Does an Increase in Serum FGF21 Level Predict 28-day Mortality of Critical Patients with Sepsis and ARDS?

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Research

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Abstract

Background

Sepsis may be accompanied by acute respiratory distress syndrome (ARDS) in patients admitted to intensive care units (ICUs). It is essential to identify prognostic biomarkers in patients with sepsis and ARDS.

Objective

Determine whether changes in the level of serum fibroblast growth factor 21 (FGF21) can predict the 28-day mortality of ICU patients with sepsis and ARDS.

Methods

Consecutive sepsis patients were divided into two groups (Sepsis+ARDS and Sepsis-only), and the Sepsis+ARDS group was further classified as survivors or non-survivors. Demographic data and comorbidities were recorded. The Sequential Organ Failure Assessment (SOFA) score and serum levels of cytokines and other biomarkers were recorded 3 times after admission. Multiple Cox proportional hazards regression was used to identify risk factors associated with 28-day mortality in the Sepsis+ARDS group.

Results

The Sepsis+ARDS group had a greater baseline SOFA score and serum levels of cytokines and other biomarkers than the Sepsis-only group; the serum level of FGF21 was almost 2-fold greater in the Sepsis+ARDS group ($P<0.05$). Non-survivors in the Sepsis+ARDS group had an almost 5-fold greater level of FGF21 than survivors in this group ($P<0.05$). The serum level of FGF21 persistently increased from the baseline to the peak of shock and death in the non-survivors, but persistently decreased in survivors ($P<0.05$). Changes in the serum FGF21 level between different time points were independent risk factors for mortality.

Conclusion

A large increase of serum FGF21 level from baseline is associated with 28-day mortality in ICU patients with sepsis and ARDS.

1. Background

Sepsis is defined as a life-threatening organ dysfunction caused by the host's dysregulated response to an infection [1]. Sepsis may lead to acute respiratory distress syndrome (ARDS), a condition characterized by acute, diffuse, and inflammatory lung injury that leads to increased non-hydrostatic extravascular lung water, reduced lung compliance, and severe hypoxemia [2].

Despite therapeutic innovations, the mortality rate of patients with sepsis is as high as 25 to 30% [3] and the mortality rate of patients with ARDS can reach 35 to 45% [4]. Sepsis and ARDS are closely related, and most of these patients receive care in intensive care units (ICUs). Up to 50% of sepsis patients admitted to ICUs develop ARDS [5], and the mortality rate of patients with sepsis and ARDS is greater than that of patients with sepsis alone or ARDS alone [6-7]. Thus, it is essential to identify the characteristics of sepsis patients who develop ARDS after ICU admission.

Sepsis and ARDS are heterogeneous inflammatory syndromes, and certain phenotypes might be associated with clinical outcomes. Several studies reported that sepsis patients with hyper-inflammation had higher mortality rates [6-7]. Similarly, some studies showed that patients with ARDS and hypo-inflammation might have better clinical outcomes than those with ARDS and hyper-inflammation [8-9]. There is also evidence that some pro- and anti-inflammatory biomarkers have prognostic value in patients with sepsis and ARDS [10-11]. However, few studies directly examined the pro- and anti-inflammatory markers of patients with sepsis and ARDS. It is also uncertain whether the levels of pro- and anti-inflammatory cytokines are associated with the development of ARDS in patients with sepsis. Thus, it is necessary to identify novel serum biomarkers that can be used to classify disease severity in patients with sepsis and ARDS.

Fibroblast growth factor 21 (FGF21) is a peptide hormone that regulates energy homeostasis and glucose-lipid metabolism that is synthesized by the liver, adipocytes, pancreas, and brain [14]. The plasma level of FGF21 is greater in patients with metabolic disorders, such as type 2 diabetes, obesity, and mitochondrial diseases, and the level also increases during aging [15-16]. Patients with inflammatory reactions, such as sepsis, pancreatitis, and systemic inflammatory response syndrome (SIRS), have increased serum levels of FGF21 [17-18]. FGF21 apparently reduces oxidative stress by decreasing the level of reactive oxygen species (ROS), repressing nuclear factor kappa B (a pro-inflammatory factor), and reducing apoptosis [19–22]. Siahianidou et al. and our previous study demonstrated that FGF21 has value as a prognostic indicator in patients with sepsis [23-24].

However, the relationship of FGF21 with prognosis in patients with sepsis and ARDS is uncertain. In this prospective cohort study, we aimed to evaluate whether changes in the serum level of FGF21 predict 28-day mortality of ICU patients who have sepsis and ARDS.

2. Patients And Methods

2.1 Patients

This prospective cohort study included 231 consecutive patients with sepsis who were admitted to the Department of Critical Care Medicine of Changsha of Traditional Chinese Medicine Hospital (Hunan, China) between January 2019 and December 2020. Sepsis was diagnosed according to the Sepsis-3 criteria [1] and ARDS was diagnosed according to the Berlin definition [2]. All included patients were older than 18 years. The exclusion criteria were cancer, hospitalization or receipt of antibiotics during the preceding 2 weeks, and re-admission to the ICU.

All eligible patients were divided into a Sepsis-only group (patients who met the Sepsis-3 criteria and had no evidence of ARDS) and a Sepsis+ARDS group. The Sepsis+ARDS group was further divided into a survival group (patients who survived 28 days after initial diagnosis) and a non-survival group (patients who died within 28 days after diagnosis).

Demographic data (including age and gender) and medical history (including cardiovascular diseases, diabetes mellitus, chronic renal failure, and chronic obstructive pulmonary disease) were recorded. Laboratory values, hemodynamic parameters, ventilator settings, and medications were recorded at disease inception, during the worst period of disease, and during the recovery period. Sequential Organ Failure Assessment (SOFA) scores were calculated. The main clinical outcome measure was 28-day mortality.

Each patient received standard treatment during the ICU stay. This study was approved by the Ethics Committee of Changsha of Traditional Chinese Medicine Hospital and informed consent was obtained from all patients or their guardians.

2.2 Cytokine measurements

Blood samples were collected within 24 h after diagnosis, during the worst period of disease, and during the recovery period. The serum levels of FGF21, interleukin 6 (IL-6), IL-10, tumor necrosis factor α (TNF α), procalcitonin (PCT), and C reactive protein (CRP) were determined using enzyme-linked immunosorbent assays (ELISAs) from Abcam (USA) according to the manufacturer's instructions. Routine blood tests and blood gas analyses were performed in the hospital's central laboratory.

2.3 Statistical analysis

The normality of the distribution of a quantitative variable was tested using the Kolmogorov-Smirnov test ($P > 0.10$). Normally distributed data are expressed as means and standard deviations (SDs), and non-normally distributed data as medians and interquartile ranges (IQRs). Qualitative data are presented as number (%). For continuous variables, two-group comparisons were performed using Student's t -test or the Mann-Whitney U test, depending on the normality of the distribution. For categorical variables, the Chi-square test, Fisher's exact test, or McNemar's test was used as appropriate. Spearman's correlation coefficient (ρ) was used to identify correlations between FGF21 level and other clinical variables. The Hotelling T^2 test was used to identify the significance of changes in the level of serum FGF21 and other markers.

To identify the risk factors for 28-day mortality of patients in the Sepsis+ARDS group, multiple Cox proportional hazards regression analyses were performed to measure the effects of different variables at three key times: (1) ICU admission; (2) peak of shock; and (3) before death or ICU discharge. The value of each measured parameter (P) is expressed as " P_t ", where ' t ' is the measurement time (1, 2, or 3); the change in a parameter between two times is expressed as " $\Delta P_{t_1-t_2}$ ", where ' t_1 ' and ' t_2 ' are the measurement times; and the percentage change in a parameter between two times is expressed as

" $\Delta P\%_{t1-t2}$ ". All statistical analyses were performed using SPSS version 24.0 software (IBM SPSS, USA). A two tailed P value below 0.05 was considered significant.

3. Results

3.1 Comparison of the Sepsis and Sepsis+ARDS groups

We initially compared the clinical characteristics of patients in the Sepsis-only and the Sepsis+ARDS groups (Table 1). The Sepsis+ARDS group had a greater respiratory rate, a lower PaO_2/FiO_2 , a greater SOFA score, and higher levels of lactate (LAC), procalcitonin (PCT), C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor α (TNF α), IL-10, and FGF21 (all $P < 0.05$). The serum level of FGF21 was almost two-times greater in the Sepsis+ARDS group.

3.2 Comparison of survivors and non-survivors in the Sepsis+ARDS group

The survivors and non-survivors in the Sepsis+ARDS group had similar age, gender, and underlying diseases (Supplementary Table 1). At baseline, the non-survivors had a significantly lower mean arterial pressure, hematocrit, and Glasgow Coma Scale (GCS) score; greater heart rate, body temperature, and SOFA score; and greater serum levels of creatinine, LAC, PCT, CRP, IL-6, TNF α , IL-10 (Table 2; all $P < 0.05$). The serum level of FGF21 was almost five-times greater in the non-survivors.

3.3 Dynamics of FGF21 in the Sepsis+ARDS group

We recorded the changes of cytokines and other biomarkers while patients in the Sepsis+ARDS group were in the ICU (Fig. 1). The serum level of FGF21 persistently increased from baseline in the non-survivors, but gradually decreased in the survivors (both $P < 0.05$). In addition, pro-inflammatory biomarkers (CRP, PCT, TNF- α , IL-6,) and SOFA score also increased in the non-survivors, and decreased in the survivors (all $P < 0.05$).

3.4 Correlation of FGF21 level with clinical indicators and cytokine levels

Analysis of patients in the Sepsis+ARDS group at baseline indicated the serum level of FGF21 was positively correlated with SOFA score and the serum levels of PCT, CRP, IL-6, IL-10, LAC, and TNF- α in these patients (Table 3, all $P < 0.05$).

3.5 Risk factors for 28-day mortality in Sepsis+ARDS patients based on measurements at 3 crucial time points

We initially analyzed variables associated with 28-day mortality based on measurements at 24 to 48 h after ICU admission (Table 4-1). The results indicated that serum FGF21 level, SOFA score, and serum level of CRP were independent risk factors for 28-day mortality (all $P < 0.05$).

We then analyzed variables associated with 28-day mortality based on initial measurements and measurements at the peak of shock (Table 4-2). The results indicated that the ΔSOFA_{2-1} , FGF21_2 , and $\Delta\text{FGF21}\%_{2-1}$ were independent risk factors for 28-day mortality (all $P < 0.05$).

We also analyzed variables associated with 28-day mortality based on measurements performed at 2 to 3 days before death or ICU discharge, measurements at the peak of shock, and initial measurements (Table 4-3). The results indicated that ΔSOFA_{3-1} , $\Delta\text{FGF21}\%_{3-1}$, $\Delta \text{LAC}\%_{3-1}$, and baseline CRP_1 were independent risk factors for 28-day mortality (all $P < 0.05$).

Discussion

In this study, we found that the serum FGF21 level at baseline was greater in ICU patients who had sepsis and ARDS than in those who had sepsis alone. Furthermore, non-survivors in the Sepsis+ARDS group had persistently increasing levels of FGF21 during their ICU stays, but survivors in the Sepsis+ARDS group had persistently declining levels. Notably, our Cox proportional hazards model indicated that an increase in the serum level of FGF21 from the baseline was a significant risk factor for 28-day mortality in the Sepsis+ARDS group. To our best knowledge, this is the first study to identify the prognostic value of dynamic changes in the serum level of FGF21 in patients with sepsis and ARDS.

Previous studies demonstrated that the serum level of FGF21 was greater in adults and newborns who had sepsis [23-24]. Our previous study demonstrated that the serum level of FGF21 was positively associated with serum inflammation biomarkers, including PCT, CRP, IL-6, and TNF α [24]. Patients with sepsis and ARDS have a greatly increased inflammatory state. Thus, it is not surprising that the serum level of FGF21 was greater in patients with sepsis and ARDS. Moreover, we found that the baseline FGF21 level correlated with the baseline levels of multiple inflammatory markers (Table 3).

Elevation of inflammatory and anti-inflammatory biomarkers can occur concurrently during the early phase of sepsis [25]. Previous studies reported that FGF21 had anti-inflammatory effects during sepsis [26]. The present study, which compared patients with sepsis alone vs. sepsis and ARDS, identified much higher levels of serum FGF21 and pro-inflammatory factors (PCT, CRP, IL-6, and TNF α) in the Sepsis+ARDS group. This suggests a more intense interaction between pro-inflammatory and anti-inflammatory factors in patients who have sepsis and ARDS.

Our analysis of disease progression in patients with sepsis and ARDS indicated the non-survivors had continuously increased serum levels of FGF21, and this was accompanied by persistent increases in the levels of multiple pro-inflammatory cytokines. In contrast, the survivors had gradually decreased levels of FGF21 and of pro-inflammatory cytokines. The presence of higher levels of pro- and anti-inflammatory biomarkers in the non-survivors is consistent with the presence of increased physiological stress.

Because the dynamic changes of pro- and anti-inflammatory markers appeared to be of vital importance in the progression of patients with sepsis and ARDS, we were interested in the following question: Which parameters can be used to predict the mortality of patients with sepsis and ARDS? Thus, we used Cox

regression analysis to assess the prognostic value of biomarkers that were measured at admission to the ICU, at the peak of shock, and before death (non-survivors) or before ICU discharge (survivors). Our measurements at admission indicated that increased FGF21, LAC, and SOFA score were associated with poor prognosis in patients with sepsis and ARDS. This result is consistent with results from our previous study [24].

Our measurements at the peak time of shock (typically 1 week after ICU admission) indicated that the percentage increase in the FGF21 from baseline ($\Delta\text{FGF21}\%_{2-1}$) and the change of SOFA score from baseline (ΔSOFA_{2-1}) were best predictors of poor prognosis. In this model, the $\Delta\text{FGF21}\%_{1-2}$ value had a much greater HR (15.269 [95% CI: 1.622~143.712] vs. 1.247 [95% CI: 1.096~1.418]). In other words, based on measurements at baseline and the peak of shock, the percentage increase of FGF21 was the best single predictor of poor prognosis in patients with sepsis and ARDS. These large changes in the serum level of FGF21 from admission to the peak of shock reflect the dynamics of pro- and anti-inflammatory factors in patients with sepsis and ARDS.

We also analyzed the relationship of the final clinical measurements (before death or ICU discharge) with patient prognosis. We found that the $\Delta\text{FGF21}\%_{3-1}$, $\Delta\text{LAC}\%_{3-1}$, and ΔSOFA_{3-1} , and CRP_1 were significant prognostic factors. Notably, $\Delta\text{FGF21}\%_{3-1}$ was best predictor of poor prognosis (HR = 25.760 [95% CI: 1.482~447.610]). This confirms that a large increase in the serum level of FGF21, either between the first and second measurements or between the first and third measurements, was strongly associated with 28-day mortality in patients with sepsis and ARDS. At the physiological level, this may be attributed to the anti-inflammation, anti-apoptotic, and anti-oxidative effect of FGF12 during sepsis.

Limitations

First, this was a single-center study, and the total number of patients with sepsis and ARDS was relatively small. However, we have been pursuing this topic and collecting the records of sepsis patients for several years. A large and multi-center study should be performed to verify our observations. Second, because pro-inflammatory and anti-inflammatory factors both increased during sepsis, it is possible that other unmeasured anti-inflammatory cytokines might have also played a crucial role. We are currently analyzing the prognostic value of other anti-inflammatory biomarkers in sepsis patients, and plan further comparisons of their functions in patients with sepsis and ARDS. Third, some sepsis patients experience a hypo-inflammation phenotype. Most of our patients experienced hyper-inflammation, and this may be attributable to our exclusion criteria, such as exclusion of patients with cancer. The effect of changes in the serum level of FGF21 on the prognosis of patients with sepsis and ARDS who have hypo-inflammation is a topic that needs further study.

Conclusion

An increase in the serum level of FGF21 after ICU admission of patients who have sepsis and ARDS is associated with a significantly increased risk of 28-day mortality.

Abbreviations

ARDS: acute respiratory distress syndrome

ICUs: intensive care units

FGF21: fibroblast growth factor 21

SOFA: Sequential Organ Failure Assessment

IL-6: interleukin 6

IL-10: interleukin 10

TNF α : tumor necrosis factor α

PCT: procalcitonin

CRP: C reactive protein

LAC: lactate

GCS: Glasgow Coma Scale

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Changsha of Traditional Chinese Medicine Hospital.

Consent for publication

An informed consent form was obtained from all the patients or their guardians.

Availability of data and material

Data will not be shared with a reason.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YL, TL, JFH, CKL, ZLD and YC finished clinical studies and collected primary data. THZ and XYZ analyzed the data. XL finished the experiment, and performed statistic analysis, and wrote the manuscript. HS participated in the design of the study and edited the manuscript. YT and ZXZ conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline clinical characteristics of patients in the Sepsis+ARDS group and the Sepsis-only group.*

Parameter	Sepsis+ARDS (n=161)	Sepsis-only (n=69)	P value
Mean arterial pressure (mmHg)	80±19	89±15	0.106
Respiratory rate (per minute)	24(12~48)	20(12~30)	0.006
Heart rate (bpm)	106±25	97±12	0.068
Temperature (°C)	37.5±1.3	37.4±0.4	0.791
White blood count (10 ⁹ /L)	14.4(0.26~54.24)	13.37(3.29~42.35)	0.690
Platelet count (10 ⁹ /L)	168(17~527)	135(55~420)	0.367
Hematocrit (%)	32.0±6.8	32.0±5.7	0.432
PaO ₂ /FiO ₂ (mmHg)	172.3±60.8	348.8±135.4	0.000
Total bilirubin (μmmol/L)	18.4(4.0~124.7)	17.6(7.3~83.35)	0.151
Creatinine (μmmol/L)	99.9(33.7~1477.9)	76.2(32.9~684.6)	0.079
LAC (mmol/L)	2.7(0.5~18.0)	2.1(0.7~5.6)	0.000
GCS score	11(3~15)	11(3~15)	1.000
SOFA score	7(2~21)	4(2~13)	0.000
CRP (mg/L)	113.1(9.77~468.0)	71.4(6.8~498.0)	0.000
PCT (ng/mL)	6.57(0.15~200.0)	1.89(0.05~21.0)	0.002
IL-6 (pg/mL)	113.4(2.93~498.1)	56.7(4.0~345.6)	0.001
TNF-α (pg/mL)	14.9(5.8~215.4)	11.9(5.9~46.3)	0.000
IL-10 (pg/mL)	154.6(10.7~798.7)	76.9(7.1~496.8)	0.009
FGF21 (pg/mL)	1108.3 (32.3~6978.5)	533.0 (41.1~3652.5)	0.000

*Here and below: Values are expressed as mean ± SD or median (IQR); ARDS, acute respiratory distress syndrome; bpm, beats per minute; GCS, Glasgow coma scale; SOFA, sequential organ failure assessment; PCT, procalcitonin; CRP, C-reactive protein; IL, interleukin; LAC, lactate; TNF, tumor necrosis factor; FGF, fibroblast growth factor.

Table 2. Baseline clinical characteristics of patients in the Sepsis+ARDS group who were survivors and non-survivors.

Parameter	Non-survivors (n=42)	Survivors (n=119)	P value
Mean arterial pressure (mmHg)	68(35~116)	87(48~120)	0.000
Respiratory rate (per minute)	24(12~40)	22(13~38)	0.125
Heart rate (bpm)	110±33	98±20	0.022
Temperature (°C)	38.1±1.4	37.2±0.8	0.019
White blood count (10 ⁹ /L)	15.0±6.6	14.3±7.2	0.682
Platelet count (10 ⁹ /L)	131(17~364)	178(35~473)	0.055
Hematocrit (%)	31.3±7.0	35.4±5.7	0.050
PaO ₂ /FiO ₂ (mmHg)	152.1±55.7	164.6±54.5	0.021
Total bilirubin (μmmol/L)	19.5(4.6~124.7)	19.0(4.8~98.5)	0.183
Creatinine (μmmol/L)	144.0(44.9~1477.9)	96.4(33.7~507.6)	0.009
Lactate (mmol/L)	3.7(0.9~18.0)	2.7(1.2~5.6)	0.000
GCS score	9(3~15)	11(3~15)	0.000
SOFA score	11(3~21)	6(2~18)	0.000
CRP (mg/L)	134.9(18.6~468.0)	100.7(9.8~200.0)	0.000
PCT (ng/mL)	16.96(1.70~200.00)	3.07(0.15~200.0)	0.000
IL-6 (pg/mL)	367.7(37.3~498.2)	89.6(2.9~462.6)	0.000
TNF-α (pg/mL)	63.9(11.1~215.4)	12.3(5.8~102.1)	0.000
IL-10 (pg/mL)	597.6(68.0~798.7)	108.6(10.7~657.9)	0.000
FGF21 (pg/mL)	3574.7 (327.3~6978.5)	986.6 (32.3~6121.3)	0.000

Table 3. Correlation of baseline FGF21 level with SOFA score and biomarkers in the Sepsis+ARDS group.

Parameter	Spearman's ρ	P value
SOFA	0.338	0.000
IL-6	0.550	0.000
TNF α	0.571	0.000
IL-10	0.634	0.000
PCT	0.368	0.000
CRP	0.217	0.000
LAC	0.307	0.000

Table 4-1. Cox proportional hazards model for mortality in the Sepsis+ARDS group based on measurements at baseline (1).

Variable	Multiple Cox model	
	HR (95% CI)	P value
SOFA ₁	1.200 (1.079~1.334)	0.001
FGF21 ₁	1.000 (1.000~1.001)	0.000
CRP ₁	1.005 (1.001~1.010)	0.025
IL-6 ₁	NA	0.309
TNF α ₁	NA	0.089
IL-10 ₁	NA	0.958
PCT ₁	NA	0.418
LAC ₁	NA	0.873

Here and below: NA, not applicable.

Table 4-2. Cox proportional hazards model for mortality in the Sepsis+ARDS group based on measurements at the peak of shock (2) and at baseline (1).*

Variable	Multiple Cox model	
	HR (95% CI)	P value
SOFA ₁	1.247 (1.096~1.418)	0.001
ΔSOFA ₂₋₁	NA	0.692
ΔSOFA% ₂₋₁	NA	0.617
FGF21 ₁	NA	0.053
FGF21 ₂	1.001 (1.000~1.001)	0.000
ΔFGF21% ₂₋₁	15.269 (1.622~143.712)	0.017
CRP ₁	NA	0.566
CRP ₂	NA	0.751
Δ CRP% ₂₋₁	NA	0.752
IL-6 ₁	NA	0.700
IL-6 ₂	NA	0.498
ΔIL-6% ₂₋₁	NA	0.303
TNFα ₁	NA	0.456
TNFα ₂	NA	0.440
ΔTNFα% ₂₋₁	NA	0.137
IL-10 ₁	NA	0.259
IL-10 ₂	NA	0.478
ΔIL-10% ₂₋₁	NA	0.087
PCT ₁	NA	0.882
PCT ₂	NA	0.717
ΔPCT% ₂₋₁	NA	0.896
LAC ₁	NA	0.730
LAC ₂	NA	0.652
	NA	0.812

$\Delta \text{LAC}\%_{2-1}$

Here and below: the difference in the value of a parameter (P) at different times is expressed as " ΔP_{t1-t2} ", where 't1' and 't2' are the measurement times; and the percentage change in a parameter at different times is expressed as $\Delta P\%_{t1-t2}$.

Table 4-3. Cox proportional hazards model for mortality in the Sepsis+ARDS group based on at measurements before death or ICU discharge (3), at the peak of shock (2), and at baseline (1).

Variable	Multiple Cox model	
	P value	HR (95% CI)
SOFA ₁	NA	0.664
SOFA ₂	NA	0.735
SOFA₃	0.019	1.148 (1.023~1.289)
Δ SOFA% ₂₋₁	NA	0.399
Δ SOFA% ₃₋₂	NA	0.955
Δ SOFA% ₃₋₁	NA	0.625
FGF21 ₁	NA	0.294
FGF21 ₂	NA	0.197
FGF21 ₃	NA	0.384
Δ FGF21% ₂₋₁	NA	0.272
Δ FGF21% ₃₋₂	NA	0.413
ΔFGF21%₃₋₁	0.026	25.760 (1.482~447.610)
CRP₁	0.003	1.008 (1.003~1.014)
CRP ₂	NA	0.476
CRP ₃	NA	0.335
Δ CRP% ₂₋₁	NA	0.210
Δ CRP% ₃₋₂	NA	0.326
Δ CRP% ₃₋₁	NA	0.426
IL-6 ₁	NA	0.139
IL-6 ₂	NA	0.264
IL-6 ₃	NA	0.310
Δ IL-6% ₂₋₁	NA	0.104
Δ IL-6% ₃₋₂	NA	0.416
	NA	0.155

Δ IL-6% ₃₋₁		
TNF α ₁	NA	0.131
TNF α ₂	NA	0.257
TNF α ₃	NA	0.235
Δ TNF α % ₂₋₁	NA	0.565
Δ TNF α % ₃₋₂	NA	0.571
Δ TNF α % ₃₋₁	NA	0.534
IL-10 ₁	NA	0.425
IL-10 ₂	NA	0.603
IL-10 ₃	NA	0.777
Δ IL-10% ₂₋₁	NA	0.601
Δ IL-10% ₃₋₂	NA	0.726
Δ IL-10% ₃₋₁	NA	0.677
PCT ₁	NA	0.206
PCT ₂	NA	0.164
PCT ₃	NA	0.150
Δ PCT% ₂₋₁	NA	0.922
Δ PCT% ₃₋₂	NA	0.325
Δ PCT% ₃₋₁	NA	0.688
LAC ₁	NA	0.838
LAC ₂	NA	0.834
LAC ₃	NA	0.830
Δ LAC% ₂₋₁	NA	0.435
Δ LAC% ₃₋₂	NA	0.639
ΔLAC%₃₋₁	0.030	1.512 (1.041~2.196)

Figures

Figure 1

Levels of different laboratory and clinical parameters in survivors and non-survivors of Sepsis+ARDS at ICU admission (time-1), peak of shock (time-2), and before death or ICU discharge (time-3).