	16.45 ± 10.85	12.84 ± 7.87	0.101
sST2 (ng/ml)	168.06 ± 36.75	81.93 ± 47.08	0.000

Table 3
Multivariate Logistic Regression Analysis of the Factors affecting Prognosis in Sepsis Patients

Detection Indexes	Standard Error	Wald	Sig.	EXP(B)	95% CI of EXP(B)	
					Lower Limit	Upper Limit
SOFA score	0.529	6.334	0.046	0.349	0.124	0.984
APACHE Ⅱ score	0.237	3.888	0.049	0.626	0.394	0.997
Lactic acid	1.850	3.954	0.047	0.025	0.001	0.949
PCT	1.094	0.003	0.959	0.945	0.111	8.061
CRP	0.017	0.085	0.771	1.005	0.973	1.038
sST2	0.029	4.337	0.037	0.941	0.889	0.996

Table 4
Diagnostic Parameters of the SOFA score, sST2, APACHE II score and lactic acid levels

Detection Indexes	AUC	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
sST2	0.912	103.055	97.4	76.3	80.4	96.7	4.11	0.03
SOFA score	0.929	4.5	86.8	81.6	82.5	86.1	4.71	0.16
APACHE Ⅱ score	0.933	13.5	89.5	89.5	89.5	89.5	8.5	0.12
Lactic acid	0.768	1.5	71.1	73.7	73.0	71.8	2.7	0.39

Discussion

Sepsis is a life-threatening organ dysfunction caused by an imbalance in the body's response to infection, leading to septic shock or multiple organ dysfunction [5]. Sepsis is a medical emergency that presents as an acute and severe disease. It is associated with high mortality that can be as high as 40% [6]. The occurrence and development of sepsis involve complex immune mechanisms [7, 8]. Sepsis is characterized by an inflammatory storm in the early stages and persistent immunosuppression in later stages. Further, it is characterized by reduced innate and acquired immune response and reduced ability for pathogen clearance, resulting in secondary opportunistic infections by pathogenic bacteria or virus, and finally, serious complications [9].

ST2 is a specific receptor of IL-33 in the IL-1 family. IL-33 / ST2 signaling pathway plays an important role in the systemic inflammatory response and immune regulation [10–13]. ST2 includes four isoforms, ST2L, sST2, ST2v, and ST2LV. sST2 is a soluble ST2 that can competitively bind to IL-33, inhibiting its biological activity and signal transduction. In severe infection, sST2 acts as a negative regulator and combines with IL-33, thus participating in immunosuppression [14, 15].

In the present study, the sST2 levels in the venous blood were higher in the sepsis group than in the non-sepsis group. This finding indicates that sST2 can be used as a diagnostic index in sepsis. Moreover, in the sepsis group, the blood levels of sST2 were significantly higher in the non-survivor group than in the survivor group, suggesting that the blood levels of sST2 have a high predictivity ability in determining the prognosis of sepsis patients. Higher blood levels of sST2 were positively correlated with a poor prognosis. Furthermore, patients with high SOFA and APACHE II scores also had high blood levels of sST2, with a poorer prognosis, consistent with other studies. Therefore, blood levels of sST2 in patients with sepsis can be used as clinical indicators to predict prognosis.

APACHE II scoring system has been widely used in ICU since its inception in 1985 [16–19]. It is of clinical significance as it can objectively evaluate the severity of the patient’s condition, guide the monitoring and treatment plans, and evaluate treatment outcomes. Furthermore, it can be used to predict and accurately evaluate the quality of care in ICU settings.

The SOFA score was described by the European Society of Intensive Care Medicine in 1944. The score aims to describe the occurrence and development of multiple organ dysfunction syndromes (MODS) and to evaluate the incidence rate [18, 19]. The SOFA score is based on objective, simple, easy to obtain, reliable, and specific continuous variables in evaluating multiple organ dysfunction. These variables are not influenced by patient source, disease type, demographic characteristics and the treatment administered. The SOFA score can distinguish the degree of multiple organ dysfunction or failure of a single organ.

Lactic acid is a metabolite of anaerobic glycolysis in the human body. Under normal circumstances, levels of lactic acid exceeding 2mmol/L overwhelm the capacity for liver clearance. The dynamic monitoring of blood lactate levels is clinically significant in the diagnosis of lactic acidosis. An increase in blood lactate levels can be used to evaluate disease severity and prognosis [20, 21].

The ROC curve analysis showed that sST2, SOFAand APACHE II scores and the lactic acid levels had a prognostic, predictive ability in sepsis, consistent with previous studies. The sST2 showed similar prognostic, predictive ability with the SOFA and APACHE II scores. However, sST2 had a higher prognostic predictive ability than lactic acid levels. In conclusion, blood levels of sST2 can be used as clinical indices for the diagnosis and prognosis of sepsis.

References

1. Kakkar, R. & Lee, R. T. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*, **7** (10), 827–840 (2008).
2. He, Z. *et al.* Mast cells are essential intermediaries in regulating IL-33/ST2 signaling for an immune network favorable to mucosal healing in experimentally inflamed colons. *Cell Death Dis*, **9** (12), 1173 (2018).
3. Li, J. *et al.* IL33 attenuates ventricular remodeling after myocardial infarction through inducing alternatively activated macrophages ethical standards statement. *Eur J Pharmacol*, **854**, 307–319 (2019).
4. Milovanovic, M. *et al.* IL-33/ST2 axis in inflammation and immunopathology. *Immunol Res*, **52** (1–2), 89–99 (2012).
5. Cecconi, M., Evans, L., Levy, M. & Rhodes, A. Sepsis and septic shock., **392** (10141), 75–87 (2018).
6. Rudd, K. E. *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study., **395** (10219), 200–211 (2020).
7. van der Poll, T., van de Veerdonk, F. L., Scicluna, B. P. & Netea, M. G. The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol*, **17** (7), 407–420 (2017).
8. Font, M. D., Thyagarajan, B. & Khanna, A. K. Sepsis and Septic Shock - Basics of diagnosis, pathophysiology and clinical decision making. *Med Clin North Am*, **104** (4), 573–585 (2020).

9. Johnston, G. R. & Webster, N. R. Cytokines and the immunomodulatory function of the vagus nerve. *Br J Anaesth*, **102** (4), 453–462 (2009).
10. Villarreal, D. O. & Weiner, D. B. Interleukin 33: a switch-hitting cytokine. *Curr Opin Immunol*, **28**, 102–106 (2014).
11. Kotsiou, O. S., Gourgoulianis, K. I. & Zarogiannis, S. G. IL-33/ST2 Axis in Organ Fibrosis. *Front Immunol*, **9**, 2432 (2018).
12. Homsak, E. & Gruson, D. Soluble ST2: A complex and diverse role in several diseases. *Clin Chim Acta*, **507**, 75–87 (2020).
13. Griesenauer, B. & Paczesny, S. The ST2/IL-33 Axis in Immune Cells during Inflammatory Diseases. *Front Immunol*, **8**, 475 (2017).
14. Fattori, V. *et al.* Targeting IL-33/ST2 signaling: regulation of immune function and analgesia. *Expert Opin Ther Targets*, **21** (12), 1141–1152 (2017).
15. Altara, R. *et al.* Conflicting vascular and metabolic impact of the IL-33/sST2 axis. *Cardiovasc Res*, **114** (12), 1578–1594 (2018).
16. Godinjak, A. *et al.* Predictive value of SAPS II and APACHE II scoring systems for patient outcome in a medical intensive care unit. *Acta Med Acad*, **45** (2), 97–103 (2016).
17. Rivers, E. *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*, **345** (19), 1368–1377 (2001).
18. Basile-Filho, A. *et al.* The use of APACHE II, SOFA, SAPS 3, C-reactive protein/albumin ratio, and lactate to predict mortality of surgical critically ill patients: A retrospective cohort study. *Med. (Baltim)*, **98** (26), e16204 (2019).
19. Feng, Q. *et al.* Characterization of Sepsis and Sepsis-Associated Encephalopathy. *J Intensive Care Med*, **34** (11–12), 938–945 (2019).
20. Okorie, O. N. & Dellinger, P. Lactate: biomarker and potential therapeutic target. *Crit Care Clin*, **27** (2), 299–326 (2011).
21. Pan, J. *et al.* Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: A meta-analysis. *Med. (Baltim)*, **98** (8), e14453 (2019).

Figures

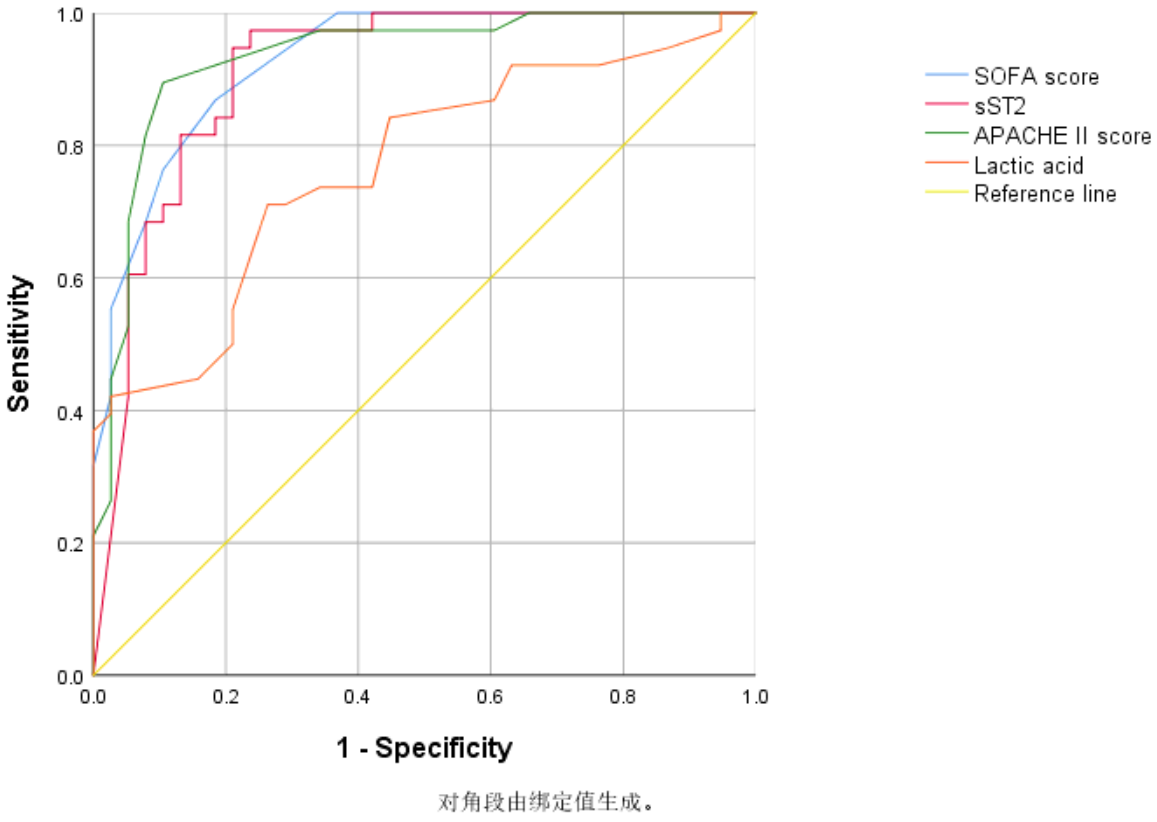

Figure 1

ROC Curve of the SOFA score, sST2, APACHE II score and lactic acid levels on the prediction of mortality