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*Original Article*

# The value of TLR-4, CRP, PCT and WBC levels in assessing the diagnosis and prognosis of sepsis patients

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**Abstract:** Aims: Sepsis has a high clinical mortality and disability rate in the absence of early diagnosis. Our goal is to investigate the correlation between the level of Toll like receptor-4 (TLR-4), procalcitonin (PCT), C reactive protein (CRP) and White Blood Count (WBC) in patient's circulation and the prognosis of sepsis. Methods: Forty patients with sepsis and 60 patients without sepsis in the Emergency Department were selected as the observation group and control group, respectively. The 40 patients with sepsis were re-divided into the death group (n=24) and survival group (n=16). Levels of TLR-4, PCT, CRP, and WBC were tested on day 1 and day 7 after admission. Count data were analyzed by Chi square test and the significant level was $\alpha$=0.05. ROC curve was used to compare the sensibility of the four indicators. Spearman's correlation analysis was used to evaluate the correlation of TLR-4, PCT, CRP and WBC levels with the scores of APECHEIII and SOFA. Results: The TLR-4 and PCT levels were increase on both day 1 and day 7 in the observation group, and the PCT level in subjects was decreased from day 1 to 7 in each group. Besides, we found the changes in TLR-4 and PCT levels have high consistency with the degrees of sepsis (reflected by SOFA and APECHEIII scores). The death cases have a higher TLR-4 and PCT levels than the survival cases in the observation group. Meanwhile, PCT (82.50%, 96.67%) has a higher sensitivity and specificity in sepsis and a better positive correlation with the APECHEIII and SOFA scores (r=0.683, 0.706; P<0.05). Conclusion: TLR-4 and PCT can be used as important markers to indicate the extent of the sepsis in the early stage and assess the severity of sepsis. The change in PCT and CRP can reveal the progression and prognosis of sepsis patients.

**Keywords:** Sepsis, Toll like receptor-4 (TLR-4), procalcitonin, C reactive protein (CPR), White Blood Count (WBC)

## Introduction

Sepsis is a kind of over activation of the innate immune system and the pro-inflammatory cascade, in response to severe microbial infection or extensive tissue damage (such as caused by burns or multiple injuries) [1]. This syndrome has a high clinical mortality and disability rate in the absence of early diagnosis [2-4]. For the purpose of improving rapid diagnosis methods and sepsis grading standards in order to provide a reliable basis for the treatment strategy and prognosis, finding out the specific and sensitive biological indicators is a matter of urgency in clinical practice.

Base on previous study, many biomarkers have been reported to be associated with sepsis, such as complement system [5], neutrophil features [6], C reactive protein (CPR) [7], Toll like receptor-4 (TLR-4) [8], procalcitonin (PCT) [9], inflammation-associated cytokines (IL-6, IL-1, TNF-α) [10], NT, oxLDL [11], and their like.

However, these parameters for sepsis diagnosis have a huge discrepancy between the theoretical research and clinical practice. The studies of the complement system in sepsis have no unified conclusion so far, in clinical studies of sepsis, increased concentrations of C3a, C4a and C5a in the plasma have been linked to poor outcome and survival [12], while C3a might have anti-inflammatory properties [13]. The inflammation-associated cytokines have shown that they are crucial factors for myocardial dysfunction caused by sepsis in animal experiments [14], but shows a contrary conclusion in real-life clinical setting [15]. Cytokines

**Table 1.** Patients' characteristics in observation and control groups

| | Observation group (n=40) | Control group (n=60) | P |
|---|---|---|---|
| Age, years | 66.5±18.3 | 65.2±20.3 | N.S |
| Gender M/F, n | 27/13 | 41/19 | N.S |
| Infection site, n (%) | | | |
| Lung | 15 (37.5%) | 20 (33.3%) | N.S |
| Blood | 8 (20%) | 10 (16.6%) | N.S |
| Gastrointestinal tract | 12 (30%) | 21 (35%) | N.S |
| Genitourinary tract | 5 (12.5%) | 9 (15%) | N.S |
| Respiratory factors | | | |
| $PaO_2$ (mm Hg) | 70.1±14.5 | 85.5±10.34 | 0.034 |
| $FiO_2$ (mm Hg) | 0.34±0.09 | 0.24±0.15 | 0.027 |
| $PaO_2/FiO_2$ | 226.1±133.2 | 360.4±97.4 | 0.016 |
| Platelets ($\times 10^3$/uL) | 238±130 | 253±107 | N.S |
| Bilirubin (mg/dL) | 0.80±0.86 | 0.94±1.71 | N.S |
| MAP (mm Hg) | 80.4±16.2 | 95.4±20.7 | 0.011 |
| GCS score | 10.4±2.7 | 15.9±2.3 | 0.000 |
| Creatinine (mg/dL) | 2.67±2.45 | 1.24±1.24 | N.S |
| Prognosis, n (%) | | | |
| Survival | 16 (40%) | 4 (6.6%) | |
| Death | 24 (60%) | 56 (93.3%) | |

may play a role in the diagnosis of sepsis, but there are many factors can affect its change *in vivo* and its specificity for sepsis still remains to be confirmed.

Nevertheless, TLR-4 is a kind of pathogen associated with molecular pattern receptor, which is closely related to the development of sepsis. When an exogenous microbial invasion of the body occurs, the TLR-4 receptor activates the innate immune system in the body and causes the inflammatory response to remove the pathogen [4, 16]. PCT was thought to be an ideal indicator for evaluation of sepsis inflammation [17, 18]. Most of the studies have shown a lower level of PCT in patients who survived from sepsis or an infectious episode than who did not [17]. Meanwhile, CPR and White Blood Count (WBC) were revealed to be of value to judge the severity of sepsis infection [18-21]. However, their specificity and sensitivity for sepsis were not satisfactory either, even though they were accessible indicators in clinic practice. Our research was designed to investigate the dynamic changes of levels of TLR-4, CRP, PCT and WBC in serum, and their clinical significance in diagnosis and assessment of patients with sepsis admitted to the ICU in our hospital.

## Material and methods

### *Patients and groups*

This was a retrospective, observational study conducted in the Emergency Department of the Hospital Affiliated to Xing Tai Medical College. The inclusion and exclusion in this study was based on the following criteria: (1) patients who were between 18 and 80 years of age, (2) clinically confirmed sepsis in the ICU, (3) available serum PCT, CRP, TLR-4 and WBC at diagnosis, (4) the follow-up data was obtainable, (5) survival for more than 7 days after administration, (6) no clinical evidence of malignancies, agranulocytosis or severe liver and renal insufficiency. The 40 patients with sepsis and 60 patients without sepsis in the ICU of our hospital were addmited from April 2018 to December 2018 and were consecutively selected as the observation group (n=40) and control group (n=60) in the present study. The 40 patients with sepsis were re-divided into the death group (n=24) and survival group (n=16). Sepsis diagnosis was conformed by the diagnostic criteria of sepsis in the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) consensus conference in 2001. The initial infection site in observation group included the lungs, blood and chest. The control group had basic diseases similar to those in the observation group, such as chest and lung diseases and mild infection symptoms, but still do not meet the diagnostic criteria for sepsis. The approval for conducting this project was granted by the ethics committee of Capital Medical University in China, and the work has been carried out in accordance with The Code of Ethics of the World Medical Association. All the patients had signed an informed consent when they were transferred to the Emergency Department, Hospital Affiliated to Xing Tai Medical College.

### *Detection method*

Double antibody ELISA kit method was used to detect the TLR-4 (Shanghai Yi Feng Biological Technology Co., Ltd.); CRP original ELISA kit (BECKMAN COULTER company, USA) and fully automatic quantitative analyzer were applied to detect CRP; Electrochemical luminescence

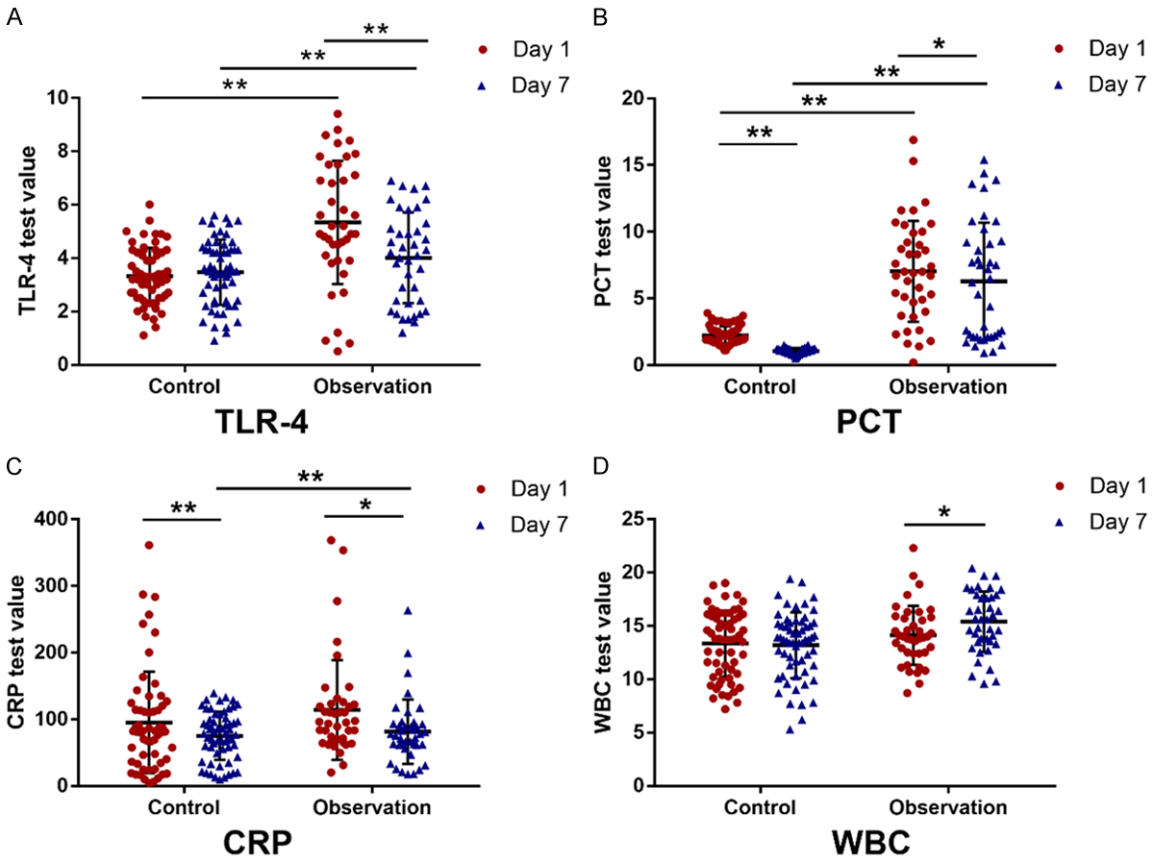


**Figure 1.** The comparison of the four indicators between the control and observation groups in Day 1 and Day 7. A. For TLR-4; B. For PCT; C. For CRP; D. For WBC. *P<0.05; **P<0.01.

**Table 2.** The comparison of 4 biomarkers between the observation and control groups on Day 1 and Day 7 (Mean ± SD)

| | Day 1 | Day 7 | #P (D1 vs D7) |
|---|---|---|---|
| TLR-4 | | | |
| Control (n=40) | 3.47±1.22 | 3.32±1.06 | 0.117 |
| Observation (n=60) | 5.33±2.30* | 4.69±2.21*,# | 0.000 |
| *P (Con vs Obser) | 0.000 | 0.000 | |
| PCT | | | |
| Control (n=40) | 2.22±0.68 | 1.05±0.21# | 0.000 |
| Observation (n=60) | 7.04±3.78* | 6.28±4.40*,# | 0.048 |
| *P (Con vs Obser) | 0.000 | 0.000 | |
| CRP | | | |
| Control (n=40) | 95.25±75.91 | 75.32±36.02 | 0.000 |
| Observation (n=60) | 114.05±74.76 | 81.34±48.10# | 0.048 |
| *P (Con vs Obser) | 0.000 | 0.000 | |
| WBC | | | |
| Control (n=40) | 13.33±3.10 | 13.19±3.08 | 0.137 |
| Observation (n=60) | 13.41±2.76 | 14.62±5.12# | 0.022 |
| *P (Con vs Obser) | 0.906 | 0.085 | |

*P<0.05, compared with control group at the corresponding day(s); #P<0.05, compared with Day 1 in the same group.

method was used to detect the PCT (ROCHE Diagnostics, 2010 model PCT kits, German). Automatic blood cell analyzer and the original accessory kit were applied to detect the WBC (SYSMEX company, Japan). All patients admitted to the ICU had collected blood samples within 2 hours, and then conducted the above four tests after plasma separation. After receiving the test report, blood culture for pathogen detection was performed for suspected sepsis patients, and the above four tests were repeated again to determine whether the patient was diagnosed with sepsis. The second test result was recorded. Levels of TLR-4, PCT, CRP, and WBC in control or sepsis patients were tested again on day 7 (d 7) after

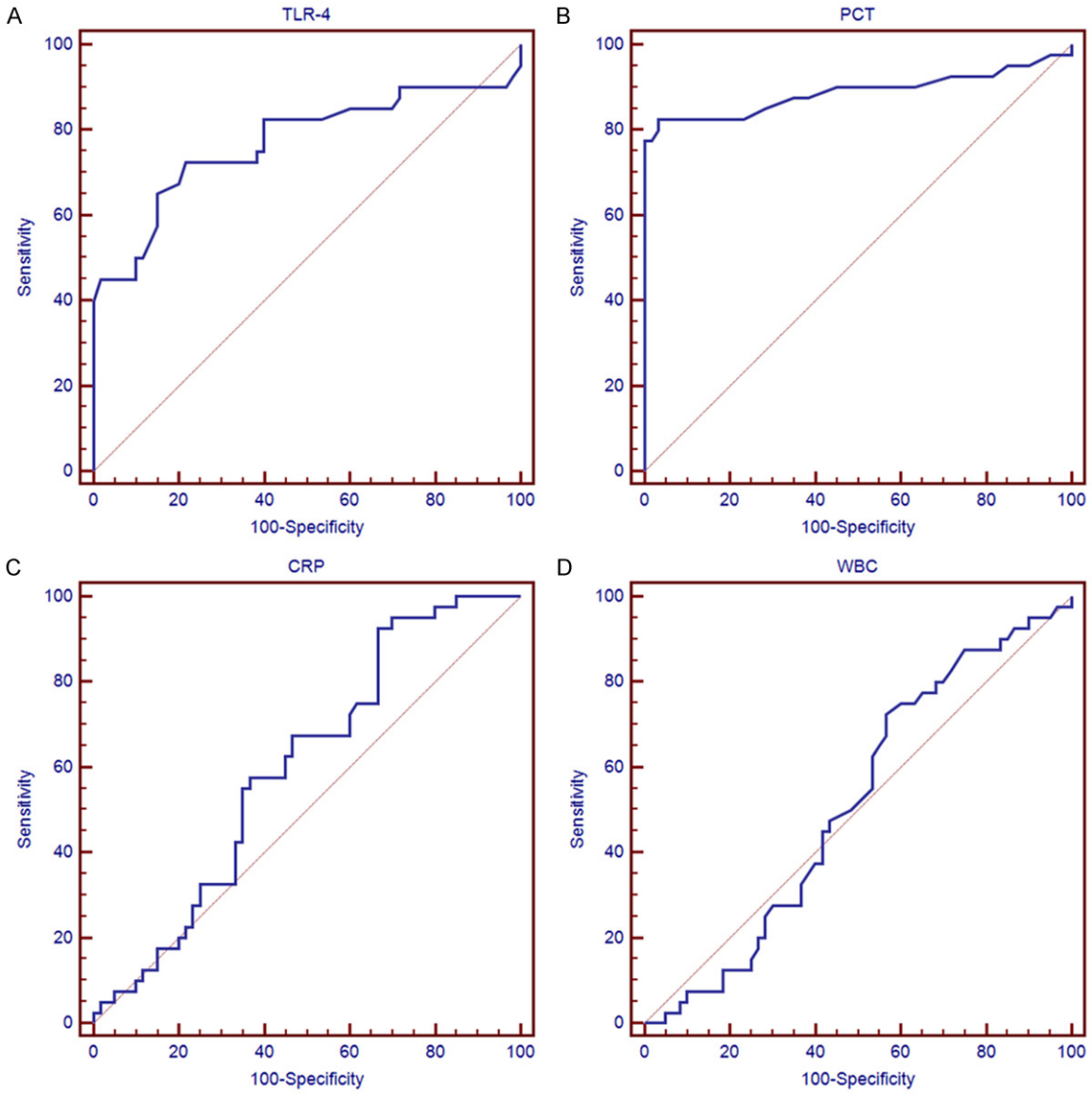


**Figure 2.** The ROC curves of the four indicators which obtained from comparison of control group and observation groups. The Area under the ROC curve and asymptotic 95% Confidence Interval are shown in **Table 3** and the Cut-off Point, Sensitivity, Specificity, Positive Likelihood Ratio and Negative Likelihood Ratio are shown in **Table 4**. A. For TLR-4, B. For PCT, C. For CRP, D. For WBC.

**Table 3.** The area under the ROC curve and asymptotic 95% Confidence Interval for the four markers

| Marker | Area under the ROC curve (AUC) | Asymptotic 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| TLR-4 | 0.770 | 0.675 | 0.848 |
| PCT | 0.888 | 0.809 | 0.942 |
| CRP | 0.598 | 0.495 | 0.695 |
| WBC | 0.516 | 0.414 | 0.617 |

being admitted to ICU. Besides, the APACHEIII [22] was calculated using variables collected at the time of ICU admission. The Sequential Organ Failure Assessment (SOFA) score [23] was calculated using the worst values recorded in the first 24 hours of the ICU admission.

*Statistical methods*

SPSS 22.0 statistical software was used for data analysis. The calculated data were expressed as the mean and SD and all were compared by normality test with Kolmogorov-Smirnov test. Group *t* test was used in comparison among groups and intra-group was compared by pair *t* test. Count data

**Table 4.** Comparison of cut-off point, sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for four indicators

| Markers | Cut-off Point | Sensitivity | Specificity | Positive Likelihood Ratio | Negative Likelihood Ratio |
|---|---|---|---|---|---|
| TLR-4 | 4.4 | 72.5 | 78.33 | 3.35 | 0.35 |
| PCT | 3.5 | 82.50 | 96.67 | 24.75 | 0.18 |
| CRP | 57.5 | 92.50 | 33.33 | 1.39 | 0.22 |
| WBC | 14.5 | 72.50% | 43.33% | 1.28 | 0.63 |

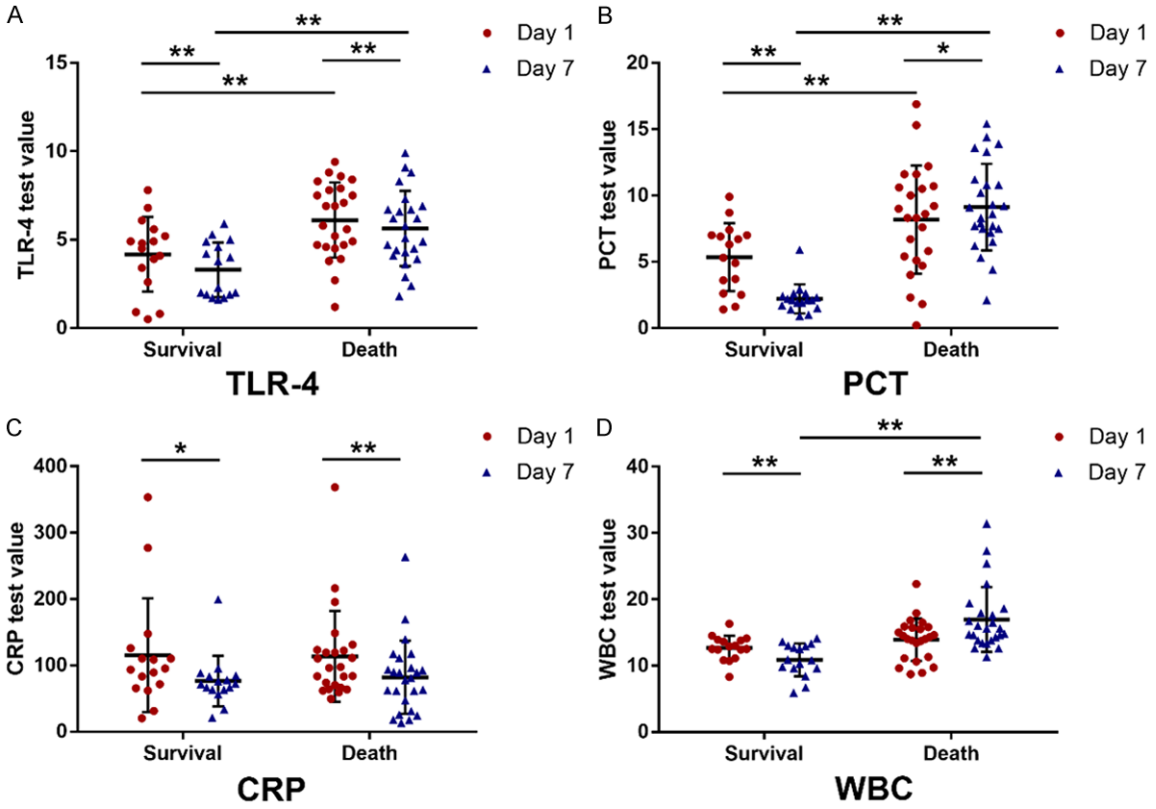


**Figure 3.** The comparison of the four indicators between the survival and death groups in Day 1 and Day 7. A. For TLR-4; B. For PCT; C. For CRP; D. For WBC. *P<0.05; **P<0.01.

were analyzed by Chi square test and the significant level was α=0.05. The ROC curve was used to compare the sensibility of the four indicators. Spearman's correlation analysis was used to evaluate the correlation of TLR-4, PCT, CRP and WBC levels with the scores of APECHEIII and SOFA.

## Results

### *Basic information of the observation group and control group*

As shown in **Table 1**, there were no differences in ages and sex was found between the two groups (68 males and 32 females; mean age 67.2±19.3 years). The initial infection site in the observation group included the lungs, blood and chest, with 20 patients (50%), 8 patients (20%) and 12 patients (30%) respectively, and the control group also had similar disease to those in the observation group which has been shown in **Table 1**.

### *Comparison of four indicators in observation and control groups*

In the comparison with control group, the TLR-4 (P=0.000) and PCT (P=0.000) levels in the observation group was obviously higher.

**Table 5.** Comparison of the four indicators in the survival and death groups (Mean ± SD)

| | Day 1 | Day 7 | #P (D1 vs D7) |
|---|---|---|---|
| TLR-4 | | | |
| Survival (n=16) | 3.57±2.11 | 2.80±1.54# | 0.004 |
| Death (n=24) | 6.11±2.12* | 5.69±2.12*,# | 0.000 |
| *P (Survival vs Death) | 0.007 | 0.001 | |
| PCT | | | |
| Survival (n=16) | 4.74±2.55 | 1.97±0.56# | 0.000 |
| Death (n=24) | 8.18±4.08* | 9.15±3.33*,# | 0.001 |
| *P (Survival vs Death) | 0.018 | 0.000 | |
| CRP | | | |
| Survival (n=16) | 115.26±85.72 | 76.08±38.00# | 0.010 |
| Death (n=24) | 113.24±68.43 | 84.85±54.30# | 0.000 |
| *P (Survival vs Death) | 0.934 | 0.579 | |
| WBC | | | |
| Survival (n=16) | 12.67±1.85 | 10.88±2.46# | 0.000 |
| Death (n=24) | 13.90±3.17 | 17.11±4.93*,# | 0.000 |
| *P (Survival vs Death) | 0.172 | 0.000 | |

*P<0.05, compared with survival group at the corresponding day(s); #P<0.05, compared with day 1 in the same group.

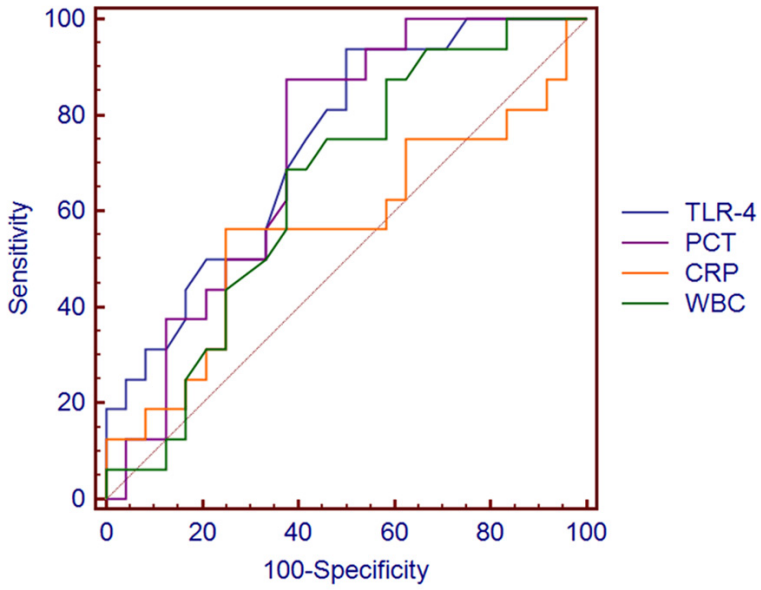


**Figure 4.** The ROC curves of the four indicators which obtained from comparison of survival group and death groups in day 1. The Area under the ROC curve and Asymptotic 95% Confidence Interval are shown in **Table 6**.

However, the levels of CRP (P=0.225) and WBC (P=0.906) between the two groups presented no significant difference. The TLR-4 and PCT levels of the observation group on day 7 were apparently lower than that of day 1 (**Figure 1** and **Table 2**). Furthermore, ROC of the PCT and TLR-4 showed the sensitivity of 72.5 % and 82.5%, and specificity of 78.33% and 96.67% respectively. TLR-4 showed Positive Likelihood Ratio of 3.35 and Negative Likelihood Ratio of 0.35, and PCT showed a higher Positive Likelihood Ratio of 24.75 and a lower Negative Likelihood Ratio of 0.18. When compared to the other markers CRP and WBC had low specificity (**Figure 2** and **Tables 3**, **4**).

*Comparison four indicators in the survival and death groups*

The TLR-4 and PCT levels of the death group were higher than that of survival group in day 1 and day 7. Nevertheless, the difference of CRP and WBC between the two groups was not significant. Compared with the same group, the level of TLR-4 and CRP in the survival group on day 7 was lower than that of day 1, and the PCT and WBC level of the death group on day 7 was significantly higher than that of day 1 (**Figure 3** and **Table 5**). Meanwhile, we further compared the ROC curves of each indicator between the death and survival groups, and the result show that among the four indicators, TLR-4 and PCT had better discriminating significance between the surviving group and the death group on the first day (**Figure 4** and **Table 6**). However, by the seventh day, WBC and PCT showed a better indication of the severity of the sepsis (**Figure 5** and **Table 7**).

*Correlation analysis of the four indicators with the scores of APECHEIII and SOFA in observation group*

In contrast with the survival group, the scores of APECHEIII and SOFA in the death group was higher. Compared within the same group,

**Table 6.** The Area under the ROC curve and asymptotic 95% Confidence Interval of the four indicators between the survival and death groups in Day 1

| Marker (Day 1) | Area under the ROC curve (AUC) | Asymptotic 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| TLR-4 | 0.736 | 0.573 | 0.862 |
| PCT | 0.725 | 0.561 | 0.854 |
| CRP | 0.565 | 0.399 | 0.721 |
| WBC | 0.648 | 0.482 | 0.792 |

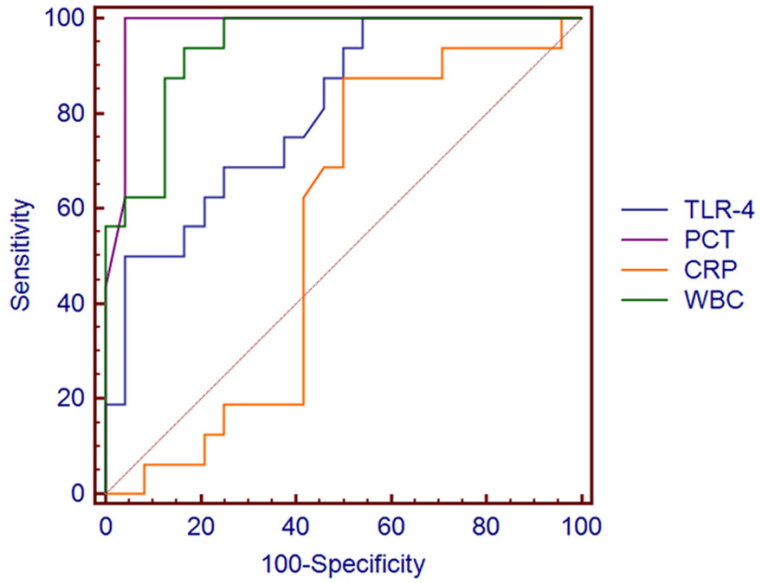


**Figure 5.** The ROC curves of the four indicators which obtained from comparison of the survival group and death groups in day 7. The Area under the ROC curve and asymptotic 95% Confidence Interval are shown in **Table 7**.

**Table 7.** The Area under the ROC curve and asymptotic 95% Confidence Interval of the four indicators between the survival and death groups in Day 7

| Marker (Day 7) | Area under the ROC curve (AUC) | Asymptotic 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| TLR-4 | 0.803 | 0.647 | 0.912 |
| PCT | 0.980 | 0.877 | 0.996 |
| CRP | 0.559 | 0.393 | 0.715 |
| WBC | 0.940 | 0.817 | 0.990 |

scores of APECHEIII and SOFA on day 7 were decreased than that of day 1 shown in **Table 8**. In addition, the Spearman correlation analysis of the TLR-4, PCT, CRP and WBC level on the first day compared with the scores of APECHEIII and SOFA revealed that PCT showed positive correlation with the scores of APECHEIII and SOFA (r=0.683, 0.706; $P$<0.05), whereas the TLR-4, CRP and WBC revealed no correlation with the score of APECHEIII and SOFA.

## Discussion

Sepsis is a systemic inflammatory response caused by infection, and its infection factors are numerous, its pathological mechanisms are complicated, thus it is a tough issue in clinical treatment [24, 25]. After sepsis, the endotoxins lead the body to produce a number of inflammatory mediators and forms a waterfall effect, so that the tissue is damaged and thus causes organ dysfunction [26, 27].

Even though a large volume of information has been collected about managing and treating septic patients [28-31], the lack of knowledge about the diagnostic criteria for sepsis by ICU teams is one of the greatest factors limiting its adequate treatment. Many efforts have been made in recent years to give a standardized definition to this syndrome and consequently make the diagnosis easier.

Previous studies showed that [4, 16, 32] abnormal activation of cell signaling pathways *in vivo* is an important reason for the inflammatory reaction. For example, TLR-4 recognizes the lipopolysaccharide, combining CD14, MyD88 and other factors to jointly mediate the NF-κB pathway, activate the mononuclear macrophage system and then induce the inflammatory reaction, resulting in the release of inflammatory cytokines including TNF alpha and IL-6 which aggravates the inflammatory reaction until sepsis occurs.

Meanwhile, PCT as the precursor of calcitonin is closely related to the severity of bacterial infection, and its level is increased along with

**Table 8.** Comparison of the CRP in the survival and death groups (Mean ± SD)

| | Day 1 | Day 7 | #P |
|---|---|---|---|
| SOFA score | | | |
| Survival (n=16) | 5.86±3.72 | 4.21±4.74# | 0.010 |
| Death (n=24) | 12.94±8.15* | 19.62±5.23*,# | 0.035 |
| *P | 0.000 | 0.000 | |
| APACHEIII score | | | |
| Survival (n=16) | 18.31±5.63 | 12.19±4.12*,# | 0.001 |
| Death (n=24) | 23.26±5.29*,# | 27.78±5.49*,# | 0.037 |
| *P | 0.000 | 0.000 | |

*P<0.05, compared with survival group at the corresponding day (s); #P<0.05, compared with day 1 in the same group.

the degree of infection [18]. On the other hand, PCT is a kind of easily detected protein and not a readily degraded soluble protein, so its concentration is significantly associated with patient prognosis. In recent years, this factor as a new bacterial indicator has played an important role in diagnosis of infectious disease [18, 33]. As for CRP and WBC, they are the basic indicators of infection, but cannot indicate the specific type of infection.

This study suggests that after infection, the levels of TLR-4 and PCT were markedly increased, and these indicator were increased significantly in sepsis, changing constantly along with the illness severity which was similar with previous study results [32, 34]. No difference in the CRP level was found between the observation and control group, and the death and survival group. However, its level on day 7 was lower than that of day 1 in each group, suggesting that CRP was not of value in diagnosis of sepsis, whereas, it could be used for monitoring the severity and prognosis of sepsis condition.

The score of SOFA and APACHEIII was used to evaluate the severity of patient illness. Results showed that SOFA and APACHEIII scores in the observation group were higher than that of the control group, while that of the death group was higher than that of the survival group. In addition, only the PCT level was positively correlated with the SOFA and APACHEIII scores, other indicators presented no correlations, which was similar with previous study results [35]. Therefore, it could be preliminarily thought that PCT level probably has a significant positive correlation with the severity of sepsis, instead, the TLR-4, CRP and WBC level might have no obvious correlation with sepsis severity [19].

This study has several limitations. First of all it is a retrospective observational study with a limited studied population number, and this could have affected prognostic results. Furthermore, it is a single center study, and we assessed only in-hospital deaths and not out of hospital events. Finally, we measured and correlated TLR-4, PCT, WBC and CRP only on day 1 and day 7 after admission to ICU but not after discharge.

In conclusion, the TLR-4 and PCT levels can serve as important reference indicators for severe patients with early stage sepsis. The PCT and CRP levels can be used as a monitoring indicators for illness severity and prognosis. However, it's not certain whether TLR-4 level could be used for risk factor prediction of the sepsis prognosis.

## Disclosure of conflict of interest

None.

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