Int J Clin Exp Med 2020;13(8):6136-6141
www.ijcem.com /ISSN:1940-5901/IJCEM0112526

Original Article

Cortisol and C-reactive protein/prealbumin ratio for evaluating prognosis in elderly patients with sepsis

Hui Lin[1*], Bixia Lin[2*], Jiandong Lin[1]

Departments of [1]Intensive Care Unit, [2]Pharmacy, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian Province, China. [*]Equal contributors and co-first authors.

Received April 14, 2020; Accepted May 22, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Objective: To explore the clinical value of cortisol (Cor) and the C-reactive protein (CRP)/prealbumin (PA) ratio in assessing the prognosis of elderly patients with sepsis. Methods: A prospective study was conducted, in which 73 elderly patients with sepsis admitted to The First Affiliated Hospital of Fujian Medical University between January 2017 and January 2019 were assigned to the sepsis group, and 73 concomitant healthy elderly people as confirmed by physical examination were assigned to the control group. The levels of plasma Cor, serum CRP and PA, and the CRP/PA ratio were compared between the sepsis and control groups. The patients with sepsis were stratified into the following three subgroups according to their individual Acute Physiology and Chronic Health Evaluation (APACHE) II scores: 0-10-score subgroup (n=21), 11-20 score subgroup (n=35) and more-than 20-score subgroup (n=17). The levels of Cor, CRP and PA, and the CRP/PA ratio of patients were compared across the three subgroups, and the correlation of the levels of Cor, CRP and PA, and the CRP/PA ratio with the APACHE II scores were also analyzed. In addition, the patients with sepsis were subdivided into a survival subset (n=53) and a death subset (n=20) on the condition if they died within 28 days. The patients of the survival and death subsets were compared with regard to the levels of Cor, CRP and PA, and the CRP/PA ratio. The Receiver Operating Characteristic (ROC) curves were analyzed to evaluate the clinical value of Cor, CRP and PA, and CRP/PA ratio in predicting the prognosis of patients with sepsis. Results: The levels of Cor and CRP and the CRP/PA ratio were higher, but the PA level was lower in the sepsis group than in the control group (all $P<0.05$). The patients with higher APACHE II scores had higher levels of Cor and CRP, and a higher CRP/PA ratio but lower levels of PA (all $P<0.05$). The levels of Cor, CRP and the CRP/PA ratio were positively correlated with the APACHE II scores, but the levels of PA were negatively correlated with the APACHE II scores. Higher levels of Cor, CRP, a higher CRP/PA ratio and lower levels of PA were observed in the death subset compared to the survival subset (all $P<0.05$). The ROC curve analysis showed that the levels of Cor, CRP and PA, and the CRP/PA ratio were of clinical value in predicting the prognosis of patients with sepsis (AUC>0.700). Conclusion: The levels of Cor, CRP and PA and the CRP/PA ratio were closely associated with the severity of sepsis in the elderly patients, and the markers had clinical value in predicting the prognosis of sepsis in such patients.

Keywords: Cortisol, C-reactive protein, prealbumin, sepsis

Introduction

Sepsis is a clinical syndrome caused by an infection that triggers an inflammatory response; if the inflammatory response is unregulated, a person may develop physiological and organ dysfunction [1]. Sepsis is frequently concurrent with such diseases as major surgery, shock, poisoning, and large-area burns [2]. Epidemiological data reveal that millions of patients develop sepsis annually in the world, and approximately one fourths of them eventually die [3, 4]. Sepsis is not only associated with high rates of morbidity and mortality but also takes up a lot of medical resources. Therefore, it is of great clinical significance to explore the pathogenesis and prognostic predictors for sepsis [5, 6]. Cortisol (Cor) is primarily synthesized from the adrenal cortex and acts to maintain the tension and integrity of blood vessels and stimulate gluconeogenesis. It also affects the water-electrolyte balance [7]. As inflammatory cytokines are over-expressed in patients with sepsis, the central nervous system promotes elevation of glucocorticoid levels through the neuroendocrine system via the hypothala-

mus pituitary adrenal axis (HPA), and then secretes a great deal of cortisol, inhibits the inflammatory response in the body, and finally successfully protects the body against inflammation and overreaction of the immune system [8]. In the course of occurrence and development of sepsis, the acute phase protein (APP) in the body varies substantially. C-reaction protein (CRP) and prealbumin (PA) belong to the family of APPs. CRP is characteristic of early presence and rapid elevation, so it can be used as a sensitivity marker to detect the inflammatory response of the body [9]. PA is a glycoprotein generated from the liver, and its concentrations reflect hepatic function, nutritional status and infection of the body. The ratio of CRP to PA has shown to be clinically useful in the progress of sepsis [10]. However, few reports are involved in investigating the above predictors for prognosis of septic patients. Given this, this study was designed to explore the clinical value of Cor, CRP, and PA and the CRP/PA ratio in evaluating the prognosis for sepsis in elderly patients, so as to provide relevant evidence for clinical diagnosis and treatment of sepsis.

Materials and methods

General data

In this prospective study, elderly patients with sepsis (n=73) admitted to The First Affiliated Hospital of Fujian Medical University from January 2017 to January 2019 were assigned to the sepsis group, while 73 concomitant healthy elderly people as demonstrated by physical examination in the same hospital were assigned to the control group. In the sepsis group, 48 patients were male and 25 were female, with a mean age of 73.44±4.51 years. In the control group, there were 50 male and 23 female patients, with a mean age of 73.58±4.92 years. Age and sex composition of patients differed insignificantly between the two groups. All the enrolled patients in this study provided written informed consent; and this study was approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University.

Inclusion and exclusion criteria

Patients with an age of 70 to 85 years were eligible for enrollment into this study if they met the criteria released in the International Guidelines for Management of Sepsis and Septic Shock, version 3.0, and had received no other treatment before admission. Patients were ineligible for enrolment if they had other severe coexisting disease or neurological or psychiatric disorders; were participating in other studies; died within 24 hours after admission or discharged; recently taken rifampicin or steroids affecting the experimental results, or had poor adherence to the treatment.

Outcome measures

Venous blood (5 mL) was extracted from each patient on the second day after enrollment and centrifuged at 3,000 r/min for 5 min. Plasma Cor level was tested using electrochemiluminescence (Elecss-2010 automatic electrochemical luminescence analyzer, Roche Pharmaceuticals), while the levels of CRP and PA were detected with the use of immunoturbidimetry (AU400 automatic biochemical analyzer, Olympus, Japan). All kits were purchased from Shanghai Beyotime Biotechnology Co., Ltd. All procedures were conducted strictly in accordance with the instructions of the instruments and reagents.

On the second day after enrollment, the Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated for the elderly septic patients on the basis of the worst values for the physiological and biochemical variables [11]. According to the resultant scores, the patients were stratified into the 0-10 score (n=21), 11-20 score (n=35) or more-than-20 score (n=17) subgroups.

Additionally, the patients with sepsis were also stratified into the survival subset (n=53) or the death subset (n=20) in accordance with the death profile of the patients within 28 days after enrollment.

Statistical analysis

Statistical analyses were performed with the use of software SPSS, version 22.0. Count data were expressed as cases and percentage, while measurement data were represented by mean ± standard deviation ($\bar{x}$ ± sd). Multiple group comparisons of the variables were made using one-way analysis of variance, and between-group comparisons were conducted by the pairwise t test. A chi-square test was used to compare count data. The correlation of the levels of Cor, CRP, and PA, and the CRP/

Table 1. Comparison of Cor, CRP, PA and CRP/PA levels

Group	Cor (μg/L)	PA (mg/L)	CRP (mg/L)	CRP/PA
Sepsis group (n=73)	261.63±51.06	87.48±16.95	84.11±21.59	1.04±0.47
Control group (n=73)	101.34±24.56	279.18±54.89	3.12±1.17	0.11±0.04
t	24.171	28.511	32.004	16.845
P	<0.001	<0.001	<0.001	<0.001

Note: Cor: cortisol; CRP: C-reactive protein; PA: prealbumin.

Table 2. Cor, CRP, PA and CRP/PA levels of patients with different APACHE II scores

Group	Cor (μg/L)	PA (mg/L)	CRP (mg/L)	CRP/PA
0-10 score subgroup (n=21)	222.55±25.83	102.84±7.54	62.10±10.85	0.61±0.12
11-20 score subgroup (n=35)	262.83±42.98[a]	89.08±10.68[a]	84.00±11.58[a]	0.96±0.19[a]
>20 score subgroup (n=17)	307.43±52.31[a,b]	65.21±11.71[a,b]	111.53±15.22[a,b]	1.75±0.33[a,b]
F	19.776	65.435	75.613	136.371
P	<0.001	<0.001	<0.001	<0.001

Note: Cor: cortisol; CRP: C-reactive protein; PA: prealbumin. Compared with 0-10 score group, [a]P<0.05; compared with 11-20 score group, [b]P<0.05.

Table 3. Correlation between APACHEII score and Cor, CRP, PA and CRP/PA levels

Statistic	Cor (μg/L)	PA (mg/L)	CRP (mg/L)	CRP/PA
R	0.594	-0.79	0.789	0.838
P	<0.001	<0.001	<0.001	<0.001

Note: Cor: cortisol; CRP: C-reactive protein; PA: prealbumin.

PA ratio with the APACHE II scores were analyzed by Pearson's correlation. The Receiver Operating Characteristic (ROC) curves were utilized to analyze the levels of Cor, CRP, and PA and the CRP/PA ratio, and to assess the clinical value of the predictors in predicting prognosis of patients with sepsis. A *P* value of less than 0.05 indicated a statistically significant difference.

Results

Comparison of levels of Cor, CRP, PA and CRP/PA ratio between the two groups

The results of comparisons show that the levels of Cor, and CRP, and the CRP/PA ratio were higher, but the PA level was lower in the sepsis group than in the control group (all P<0.001; **Table 1**).

Comparison of levels of Cor, CRP, PA and CRP/PA ratio among patients with diverse APACHE II scores

The results of comparisons indicate that as the APACHE II scores went higher, the levels of Cor and CRP, and the CRP/PA ratio were higher, but the PA level was lower (P<0.001; **Table 2**).

Correlation of the APACHE II scores with Cor, CRP, and PA levels and the CRP/PA ratio

In patients of the sepsis group, Cor and CRP levels and the CRP/PA ratio were positively correlated with the APACHE II scores, whereas the PA levels were inversely correlated with the APACHE II scores (**Table 3**).

Comparison of the markers of patients between the survival subset and the death subset

Comparison of death and survival among patients with sepsis showed higher levels of Cor and CRP, and a higher CRP/PA ratio in the death subset, but lower PA levels in the survival subset (all P<0.001; **Table 4**).

ROC curves

Analysis of the ROC curves revealed that Cor, CRP, and PA levels and the CRP/PA ratio had some clinical value in evaluating the prognosis of septic patients (AUC>0.700; **Figure 1** and **Table 5**).

Discussion

Conventional studies demonstrate that sepsis is an inflammatory response caused by pathogens and their toxins. Nevertheless, with further investigation, medical researchers have

Table 4. Comparison of various indicators in the survival group and the death group

Group	Cor (μg/L)	PA (mg/L)	CRP (mg/L)	CRP/PA
Survival group (n=53)	246.31±46.80	93.44±12.22	78.18±19.16	0.87±0.30
Death group (n=20)	302.22±38.70	71.68±17.82	99.84±20.09	1.51±0.54
t	4.759	5.947	4.252	6.508
P	<0.001	<0.001	<0.001	<0.001

Note: Cor: cortisol; CRP: C-reactive protein; PA: prealbumin.

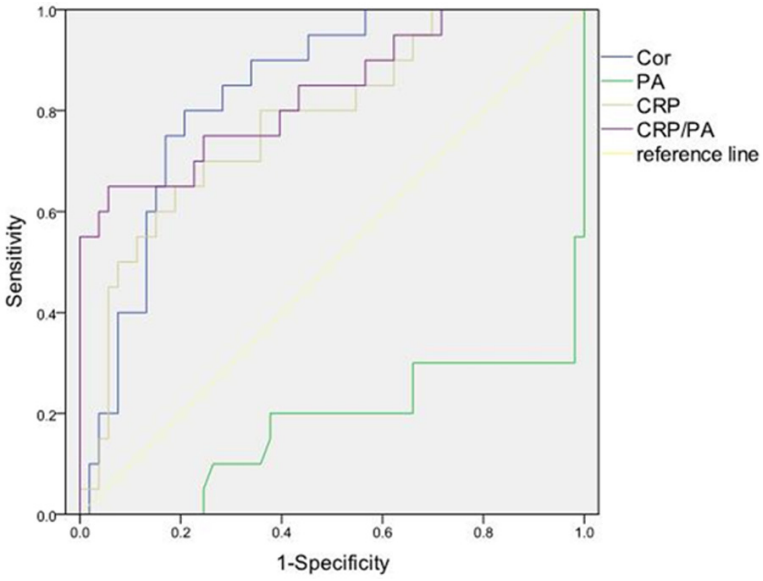

Figure 1. ROC curve. ROC: receiver operating characteristic.

Table 5. ROC curve results

Indicator	Cor (μg/L)	PA (mg/L)	CRP (mg/L)	CRP/PA
Cutoff value	280.534	70.939	91.712	1.35
AUC	0.836	0.824	0.778	0.835
95% CI	0.742, 0.929	0.697, 0.950	0.659, 0.897	0.722, 0.947
Sensitivity	0.8	0.981	0.65	0.65
Specificity	0.792	0.7	0.811	0.943
P	<0.001	<0.001	<0.001	<0.001

Note: ROC: receiver operating characteristic; Cor: cortisol; CRP: C-reactive protein; PA: prealbumin.

found that the occurrence and development of sepsis may also be closely associated with the neuroendocrine immunoregulatory network [12]. Previous studies have shown that when sepsis occurs, the body stimulates the HPA axis, and then promotes secretion of large quantities of adreno-cortico-tropic hormone (ACTH) from the pituitary gland through the neuroendocrine regulatory mechanisms [13]. However, ACTH has a regulatory effect with short feedback by controlling its secretions. When ACTH level elevates, the body's first response to adrenocortical dysfunction is also its compensatory performance to maintain the normal level of adrenocortical hormone. ACTH over-expression promotes the production and release of cortisol, which in turn suppresses inflammatory response of the body. It further inhibits the cascade reaction of cytokines resulting from lymphocyte over-activation, and prevents circulatory abnormalities and multiple organ dysfunction in the body. A prior study revealed that the expression and activity of metabolic enzyme for cortisol reduced in critically-ill patients, resulting in decreased plasma cortisol decomposition and elevated cortisol levels [14]. As a result, cortisol level in blood, to a certain extent, reflects the disease severity in critically ill patients. A previous study showed that patients in the sepsis group had higher cortisol levels than those in the control group, which suggests more severe sepsis indicating higher cortisol levels in septic patients [15]. In this study, as compared with the healthy elderly population, the plasma cortisol levels elevated significantly in patients with sepsis, and cortisol level was positively correlated with the APACHE II scores. The finding is consistent with the results of the above-mentioned studies, and it might be attributed to the following causes [16]. First, production of albumin and cortisol-binding globulin reduced is in sepsis patients, resulting in a remarkable elevation of cortisol

levels. Second, a large number of inflammatory cytokines which enhanced the generation of cortisol were present in septic patients. Third, cytokines released after inflammation-induced tissue injury directly acted to the IL-6 receptor on the renin gland, thereby promoting the synthesis and secretion of cortisol. Analysis of the ROC curves showed that AUC was 0.836 when the cutoff value was 280.534 μg/L, which also implies that AUC has high clinical value in evaluating the prognosis of patients with sepsis.

PA, also known as transthyretin, is primarily synthesized by the liver. PA is one of the clinical indicators to assess the nutritional status of the body and monitor the therapeutic effect of nutritional support, so it is used for early diagnosis of malnutrition. PA is also a negative acute phase protein and a non-specific host defense substance. PA has been demonstrated to be closely associated with the pathological and physiological status of the body. When bacterial infection occurs in the human body, the body will consume a variety of serum PA to eliminate the harmful substances generated by metabolism due to infection. Infection will cause hypoxia in the tissues and organs, and damage the hepatocytes, resulting in the liver's weaker ability to synthesize PA, as well as a decline in the immune function of the body [17, 18]. CRP, an inflammatory acute-phase protein, is characterized by early presence and rapid elevation, and is sensitive to the inflammatory and stress states of the body. When an infectious disease occurs, CRP levels will elevate in varying magnitudes. CRP, as a sensitivity marker used to detect the inflammatory response of the body, elevates significantly several hours after an infection occurs. The changes in CRP levels are not affected by the drugs for radiation/chemotherapy and hormone agents. CRP level increases significantly in critically ill patients, and it elevates with the severity of the disease [19-21]. The results of this study indicated that when compared with the healthy elderly population, patients with sepsis had a substantial decrease in serum PA levels, but the CRP levels elevated substantially. CRP was positively correlated with the severity of the disease, but PA was negatively correlated with the severity of the disease. We also explored the correlation between the CRP/PA ratio and sepsis, and found that the CRP/PA ratio was positively correlated with the severity of sepsis in the patients. The possible causes are as follows: first, infection, hypoxia and ischemia stimulated the generation of large quantities of inflammatory cytokines and oxygen radicals in the body, which induced injury and apoptosis of hepatocytes; second, due to severe stress state in septic patients, the proteins in the liver predominantly synthesized acute phase protein instead of structural protein in plasma; third, hypermetabolism, insufficient nutrition intake, and hepatic ischemia occurred in patients with sepsis or other critical diseases, which suppressed synthesis and secretion of the liver. The ROC curves further suggested that PA, CRP and the CRP/PA ratio had good clinical value in evaluating the prognosis of patients with sepsis.

In conclusion, the levels of Cor, CRP and PA, and the CRP/PA ratio were closely correlated with the severity of sepsis in the elderly patients, and had great clinical value in evaluating the prognosis of sepsis in such patients. Nevertheless, there are still some limitations in this study, such as being a single center study, having a small sample size, and lack of dynamic observation of the changes in various markers. Hence, additional studies are needed for further validation.

Disclosure of conflict of interest

None.

Address correspondence to: Hui Lin, Department of Intensive Care Unit, The First Affiliated Hospital of Fujian Medical University, No.20 Chazhong Road, Fuzhou 350005, Fujian Province, China. Tel: +86-0591-28571065; E-mail: linhuify13@163.com

References

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL and Angus DC. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315: 801-810.

[2] Lin JJ, Hsiao HJ, Chan OW, Wang Y, Hsia SH and Chiu CH. Increased serum thrombomodulin level is associated with disease severity and mortality in pediatric sepsis. PLoS one 2017; 12: e0182324.

[3] Bolia R, Srivastava A, Marak R, Yachha SK and Poddar U. Role of procalcitonin and C-reactive protein as biomarkers of infection in children with liver disease. J Pediatr Gastroenterol Nutr 2016; 63: 406-411.
[4] Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC and Reinhart K; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193: 259-272.
[5] Frencken JF, van Vught LA, Peelen LM, Ong DSY, Klein Klouwenberg PMC, Horn J, Bonten MJM, van der Poll T and Cremer OL. An unbalanced inflammatory cytokine response is not associated with mortality following sepsis: a prospective cohort study. Crit Care Med 2017; 45: e493-e499.
[6] Arefian H, Heublein S, Scherag A, Brunkhorst FM, Younis MZ, Moerer O, Fischer D and Hartmann M. Hospital-related cost of sepsis: a systematic review. J Infect 2017; 74: 107-117.
[7] Li-Tempel T, Larra MF, Sandt E, Mériaux SB, Schote AB, Schächinger H, Muller CP and Turner JD. The cardiovascular and hypothalamus-pituitary-adrenal axis response to stress is controlled by glucocorticoid receptor sequence variants and promoter methylation. Clin Epigenetics 2016; 8: 12-28.
[8] Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Meduri GU, Olsen KM, Rochwerg B, Rodgers SC, Russell JA and Van den Berghe G. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intens Care Med 2017; 43: 1781-1792.
[9] Neuville M, Vinclair C, Cally R and Bouadma L. Place of biomarkers in the management of pulmonary infections. Rev Mal Respir 2019; 36: 405-414.
[10] Tanrıverdi H, Örnek T, Erboy F, Altınsoy B, Uygur F, Atalay F and Tor MM. Comparison of diagnostic values of procalcitonin, C-reactive protein and blood neutrophil/lymphocyte ratio levels in predicting bacterial infection in hospitalized patients with acute exacerbations of COPD. Wien Klin Wochenschr 2015; 127: 756-763.
[11] Knaus WA, Draper EA, Wagner DP and Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13: 818-829.
[12] Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden YM, Spriet I, Wouters PJ, Vander Perre S, Langouche L, Vanhorebeek I, Walker BR and Van den Berghe G. Reduced cortisol metabolism during critical illness. N Engl J Med 2013; 368: 1477-1488.
[13] Kanczkowski W, Sue M, Zacharowski K, Reincke M and Bornstein SR. The role of adrenal gland microenvironment in the HPA axis function and dysfunction during sepsis. Mol Cell Endocrinol 2015; 408: 241-248.
[14] Nguyen DN, Huyghens L, Schiettecatte J, Smitz J and Vincent JL. High cortisol levels are associated with brain dysfunction but low prolactin cortisol ratio levels are associated with nosocomial infection in severe sepsis. J Crit Care 2015; 30: 847.
[15] Boonen E and Van den Berghe G. Understanding the HPA response to critical illness: novel insights with clinical implications. Intens Care Med 2015; 41: 131-133.
[16] de Jong MF, Molenaar N, Beishuizen A and Groeneveld AB. Diminished adrenal sensitivity to endogenous and exogenous adrenocorticotropic hormone in critical illness: a prospective cohort study. Crit Care 2015; 19: 1.
[17] Koch L, Bosk A, Sasse M, Ruef P and Poeschl J. Managing neonatal severe sepsis in Germany: a preliminary survey of current practices. Klin Padiatr 2015; 227: 23-27.
[18] Salvetti DJ, Tempel ZJ, Goldschmidt E, Colwell NA, Angriman F, Panczykowski DM, Agarwal N, Kanter AS and Okonkwo DO. Low preoperative serum prealbumin levels and the postoperative surgical site infection risk in elective spine surgery: a consecutive series. J Neurosurg Spine 2018; 29: 549-552.
[19] Üstündağ Y and Sarıtaş Ü. C-reactive protein levels together with the ranson scoring system to differentiate the mild and severe forms of acute pancreatitis. Turk J Gastroenterol 2017; 28: 157-158.
[20] Stirling AD, Moran NR, Kelly ME, Ridgway PF and Conlon KC. The predictive value of C-reactive protein (CRP) in acute pancreatitis - is interval change in CRP an additional indicator of severity? HPB (Oxford) 2017; 19: 874-880.
[21] Mańkowska-Wierzbicka D, Karczewski J, Poniedziałek B, Grzymisławska M, Staszewski R, Królczyk A, Dobrowolska A and Grzymisławski M. C-reactive protein as a diagnostic and prognostic factor in inflammatory bowel diseases. Postepy Hig Med Dosw (Online) 2016; 70: 1124-1130.