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Original Article

Prognostic values of serum procalcitonin and C-reactive protein levels in infective endocarditis

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Abstract: Infective endocarditis (IE) causes a high risk of morbidity and mortality. Rapid diagnosis, effective treatment, and prompt recognition of complications are important for good patient outcomes. The prognostic value of serum procalcitonin (PCT) and C-reactive protein (CRP) levels in IE were explored in this study. IE patients and healthy individuals were selected. Serum PCT levels and serum CRP levels were measured. After treatment, patients were classified into a survival group and a death group. The receiver operating characteristic (ROC) curve was drawn to evaluate the predictive values of PCT and CRP in IE prognosis. Logistic regression analysis was performed to estimate independent risk factors for prognosis of IE patients. The IE group exhibited higher serum PCT and CRP levels than the control group. After treatment, the serum PCT and CRP levels in the IE patients were reduced. Additionally, the survival group showed greater decreases in serum PCT and CRP levels than the death group before and after treatment. The positive rates of PCT and CRP were higher in the survival group than in the death group. In predicting IE prognosis, the serum PCT levels exhibited sensitivity of 84.21% and specificity of 80.60% and the serum CRP levels exhibited sensitivity of 78.95% and specificity of 83.58%. Logistic regression analysis indicated that hemoglobin (Hb), serum albumin, serum PCT, and CRP levels were independent risk factors for IE prognosis. Our study demonstrates that serum PCT and CRP levels may act as predictive indicators for IE prognosis.

Keywords: Procalcitonin, C-reactive protein, infective endocarditis, prognosis, prediction

Introduction

Infective endocarditis (IE) is an inflammation of the heart valve caused by bacteria liked Staphylococcus aureus, fungi, and other microorganisms [1]. IE can lead to extracardiac effects, for example, various immunological phenomena and disseminated infected emboli, and intracardiac effects, like congestive heart failure and severe valvular insufficiency [2]. In the acute phase, nearly half of patients need cardiac surgery, but IE morbidity and mortality are still relatively high, with the in-hospital mortality rate of 10%~30% [3]. Early diagnosis contributes to better IE prognosis due to early medical and surgical treatments, such as administration of antibiotics [4]. In IE, age, neoplasm and causative microorganisms are known predictive factors, however, clinical courses of patients differ significantly from individual to individual [5]. Thus, potential biomarkers, with high specificity and sensitivity, will largely improve the diagnosis and treatment outcomes of IE.

Procalcitonin (PCT), secreted by K cells in the lung as well as C cells in thyroid gland, is a precursor of calcitonin, and has been proven to be elevated in inflammation and bacterial infections [6, 7]. In suspected IE patients, PCT may exhibit diagnostic value [7]. C reactive protein (CRP) substantially increases in the plasma when patients were infected or injured and is considered as an important blood marker for inflammation, and its elevation indicates negative prognostic implications under a great deal of conditions [8]. As an acute-phase reactant, CRP is of great clinical value in patients with various infections, including septicemia, IE and meningitis [9]. The CRP level may be beneficial to diagnosing community-acquired pneumonia [9]. Alavi and his partners proved that CRP is a good marker for monitoring treatment of IE [10]. Yoshikawa et al. pointed out that PCT is a highly

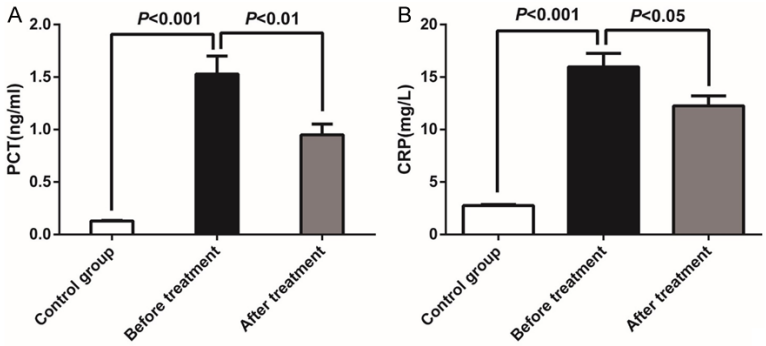

Figure 1. Serum PCT and CRP levels between the IE and control groups. Note: (A) Serum PCT levels between the IE and control groups; (B) Serum CRP levels between the IE and control groups; PCT, procalcitonin; CRP, C-reactive protein; IE, infective endocarditis.

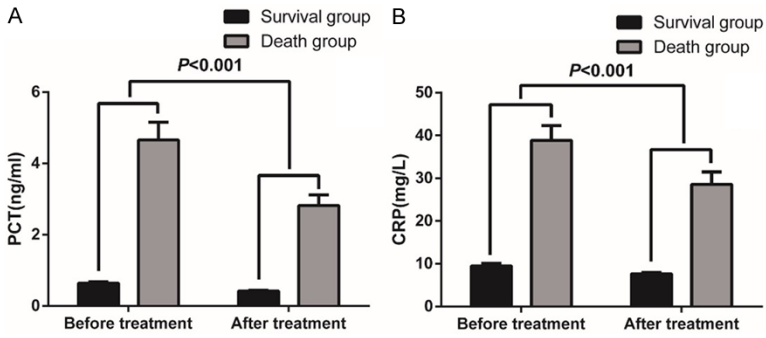

Figure 2. Serum PCT and CRP levels between the survival and death groups. Note: (A) Serum PCT levels between the survival and death groups; (B) Serum CRP levels between the survival and death groups; PCT, procalcitonin; CRP, C-reactive protein.

Table 1. Comparison of serum PCT and CRP levels between the survival and death groups

Group	Survival group	Death group	X^2	*P*
PCT			111.30	< 0.001
Negative (%)	216 (80.60)	12 (15.79)		
Positive (%)	52 (19.40)	64 (84.21)		
CRP			109.80	< 0.001
Negative (%)	224 (83.58)	16 (21.05)		
Positive (%)	44 (16.42)	60 (78.95)		

Note: PCT, procalcitonin; CRP, C-reactive protein.

specific and innovative marker for diagnosis of sepsis and relevant bacterial infections, and they found that PCT might be a more appropriate marker for IE treatment when compared with CRP [11]. PCT and CRP are useful markers for diagnosis of early infectious illnesses [12]. Although the roles of PCT and CRP in IE have been reported extensively, the prognostic values of PCT and CRP have not been fully investigated in IE in large sample size. In this study, 344 IE patient samples were collected and the predictive values of serum PCT and CRP levels in prognosis were determined.

Materials and methods

Ethics statement

This study was approved by the Ethics Committee of Tangshan Worker's Hospital, and all patients were informed and have signed informed consent.

Study subjects

From June 2012 to June 2016, 344 IE patients (232 males and 112 females) in Tangshan Worker's Hospital were selected as the IE group, with mean age 41.17 ± 15.88 years. Among 344 IE patients, there were 36 cases with prosthetic valve endocarditis (PVE), 308 cases with native valve endocarditis (NVE), 100 cases without heart disease, and 244 cases with heart diseases (56 cases of rheumatic valvular heart disease, 54 cases of mitral valve prolapse, 60 cases of congenital heart disease (CHD), 42 cases of degenerative heart disease, and 32 cases of hypertensive heart disease). All patients were diagnosed according to the Duke criteria [13]. Major criteria included positive blood culture or echocardiography, while minor criteria included fever, serological evidence of infection, ultrasound examination, inducing factors and vascular syndrome. Meanwhile, 344 healthy individuals (mean age: 42.02 ± 16.14 years) who received physical examination were selected as the control group, including 208 males and 136 females. No significant differences were found in age, gender and other general clinical characteristics between the two groups ($P > 0.05$).

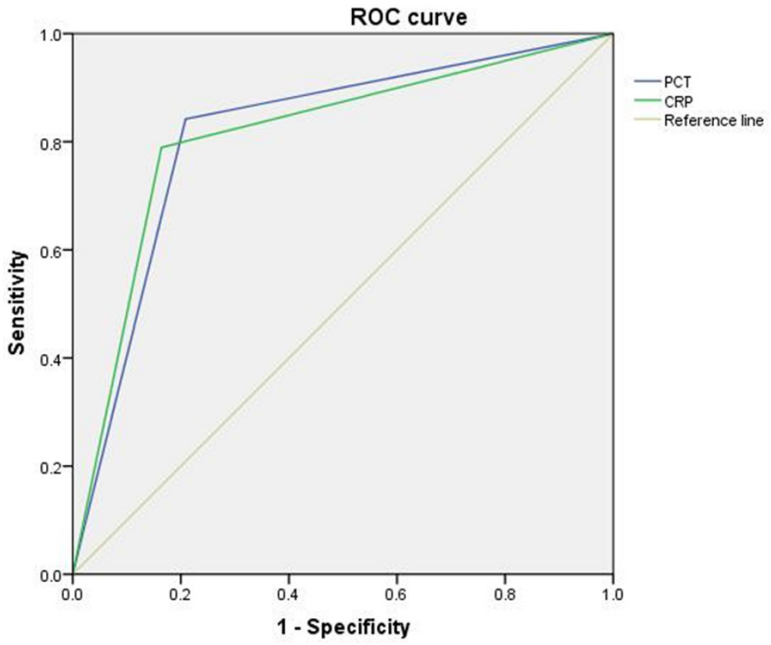

Figure 3. ROC curves for predictive value of PCT and CRP in the prognosis of IE. Note: ROC, receiver operating characteristic; PCT, procalcitonin; CRP, C-reactive protein; IE, infective endocarditis.

Therapeutic regimens

All IE patients received a group of treatment, lasting for 4 weeks, including oxygen uptake, cardiotonics, diuresis, correction of water-electrolyte disorders, and controlling acid-base equilibrium. Additionally, the patients were intravenously injected with daptomycin (6 mg/kg) every 24 hours if the creatinine clearance rate ≥ 30 ml/min, or every 48 hours if the creatinine clearance rate < 30 ml/min. After treatment, the patients were assigned to a survival group and a death group.

Data collection

Clinical data of all patients were recorded, including heart disease, clinical manifestations, routine blood parameters, liver function, renal function, erythrocyte sedimentation rate (ESR), blood culture, echocardiography, etc. Fasting blood (3 ml) was obtained from cubital vein of IE patients and healthy individuals on the morning before and after treatment, and on physical examination day. The collected blood was anticoagulated with ethylenediaminetetraacetic acid (EDTA), and centrifuged for 10 minutes to separate serum PCT and CRP. Serum PCT levels were measured using the mini VIDAS automated immunoassay chemistry system (bioMerieux, Lyon, France) and serum CRP levels using beckman coulter's IMMAGE (R) immunochemistry system (Beckman Coulter, Inc., CA, USA). All reagents that were used, such as the solution for calibration and quality control were obtained from manufacturers, and the operation was in strict accordance with the instructions. Serum PCT level > 0.5 ng/ml was regarded as positive, and serum CRP level > 8 mg/L represented positive.

Statistical analysis

Data were processed and analyzed by statistical package for social sciences (SPSS) 22.0 software (SPSS Inc., Chicago, IL, USA). Measurement data are expressed as standard ± deviation. The comparison between two groups was analyzed using t-test. Categorical data are presented as the ratio or percentage, and were analyzed by Chi-square test. A receiver operating characteristic (ROC) curve was drawn to evaluate the predictive values of PCT and CRP in IE prognosis. Univariate and multivariate analyses were performed to estimate independent risk factors for IE prognosis. Differences that produced *p*-values less than 0.05 were accepted as significant.

Results

Serum PCT and CRP levels increased in IE patients

As shown in **Figure 1**, the IE group exhibited higher serum PCT level than the control group ($P < 0.05$), and the serum CRP level was increased in the IE group than in the control group ($P < 0.05$). After treatment, the serum PCT and CRP levels were reduced in the IE patients ($P < 0.05$).

Serum PCT and CRP levels decreased in IE patients with poor prognosis

After treatment, the patients were assigned to the survival and death groups. There were 268 IE patients (180 males and 88 females) with a

Table 2. Univariate analysis for risk factors influencing IE prognosis

Factor	N	Fatality number	Mortality	*P*
Age (years)				0.093
≥ 65	28	10	35.71	
< 65	316	66	20.89	
Gender				0.166
Male	232	46	19.83	
Female	112	30	26.78	
Heart disease				0.256
Yes	244	58	23.77	
No	100	18	18.00	
Heart murmur				0.124
Yes	80	23	28.75	
No	264	53	20.08	
Embolism				0.130
Yes	84	24	28.57	
No	260	52	20.00	
Valve type				0.018
Native valve	308	62	20.13	
Prosthetic valve	36	14	38.89	
Fever (°C)				0.019
≥ 39	184	50	27.17	
< 39	160	26	16.25	
Hemoglobin (g/L)				< 0.001
≥ 90	244	36	14.75	
< 90	100	40	40.00	
Serum albumin (g/L)				< 0.001
≥ 30	186	24	12.90	
< 30	158	52	32.91	
Blood culture				0.180
Positive	216	53	24.54	
Negative	128	23	17.97	
Neoplasm				0.180
Yes	290	62	21.37	
No	54	12	22.22	
Electrocardiogram				0.208
Normal	108	19	17.59	
Abnormal	236	57	24.15	
PCT (ng/ml)				< 0.001
> 0.5	116	64	55.17	
≤ 0.5	228	12	5.26	
CRP (mg/L)				< 0.001
> 8	104	60	57.69	
≤ 8	240	16	6.67	

Note: PCT, procalcitonin; CRP, C-reactive protein.

mean age of 41.90 ± 15.80 years in the survival group. In the death group, there were 76 IE patients (54 males and 22 females), with a mean age of 38.60 ± 16.09 years. The two groups presented no significant difference in age and gender ($P > 0.05$). The serum PCT and CRP levels were significantly lower in the survival group than in the death group before and after treatment ($P < 0.05$). In comparison to those before treatment, the serum PCT and CRP levels were significantly decreased after treatment in both two groups ($P < 0.05$) (**Figure 2**).

Serum PCT and CRP levels exhibited relatively high values in predicting IE prognosis

PCT > 0.5 ng/ml and CRP > 8 mg/L were considered as positive. The positive rates of PCT and CRP were higher in the survival group than in the death group ($P < 0.05$). The sensitivity and specificity of PCT in predicting prognosis of IE patients were 84.21% and 80.60%, respectively, with the positive predictive value of 84.21% and the negative predictive value of 80.60%. The sensitivity and specificity of CRP in predicting prognosis of IE patients were 78.95% and 83.58%, respectively, with the positive predictive value of 78.95% and the negative predictive value of 83.58%. No significant difference was found between PCT and CRP in sensitivity, specificity, positive predictive value and negative predictive value in predicting prognosis of IE ($P > 0.05$) (**Table 1**, **Figure 3**).

Univariate analysis for risk factors influencing IE prognosis

Possible influencing factors for prognosis of IE patients were included for univariate analysis. The results showed that influencing factors for prognosis of IE patients were prosthetic valve, fever (≥ 39°C), Hemoglobin (Hb) < 90 g/L, serum albumin < 30 g/L, PCT > 0.5 ng/mL and CRP > 8 mg/L ($P < 0.05$). However, there was no correlation of prognosis with age, gender, and basic heart disease, heart murmur,

Table 3. Logistic regression analysis for independent risk factors for IE prognosis

	B	S.E	Wald	df	*P*	Exp (B)	95% CI
Valve type	0.736	0.761	0.937	1	0.333	0.479	0.108~2.127
Fever	0.571	0.476	1.438	1	0.231	0.565	0.222~1.437
Hemoglobin	2.338	0.519	20.249	1	< 0.001	10.357	3.742~28.670
Serum albumin	2.087	0.504	17.123	1	< 0.001	8.064	3.000~21.672
PCT	3.812	0.567	45.221	1	< 0.001	0.022	0.007~0.067
CRP	3.905	0.57	46.918	1	< 0.001	0.020	0.007~0.062

Note: PCT, procalcitonin; CRP, C-reactive protein; B, regression coefficient; S.E, standard error; df, degree of freedom; CI, confidence interval.

embolism, positive blood culture, neoplasm, and electrocardiogram (ECG) of IE patients ($P > 0.05$) (**Table 2**).

Logistic regression analysis for independent risk factors for IE prognosis

Logistic regression analysis was conducted, with prognosis of IE patients as the dependent variable, and valve type, fever, hemoglobin, serum albumin, PCT and CRP as independent variables. As presented in **Table 3**, the hemoglobin, serum albumin, PCT and CRP were independent risk factors for prognosis of IE patients ($P < 0.05$), while valve type and fever were not risk factors for prognosis of IE patients ($P > 0.05$).

Discussion

IE is a life-threatening disease, despite great improvements achieved in diagnosis, management, and treatment [14]. This study intended to explore the values of serum PCT and CRP levels in predicting IE prognosis. The results indicate that Hb, serum albumin, PCT and CRP are independent risk factors for IE prognosis, and serum PCT and CRP levels may act as predictive indicators for IE prognosis.

Initially, this study showed that the serum PCT level was significantly decreased in the survival group more so than in the death group before and after treatment. Furthermore, IE patients exhibited elevated serum PCT level compared with healthy individuals, suggesting that PCT is correlated with infection and can be a prognostic factor for IE. PCT is undetectable or serum PCT level is really low in healthy individuals [15]. In the course of fungal, bacterial, or parasitic infections, the PCT secreted by thyroid gland is elevated, whereas, PCT is also produced by monocytes, macrophages, and neuroendocrine cells of various solid organs, such as kidney, lung and liver, thus causing significantly increase of PCT level [16, 17]. The concentration of PCT is positively correlated with the severity of infection [18]. As a diagnostic biomarker for infectious diseases like bacteremia, PCT presents a good sensitivity and specificity [19]. But PCT is normal or slightly elevated in nonspecific inflammatory diseases or viral infections [20]. JEREB et al. found that PCT is a promising early marker for diagnosis of bacteremia in febrile neutropenia at emergency department [21].

Moreover, our results also demonstrate that serum CRP level was reduced in IE patients with relatively good prognosis. Additionally, IE patients showed elevated serum CRP level than healthy individuals, which proved that CRP is also associated with infectious diseases and can be used as a prognostic factor for IE. CRP, an acute phase protein, is involved in systemic inflammation [22], and the CRP level begins to rise at 6 hours, then reaches its peak value at 24 hours [23]. CRP is mainly produced because of induction of inflammatory cytokines, originally in hepatocytes according to D Deme and A Telekes, and they find a decreased CRP level indicates better prognosis in metastatic or locally advanced stages, suggesting that CRP potentially plays a predictive and prognostic role in oncological diseases [23]. Okada et al. finds that the outcome of surgical treatment is poor in patients with higher preoperative CRP level, and better prognosis is expected in IE patients with lower preoperative CRP level [24]. The research conducted by Alavi et al. reports that CRP is a promising tool to monitor the treatment outcome of IE patients, and the serum CRP level was decreased in patients who were cured of IE, which is consistent with

our results [10]. As Elbey et al. concluded, high CRP level is an independent risk factor in predicting the mortality of IE patients during hospitalization [14].

In addition, logistic regression analysis revealed that Hb, serum albumin, PCT, and CRP were independent risk factors for IE prognosis. Anemia is one of the most common symptoms of IE, mainly caused by the infection [25]. Additionally, low Hb was associated with an increased incidence of infectious diseases, such as silent cerebral infarction [26]. According to Wang Li et al., higher hsCRP level, lower serum albumin and lower Hb are independent risk factors for prognosis of IE patients [27]. In addition, Hb and serum albumin are strongly indicative to prognosis of HIV infection, which may be used in management of HIV disease [28].

In conclusion, our study indicates that Hb, serum albumin, PCT, and CRP are independent risk factors for IE prognosis, and serum PCT and CRP levels may act as predictive indicators for IE prognosis. However, further studies with larger sample size are still needed to analyze whether PCT and CRP can be combined to highly predict IE prognosis, thus improving accuracy in predicting prognosis of IE patients.

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Disclosure of conflict of interest

None.

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