Prognostic significance of PCT and CRP evaluation for adult ICU patients with sepsis and septic shock: retrospective analysis of 59 cases

Na Cui[1],*, Hongwei Zhang[1],* ⓘ, Zhi Chen[2] and Zhanbiao Yu[1]

Abstract

Objective: To investigate the prognostic significance of serum procalcitonin (PCT) and C-reactive protein (CRP) in patients with sepsis and those with septic shock.

Methods: Fifty-nine patients were divided into sepsis and septic shock groups, as well as survivor and non-survivor groups, according to the severity of the disease and patient survival. Serum PCT and CRP measurements at the time of hospitalization in the intensive care unit were examined.

Results: On the 2nd, 3rd, and 5th days, the CRP level was higher in the non-survivor group than in the survivor group, and the serum CRP level was higher in patients in the septic shock group than in patients in the sepsis group. Regarding changes in serum PCT level in each group, the levels of PCT were significantly different between non-survivor and survivor groups, whereas they did not differ between patients in the sepsis and septic shock groups. Serum PCT kinetics (ΔPCT) were similar between groups.

Conclusions: Serum PCT and CRP have good clinical diagnostic and prognostic value for patients with sepsis and septic shock. Kinetic studies of PCT and CRP can improve sensitivity and accuracy when evaluating the prognosis of patients with sepsis and those with septic shock.

*These authors contributed equally to this work.

[1]Department of ICU, Affiliated Hospital of Hebei University, Baoding, Hebei, P. R. China
[2]Department of Hepatobiliary Surgery, Affiliated Hospital of Hebei University, Baoding, Hebei, P. R. China

Corresponding author:
Hongwei Zhang, Department of ICU, Affiliated Hospital of Hebei University, No. 212 Yuhua East Road, Baoding, Hebei, 071000, P. R. China.
Email: jqz543@163.com

Introduction

Sepsis and septic shock are the most common causes of death in hospitals. Sepsis is a frequently encountered systemic inflammatory response syndrome caused by infection; annually, 18 million patients receive treatment for sepsis.[1] A state of sepsis is extremely dangerous, and can develop rapidly, with a high fatality rate. Notably, sepsis (secondary to infection) and septic shock (sepsis accompanied by hypotension that is difficult to reverse with fluid resuscitation) are major causes of death for non-heart disease patients in the intensive care unit (ICU).[2] Currently, the diagnosis of such diseases is primarily based on biochemical indexes or pathogen detection through bacterial culture. Relevant biochemical tests lack high specificity, which leads to increased uncertainty in the diagnostic process and is challenging for clinicians. Importantly, the inability to accurately diagnose according to exact biochemical indicators often leads to delay or failure to carry out the appropriate clinical treatment, and clinicians cannot assess changes in blood conditions with sufficient time to modify treatment.[3–5] Bacterial culture has high specificity, but requires an extended incubation period; this leads to treatment delay, as well as antibiotic misuse and abuse. Because patients with sepsis and septic shock often exhibit cardiovascular and cerebrovascular diseases or endocrine diseases, the diagnostic process is highly complex and variable. The physical conditions of patients with sepsis or septic shock are severe, and these patients are often transferred to the ICU from emergency departments. Rapid and accurate disease diagnosis, as well as timely medical intervention, can help clinicians confirm the disease in an appropriate timeframe and make necessary treatment decisions. For example, according to the specificity of the biochemical indicators to determine the severity of infection, timely control of infection can be achieved through effective antibiotics or surgery to reverse the progress of the disease; clinicians can also monitor changes in disease. Procalcitonin (PCT), a prohormone of calcitonin, is encoded by the calcitonin-I (*CALC-1*) gene on chromosome 11, and comprises 114–116 amino acids. C-reactive protein (CRP) is an acute-phase reactive protein that can interact with capsule C polysaccharides of *Streptococcus pneumoniae*. Among the clinically useful biochemical detection indexes, PCT has shown superiority as an important reference marker for infection, as well as antibiotic management guidance.[6,7] Furthermore, some studies have shown that changes in PCT and CRP concentrations are related to the prognosis of patients with sepsis.[8] Use of these parameters may improve accuracy of judgment regarding the prognosis of infection. Thus, this study was performed involving adult patients who were hospitalized in the ICU due to sepsis or septic shock, to investigate the clinical significance of changes in serum PCT and CRP in these patients.

Materials and methods

Criteria for inclusion in the study

The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Hebei University. Adult patients selected for this study were hospitalized in the ICU of the Affiliated Hospital of Hebei University during the period from March 2016 to July 2018. Inclusion criteria: 1) patients who met clinical diagnostic criteria for sepsis or septic shock; 2) patients who were between 55 and 80 years of age; 3) patients who provided written informed consent to participate in the study. Exclusion criteria: 1) patients who exhibited other cardiovascular and cerebrovascular diseases; 2) patients who exhibited an unrecoverable state of death or dying.

Kinetic study of PCT and CRP

During early morning fasting, 5 mL of blood were collected from the elbow vein and added to an EDTA tube for 2 hours. The serum CRP level was detected by three processes: ELISA, CX20 automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA), and immune turbidimetry. PCT was determined by electrochemiluminescence immunoassay (Cobas E601, Roche, Basel, Switzerland); calibration solution, reagent, and quality control products were also provided by Roche. PCT analysis was performed in accordance with the verification requirements of the Clinical and Laboratory Standards Institute (Guidelines EP15-A2). PCT kinetic changes were expressed as ΔPCT, and CRP kinetic changes were expressed as ΔCRP. PCT_i referred to the PCT value of the ith day, and CRP_i referred to the CRP value of the ith day, where $i = 1, 2, 3, 5$ (1 represents the day of hospitalization). $\Delta PCT_i/1 = |(PCT_i - PCT_1)|/PCT_1$, $\Delta CRP_i/1 = |(CRP_i - CRP_1)|/$ CRP1, where $i = 2, 3, 5$; |indicates absolute value in the preceding equation.

Statistical analysis

SPSS 21.0 statistical software was used for data analysis. The measurement data did not conform to a normal distribution; therefore, medians were used for statistical description (interquartile range). The A nonparametric rank-sum test (Mann-Whitney U test) was used for inter-group comparison. A two-sided P-value of <0.05 was considered to indicate statistical significance.

Results

Patient Groups

Fifty-nine patients met the criteria for inclusion in this study. In accordance with the disease severity and patient survival, the 59 patients were divided into septic shock (i.e., an acute circulatory disorder resulting from sepsis and hypoperfusion caused by systemic shock) and sepsis groups, as well as non-survivor and survivor groups (Table 1). There were 37 patients in the survivor group (63%) and 22 patients in the non-survivor group (37%); there were 37 patients in the sepsis group (63%) and 22 patients in the septic shock group (37%).

Comparison of serum CRP changes

CRP levels in the non-survivor group on the 2nd, 3rd, and 5th days were higher than those in the survivor group ($P = 0.0009$, $P = 0.0007$, and $P = 0.0001$; Table 2). In CRP kinetics comparison, the differences in CRP levels between the 2nd and 1st day, compared with CRP level on the 1st day (ΔCRP2/1); the differences in CRP levels between the 3rd and 1st day, compared with CRP level on the 1st day (ΔCRP3/1); and the differences in CRP levels between the 5th day and 1st day, compared with CRP level on the 1st day

Table 1. Grouping of elderly patients in ICU.

Group	Survivor	Non-survivor	Sepsis	Septic shock
No. (n)	37	22	37	22
Age	67.2 ± 13.2	70.1 ± 12.6	67.1 ± 14.2	70.0 ± 10.9
Sex (male:female)	23:14	14:8	22:15	15:7

Note: Sex is number of patients shown as a ratio.

Table 2. Comparison of serum C-reactive protein level (mg/L).

Group	CRP1	CRP2	CRP3	CRP5
Survivor	115.0 (129.77)	91.9 (86.95)	71.0 (65.75)	31.2 (62.98)
Non-survivor	163.3 (226.9)	169.3 (86.9)	136.4 (77.0)	95.7 (131.05)
P	0.312	0.0009	0.0007	0.0001
Sepsis	100.6 (132.18)	88.2 (59.15)	68.7 (80.6)	50.2 (112.1)
Septic shock	138.0 (73.99)	197.05 (92.33)	196.5 (149.15)	234.1 (166.6)
P	0.0818	0.0250	0.0431	0.0317

Note: Median outside parentheses and quartile spacing inside parentheses. CRP: C-reactive protein.

(ΔCRP5/1) were statistically significant (P = 0.012, P = 0.004, and P = 0.0001; Table 3). On the 2nd, 3rd, and 5th days, serum CRP levels of patients in the septic shock group were higher than those of patients in the sepsis group (P = 0.025, P = 0.043, and P = 0.032; Table 2). In kinetics comparison, only ΔCRP3/1 showed a significant difference (P = 0.025; Table 3).

Comparison of serum PCT level change

Regarding changes in serum PCT level, levels in the non-survivor group on the 2nd, 3rd, and 5th days were higher than those in the survivor group (P = 0.0001 for all comparisons; Table 4), whereas the sepsis and septic shock groups showed no statistical differences (Table 4). In serum PCT kinetics comparison of survivor and non-survivor groups, the differences in PCT levels between the 2nd and 1st day, compared with PCT level on the 1st day (ΔPCT2/1), and the differences in PCT levels between the 3rd and 1st day, compared with PCT level on the 1st day (ΔPCT3/1) were statistically significant

Table 3. Comparison of serum C-reactive protein kinetics (ΔCRP in mg/L).

Group	ΔCRP2/1	ΔCRP3/1	ΔCRP5/1
Survivor	0.35 (0.19)	0.54 (0.26)	0.79 (0.31)
Non-survivor	0.26 (0.21)	0.40 (0.22)	0.50 (0.29)
P	0.0123	0.0036	0.0001
Sepsis	0.34 (0.14)	0.53 (0.26)	0.66 (0.37)
Septic shock	0.29 (0.24)	0.41 (0.31)	0.62 (0.43)
P	0.4373	0.0254	0.3884

Note: Median outside parentheses and quartile spacing inside parentheses. CRP: C-reactive protein.

(P = 0.012, P = 0.004; Table 5). In contrast, the differences in PCT levels between the 5th day and 1st day, compared with PCT level on the 1st day (ΔPCT5/1), did not show a significant difference. In serum PCT kinetics comparison of sepsis and septic shock groups, there were no statistical differences (Table 5).

Discussion

Currently, PCT level kinetics and CRP level kinetics have become the focus of research

Table 4. Comparison of serum procalcitonin level (ng/L).

Group	PCT1	PCT2	PCT3	PCT5
Survivor	8.36 (22.98)	2.64 (11.08)	1.22 (8.55)	0.66 (6.34)
Non-survivor	53.60 (40.73)	34.66 (24.77)	19.36 (14.32)	15.46 (16.05)
P	0.0001	0.0001	0.0001	0.0001
Sepsis	23.39 (39.82)	11.37 (31.93)	8.77 (20.39)	2.88 (12.70)
Septic shock	21.20 (61.02)	9.04 (36.02)	6.45 (16.77)	3.88 (19.84)
P	0.9875	0.8878	0.8693	0.4612

Note: Median outside parentheses and quartile spacing inside parentheses. PCT: procalcitonin.

Table 5. Comparison of serum procalcitonin kinetics (ΔPCT in ng/L).

Group	ΔPCT2/1	ΔPCT3/1	ΔPCT5/1
Survivor	0.66 (0.49)	0.80 (0.28)	0.88 (0.27)
Non-survivor	0.28 (0.25)	0.56 (0.28)	0.71 (0.18)
P	0.0003	0.0005	0.0322
Sepsis	0.42 (0.50)	0.70 (0.33)	0.80 (0.26)
Septic shock	0.44 (0.46)	0.71 (0.31)	0.74 (0.31)
P	0.6325	0.8019	0.1956

Note: Median outside parentheses and quartile spacing inside parentheses. PCT: procalcitonin.

efforts for identification and assessment of disease prognosis.[9,10] Under normal physiological conditions, the levels of serum PCT and CRP are very low, and are maintained at a relative equilibrium in the body. When sepsis is caused by an inflammatory stimulus due to pathogen infection, the levels of serum PCT and CRP increase rapidly due to the host response to infection. PCT is an effective biochemical indicator of the severity of infection in patients with sepsis. PCT of 2 ng/mL indicates sepsis or septic shock.[11–13] CRP values can increase over 100-fold greater than baseline values, which indicate an active state of infection.

In this study, PCT and CRP tests were conducted for 59 elderly patients in the ICU who were diagnosed with sepsis/septic shock to further assess the significance of PCT, CRP, and dynamic changes in their levels with regard to the diagnosis and prognosis of sepsis and septic shock. Sepsis and septic shock, as well as multiple organ dysfunction syndrome (caused by the onset of sepsis), are the primary causes of death among ICU patients.[14] Thus far, the annual fatality rate of sepsis (secondary to infection) and septic shock (sepsis accompanied by hypotension that is difficult to reverse with fluid resuscitation) has continued to increase (up to 80%).[15] Some studies have indicated that PCT and CRP may serve as references with regard to the diagnosis of sepsis, but their abilities to support determination of sepsis prognosis need further investigation.[16,17] By comparing changes in the kinetics of serum PCT and CRP levels of patients with sepsis and those with septic shock, we found that increasing levels of PCT can distinguish sepsis or septic shock. Thus, PCT can serve as an effective chemical biomarker to evaluate the degree of infection among patients with sepsis.

Sepsis is not a single disease, and clinically manifests as a highly heterogeneous syndrome. Importantly, it is the result of interactions between host and pathogen.[18] Among elderly patients, sepsis and septic shock are often accompanied by compromised cardiac function, pathologic pulmonary changes, and urinary system abnormalities.[19,20] In the present study, we investigated the use of changes in PCT and CRP as biomarkers of sepsis severity, specifically among elderly patients.

The complicated pathological and physiological changes of elderly patients with sepsis involve changes in multiple biomarkers, as well as in multiple tissue and organ systems. Regarding changes in serum PCT levels, there were significant differences between survivor and non-survivor groups, while the sepsis and septic shock groups showed no statistical differences. The results of serum PCT kinetics (ΔPCT) analyses were similar. This study showed that, compared with the levels in the survivor group, PCT and CRP levels of the non-survivor group on the 5th day exhibited an increasing trend. Notably, increased CRP level was indicative of poor prognosis. We found that, when assessing the severity of sepsis in elderly patients, PCT was more clinically useful than CRP. Furthermore, studies of PCT kinetics were more useful than studies of the unadjusted PCT level. Compared with CRP, PCT is a favorable marker for assessing changes in clinical symptoms and patient prognosis. PCT can enhance the judgment of disease severity among patients with sepsis and those with septic shock, thereby improving the ability of clinicians to accurately assess disease prognosis.[21] Thus, we propose that PCT should be assessed daily for patients with sepsis who are hospitalized in the ICU.

Conclusion

In conclusion, PCT and CRP may aid in diagnosis and judgment of the prognosis of sepsis. Thus, these markers may change the nature of sepsis from a clinically defined physiological syndrome to a disease entity that can be defined by specific biochemical indexes; this change may further contribute to the development of better biochemical diagnosis capabilities and effective assistance in infection treatment. Therefore, research and development of specific biochemical markers and molecular diagnoses for sepsis and septic shock can improve assessment of patients' disease and facilitate detection of pathogens; it can also promote more accurate drug use and improved clinical management of sepsis. Importantly, PCT and CRP cannot meet all needs and expectations for diagnosis and management of treatment for patients with sepsis and those with septic shock. Finally, a combination of PCT and CRP biomarkers may serve as an enhanced index to assess the prognosis of patients with sepsis and septic shock, and should be investigated in future studies.

ORCID iD

Hongwei Zhang http://orcid.org/0000-0001-6375-5003

References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315: 801–810.
2. Maestraggi Q, Lebas B, Clere-Jehl R, et al. Skeletal muscle and lymphocyte mitochondrial dysfunctions in septic shock trigger ICU-acquired weakness and sepsis-induced immunoparalysis. *Biomed Res Int* 2017; 2017: 7897325.
3. Intke C, Korpelainen S, Hämäläinen S, et al. Interleukin-1 receptor antagonist as a biomarker of sepsis in neutropenic haematological patients. *Eur J Haematol* 2018. doi: 10.1111/ejh.13161
4. Erikson K, Ala-Kokko TI, Koskenkari J, et al. Elevated serum S-100β in patients with septic shock is associated with delirium. *Acta Anaesthesiol Scand* 2018; 63: 69–73.

5. Qiu Z, Shen K, Shu M, et al. [Value of Hepcidin as a diagnostic biomarker of sepsis in critically ill adults]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2018; 30: 652–657.

6. Gai L, Tong Y and Yan BQ. Research on the diagnostic effect of PCT level in serum on patients with sepsis due to different pathogenic causes. *Eur Rev Med Pharmacol Sci* 2018; 22: 4238–4242.

7. Zhao JJ, Lou XL, Chen HW, et al. Diagnostic value of decoy receptor 3 combined with procalcitonin and soluble urokinase-type plasminogen activator receptor for sepsis. *Cell Mol Biol Lett* 2018; 23: 22.

8. Mustafić S, Brkić S, Prnjavorac B, et al. Diagnostic and prognostic value of procalcitonin in patients with sepsis. *Med Glas (Zenica)* 2018; 15: 93–100.

9. Li Q and Gong X. Clinical significance of the detection of procalcitonin and C-reactive protein in the intensive care unit. *Exp Ther Med* 2018; 15: 4265–4270.

10. Aktug DN, Sumer S, Celik G, et al. How should procalcitonin and C-reactive protein levels be interpreted in hemodialysis patients. *Intern Med J* 2018; 48: 1222–1228.

11. Kade G, Literacki S, Rzeszotarska A, et al. Removal of procalcitonin and selected cytokines during continuous veno-venous hemodialysis using high cutoff hemofilters in patients with sepsis and acute kidney injury. *Blood Purif* 2018; 46: 153–159.

12. Pravin Charles MV, Kalaivani R, Venkatesh S, et al. Evaluation of procalcitonin as a diagnostic marker in neonatal sepsis. *Indian J Pathol Microbiol* 2018; 61: 81–84.

13. Wu CC, Lan HM, Han ST, et al. Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. *Ann Intensive Care* 2017; 7: 91.

14. Siddiqui I, Jafri L, Abbas Q, et al. Relationship of serum procalcitonin, C-reactive protein, and lactic acid to organ failure and outcome in critically Ill pediatric population. *Indian J Crit Care Med* 2018; 22: 91–95.

15. Zhou X, Liu J, Ji X, et al. [Predictive value of inflammatory markers for acute kidney injury in sepsis patients: analysis of 753 cases in 7 years]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2018; 30: 346–350.

16. Braha B, Mahmutaj D, Maxhuni M, et al. Correlation of procalcitonin and C-reactive protein with intra-abdominal hypertension in intra-abdominal infections: their predictive role in the progress of the disease. *Open Access Maced J Med Sci* 2018; 6: 479–484.

17. Liu Y, Yang W and Wei J. Guiding effect of serum procalcitonin (PCT) on the antibiotic application to patients with sepsis. *Iran J Public Health* 2017; 46: 1535–1539.

18. Kumar N, Dayal R, Singh P, et al. A comparative evaluation of presepsin with procalcitonin and CRP in diagnosing neonatal sepsis. *Indian J Pediatr* 2018. doi: 10.1007/s12098-018-2659-3

19. Gao Y, Zhu J and Yin C. Effects of target temperature management on the outcome of septic patients with fever. *Biomed Res Int* 2017; 2017: 3906032.

20. Sun Y, Jiang L and Shao X. Predictive value of procalcitonin for diagnosis of infections in patients with chronic kidney disease: a comparison with traditional inflammatory markers C-reactive protein, white blood cell count, and neutrophil percentage. *Int Urol Nephrol* 2017; 49: 2205–2216.

21. Samsudin I and Vasikaran SD. Clinical utility and measurement of procalcitonin. *Clin Biochem Rev* 2017; 38: 59–68.