Int J Clin Exp Med 2019;12(7):9005-9010
www.ijcem.com /ISSN:1940-5901/IJCEM0088480

Original Article

ROC curve analysis of the significance of PCT combined with MR-proADM in the early diagnosis of childhood sepsis

Junwei Lan[1], Yali Zhang[1], Zengxian Sun[1], Weiling Liu[2], Chenmei Zhang[3], Juhong Lan[1], Lijun Qian[1]

[1]Department of Pediatrics, Lishui Hospital, Zhejiang University School Of Medicine, Lishui 323000, Zhejiang, China; [2]Department of Respiration, Lishui Hospital, Zhejiang University School Of Medicine, Lishui 323000, Zhejiang, China; [3]Department of Pediatrics, The Children's Hospital, Zhejiang University School of Medicine, Lishui 323000, Zhejiang, China

Received November 16, 2018; Accepted January 7, 2019; Epub July 15, 2019; Published July 30, 2019

Abstract: Procalcitonin (PCT) is associated with severity of infection in sepsis. The sensitivity and specificity of the adrenomedullin precursor (MR-proADM) for the diagnosis of sepsis is higher than that of PCT. This study explored the role of MR-proADM and PCT in the early diagnosis of childhood sepsis, aiming to provide a basis for the diagnosis of clinical infectious diseases. In total, 94 septic children who were admitted to the intensive care unit (ICUs) were divided into three groups, including 31 sepsis patients in group A, 33 severe sepsis patients in group B, and 30 septic shock patients in group C. Another 25 patients with systemic inflammatory response syndrome (SIRS) were enrolled as group D, and 20 healthy children were selected as the control group E. Blood sample was taken within 1 hour of ICU to detect plasma MR-proADM and PCT concentrations. PCT was tested by highly sensitive luminescence immunoassay. MR-proADM was determined by novel sandwich immunofluorescence assay. Receiver operating characteristic (ROC) curve was established to analyze the role of MR-proADM and PCT in the early diagnosis of childhood sepsis. MR-proADM and PCT levels gradually increased in the sepsis group following severity enhancement as C > B > A > C > E group ($P < 0.05$). They were gradually elevated with the children's critical illness score (PCIS) decreased ($P < 0.05$). MR-proADM and PCT levels were negatively correlated with PCIS scores ($r=-0.618$, -0.456, $P < 0.05$). The area under the curve for the diagnosis of sepsis of MR-proADM and PCT was 0.869 and 0.757, respectively. The diagnostic efficacy of MR-proADM was better than PCT. The sensitivity and specificity of MR-proADM > 3.46 mmol/L and PCT > 0.41 μg/L as positive in sepsis children were 85.11%, 74.47%, 71.11%, and 66.67%, respectively. The sensitivity of combined detection to diagnose sepsis in children was improved. PCT and MR-proADM concentrations were significantly increased following sepsis child worse. The diagnostic effect of MR-proADM on children with sepsis was better than that of PCT. Their combined detection effect was better than the single test.

Keywords: Sepsis, PCT, MR-proADM, ROC curve

Introduction

Sepsis is a common critical illness in the ICU with incomplete elucidated pathogenesis [1, 2]. Although the rescue technique for sepsis has greatly progressed, the incidence and mortality of severe sepsis and septic shock are still high [3, 4]. In the Emergency Department and ICU, sepsis, septic shock, and diagnosed multiple organ failure (MODS) are the most common causes of death in critically ill children. Appropriate interventions in the early stage of sepsis will reverse the occurrence of irreversible organ damage [5, 6]. Therefore, the key to improve the success rate of pediatric sepsis depends on early identifying the severe infections and septic shock. A number of studies confirmed that C-reactive protein (CRP) has certain clinical value in early infection. Interleukin-6 (IL-6), IL-10, tumor necrosis factor (TNF-α), and interferon-γ (INF-γ) are the core members of cytokines, which upregulate earlier than CRP in patients with sepsis. However, the huge different results limit their use as diagnostic markers for sepsis [7, 8]. There is a certain correlation between PCT and the severity of infection in sepsis. MR-proADM is more sensitive and specific than PCT in the diagnosis of sepsis, thus

plays an important role in the prognosis evaluation of severe patients. The combined detection of PCT and MR-proADM can improve the sensitivity and specificity of early diagnosis of adult sepsis [9, 10]. However, there is still a lack of investigation about the combined detection of PCT and MR-proADM in childhood sepsis. Therefore, to further understand the changes of PCT and MR-proADM in children with sepsis, this study investigated the relationship between plasma PCT, MR-proADM, and PCIS and prognosis in children with sepsis by using ROC curve. It is expected to provide more valuable evaluation indicators for early diagnosis and prognosis of childhood sepsis.

Materials and methods

General information

A total of 94 children with sepsis admitted to ICU from June 2016 to April 2018 were selected as subjects in Lishui Hospital, Zhejiang University School Of Medicine (Lishui, Zhejiang, China). All children were diagnosed according to the sepsis guideline 3.0 of the 2016 American Society of Critical Care Medicine (SCCM) and the European Society for Critical Care Medicine (ESICM) [9]. Exclusion criteria: severe chronic disease, diabetes taking drugs that affect blood lactate concentration (e.g. biguanide), use drugs that affect blood lactate concentration before admission, acute myocardial infarction, organ transplantation, high-dose catecholamines, multiple burns, congenital heart disease, and rheumatic heart disease, incomplete clinical data, and died within 24 h after admission. There were 67 males and 27 females with mean age of 8.37 ± 2.15 (6-12) years old. The children with sepsis were divided into sepsis group A (31 cases), severe sepsis group B (33 cases), and septic shock group C (30 cases). Another 25 patients were selected as SIRS group D, and 20 healthy children were enrolled as control. The blood was extracted within 1 hour after being admitted to the ICU to test serum MR-proADM and PCT concentrations. The PCIS score was evaluated within 24 hours. The children were divided into 3 groups according to the score, as extremely critical group (PCIS ≤ 70 points), and severe group (PCIS between 71 and 80 points), and non-severe group (PCIS between 80 and 100 points). The patients were divided into the survival group and the death group according to clinical outcome. Prognosis and outcome of children at 1 month after treatment were recorded.

This study was approved by the Ethics Committee in Lishui Hospital, Zhejiang University School Of Medicine (Lishui, Zhejiang, China).

Methods

The general clinical data were collected. There were no statistical differences on age and gender among groups. Liver function, kidney function, and blood routine examination were tested. PCT value was detected by high sensitivity immunoassay, and MR-proADM was detected by immunofluorescence assay [7, 9].

Statistical analysis

All data analyses were performed by SPSS19.0 statistical software. The measurement data conforming to the normal distribution is presented as mean ± standard deviation ($\bar{X} \pm S$) and compared by ANOVA or t test. The rate was compared by χ^2 test. The grade data was tested by nonparametric test. Correlation analysis was performed by Spearman. ROC curve was used to evaluate the prognosis of sepsis. Logistic regression model was established by combination of various indicators. ROC curve analysis was used to determine the value of combined detection in sepsis diagnose. Combined detection was compared with z test. $P < 0.05$ was defined as statistical significance.

Results

Comparison of MR-proADM and PCT levels in septic children with different degrees of infection

MR-proADM and PCT levels gradually increased in the sepsis group following severity enhancement as C > B > A > C > E group ($P < 0.05$) (**Figure 1**).

Comparison of MR-proADM and PCT levels in septic children with different PCIS

MR-proADM and PCT levels were gradually elevated with the children's critical illness score (PCIS) decreased ($P < 0.05$) (**Figure 2**). MR-proADM and PCT levels were negatively corre-

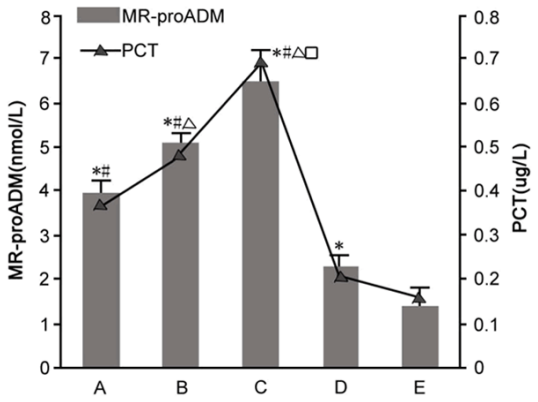

Figure 1. Comparison of MR-proADM and PCT levels in septic children with different degrees of infection. A, Sepsis group. B, Severe sepsis group. C, Septic shock group. D, SIRS group. E, Control. $^{*}P < 0.05$, compared with group E. $^{\#}P < 0.05$, compared with group D. $^{\Delta}P < 0.05$, compared with group A. $^{\square}P < 0.05$, compared with group B.

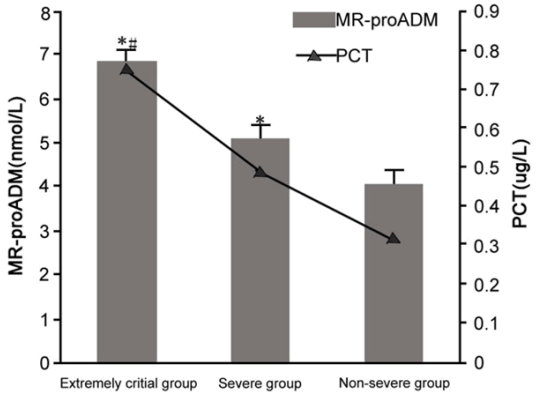

Figure 2. Comparison of MR-proADM and PCT levels in septic children with different PCIS. $^{*}P < 0.05$, compared with non-severe group. $^{\#}P < 0.05$, compared with severe group.

lated with PCIS scores (r=-0.618, -0.456, P < 0.05).

Diagnostic evaluation of MR-proADM and PCT levels on septic children

The area under the curve for the diagnosis of sepsis of MR-proADM and PCT was 0.869 and 0.757, respectively. The diagnostic efficacy of MR-proADM was better than PCT (**Figure 3**). The sensitivity and specificity of MR-proADM > 3.46 mmol/L and PCT > 0.41 μg/L as positive in sepsis children were 85.11%, 74.47%, 71.11%, and 66.67%, respectively (**Table 1**). The sensitivity of combined detection to diagnose sepsis in children was improved.

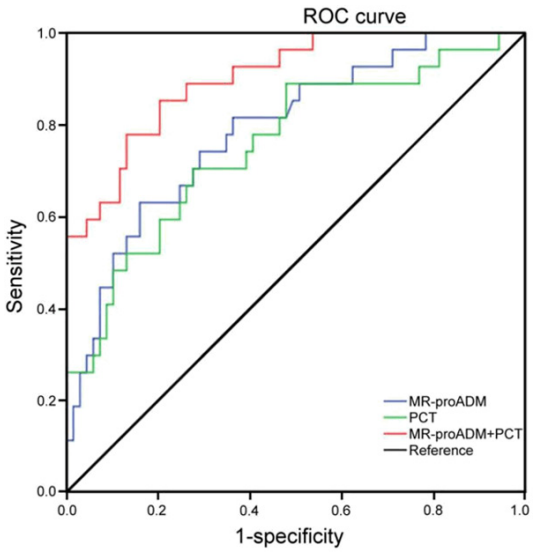

Figure 3. ROC curve analysis of MR-proADM and PCT in the diagnosis of childhood sepsis.

Discussion

Sepsis, septic shock, and diagnosed multiple organ failure (MOF) are the most common causes of death in critically ill children [11]. The key to improve the success rate of pediatric sepsis depends on early identification of the severe infections and septic shock [12, 13]. At present, the gold standard for the diagnosis of sepsis is blood culture. However, because of the small amount of pediatric blood culture samples, the detection sensitivity is low [14, 15]. WBC can be treated as a reference indicator for the diagnosis of sepsis. However, it is not a diagnostic indicator as is affected by the detection and collection method [16, 17]. It was reported that CRP has certain clinical value in early infection [18, 19]. IL-6, IL-10, TNF-α, and INF-γ elevate earlier in patients with sepsis than CRP. However, their values vary widely in different populations, thus limiting their application in sepsis. PCT is mainly produced in thyroid medulla C cells. Endotoxemia or bacterial infection cause cytokines (IL-6, IL-10, TNF-α, or lipopolysaccharide) to stimulate its expression in cells and tissues. Virus infection can increase INF-γ, whereas interferon can inhibit the elevation of PCT, so that PCT has better specificity for bacterial infection [15-17]. PCT can be rapidly detected in plasma at 2 hours after infection and reaches peak at 24 to 48 hours. When the infection is controlled, PCT can be reduced to 50% of the peak. PCT should be monitored in

Table 1. Sensitivity and specificity analysis of MR-proADM and PCT in diagnosis of childhood sepsis

Index	Positive cut-off value	AUC	Sensitivity/%	Specificity/%
MR-proADM	> 3.46 mmol/L	0.869	85.11 (80/94)	71.11 (32/45)
PCT	> 0.41 ug/L	0.757	74.47 (70/94)	66.67 (30/45)
MR-proADM + PCT		0.931	96.20	47.41

ICU. Although the mortality rate of inpatients did not change significantly, it can obviously shorten anti-infective treatment and change anti-infective strategies [20, 21].

At present, MR-proANP and MR-proADM showed great application prospects in predicting the severity of sepsis. Serum ADM level is elevated in sepsis. Due to the short half-life, it is difficult to measure ADM release level in circulating blood. The ADM is masked by the binding protein. MR-proADM is more stable in the blood circulation and directly reflects the rapidly diminished ADM active peptide level, which has been validated in patients with septic shock [22]. PCIS can accurately determine the criticality and predict the risk of death. However, the critical case scoring system has the disadvantages of being time-consuming and subjective. Sensitive biomarkers are objective and accurate. It was found that the combined application of critical scoring system indicator and biomarkers could improve the accuracy of risk classification and prognosis in critically ill patients. Combined use of pneumonia critical index and MR-proADM was more valuable than community pneumoconiosis index alone in the assessment of community-acquired pneumonia [19, 22]. The combined use of PCT and MR-proADM obtained progress in the early diagnosis and classification of adult sepsis [22]. Karakike E et al. indicated that the combined detection of PCT and MR-proADM can improve the sensitivity and specificity of early sepsis diagnosis. In the logistic test, Lundberg OH and Di Somma S revealed that Pro-ADM is an independent risk factor for patient prognosis [19, 21]. However, there has been a lack of investigation about the combined detection of PCT and MR-proADM in childhood sepsis. Therefore, to further understand the changes of PCT and MR-proADM in children with sepsis, this study investigated the relationship between plasma PCT, MR-proADM, and PCIS and prognosis in children with sepsis by using ROC curve. It was expected to provide more valuable evaluation indicators for early diagnosis and prognosis of childhood sepsis.

In this study, MR-proADM and PCT levels gradually increased in the sepsis group following severity enhancement as C > B > A > C > E group. They were gradually elevated with the children's PCIS decreased. MR-proADM and PCT levels were negatively correlated with PCIS scores, indicating that MR-proADM and PCT levels can reflect the severity of sepsis children, which is helpful for early diagnosis and prognosis evaluation. The diagnostic efficacy of MR-proADM was better than PCT. The sensitivity and specificity of MR-proADM > 3.46 mmol/L and PCT > 0.41 μg/L as positive in sepsis children were 85.11%, 74.47%, 71.11%, and 66.67%, respectively. The sensitivity of combined detection to diagnose sepsis in children was improved, suggesting that the combined detection has complementary effects, which is helpful for early and rapid assessment of sepsis. Considering the limitations of single index, multiple detection observations should be combined in the clinical diagnosis and evaluation process. PCT was better at distinguishing between sepsis and systemic inflammatory response syndrome [19, 21]. Its diagnostic value on sepsis is 24 to 48 hours earlier than CRP, with the best cutoff value of 0.47 μg/L, the sensitivity of 83%, and the specificity of 81%, respectively. However, PCT was not consistent with the severity of infection. The use of Pro-ADM combined with CRP and IL-6 for the diagnosis of neonatal sepsis has higher sensitivity and specificity. The combined use of MR-proADM and MEDS scores is more valuable in the early diagnosis and prognostic evaluation of sepsis than MR-proADM or MEDS scores alone [16, 17, 20]. The middle segment of ADM precursor has the best prediction accuracy at 3.9 nmol/L with sensitivity of 83.3% and specificity of 87.8%. The accuracy of this prediction is better than CRP and PCT [19, 21]. Similarly, Pro-ADM and PCT exhibited higher sensitivity and specificity in the diagnosis of childhood sepsis. MR-proADM is superior to PCT in the diagnosis of sepsis with better AUC value, sensitivity, and specificity. The sample size was limited in this study, and larger scale investigation is needed in the future.

Conclusion

PCT and MR-proADM concentrations were significantly increased following sepsis child worse. The diagnostic effect of MR-proADM on children with sepsis was better than that of PCT. Their combined detection effect was better than the single test.

Acknowledgements

This work was supported by Zhejiang Provincial Medical and Health Science and Technology Project (study on the early diagnosis and prognosis of children sepsis by serum adrenergic precursors and procalcitonin, No. 2016KYB337).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lijun Qian, Department of Pediatrics, Lishui Hospital, Zhejiang University School Of Medicine, No. 289 Kuocang Road, Lishui 323000, Zhejiang, China. Tel: +86-0578-2285222; Fax: +86-0578-2285222; E-mail: n59f73@sina.com

References

[1] Viaggi B, Poole D, Tujjar O, Marchiani S, Ognibene A, Finazzi S. Mid regional pro-adrenomedullin for the prediction of organ failure in infection. Results from a single centre study. PLoS One 2018; 13: e0201491.

[2] Elke G, Bloos F, Wilson DC, Brunkhorst FM, Briegel J, Reinhart K, Loeffler M, Kluge S, Nierhaus A, Jaschinski U, Moerer O, Weyland A, Meybohm P; SepNet Critical Care Trials Group. The use of mid-regional proadrenomedullin to identify disease severity and treatment response to sepsis-a secondary analysis of a large randomised controlled trial. Crit Care 2018; 22: 79.

[3] Spoto S, Cella E, de Cesaris M, Locorriere L, Mazzaroppi S, Nobile E, Lanotte AM, Pedicino L, Fogolari M, Costantino S, Dicuonzo G, Ciccozzi M, Angeletti S. Procalcitonin and MR-Proadrenomedullin combination with SOFA and qSOFA scores for sepsis diagnosis and prognosis: a diagnostic algorithm. Shock 2018; 50: 44-52.

[4] Charles PE, Péju E, Dantec A, Bruyère R, Meunier-Beillard N, Dargent A, Prin S, Wilson D, Quenot JP. Mr-Proadm elevation upon Icu admission predicts the outcome of septic patients and is correlated with upcoming fluid overload. Shock 2017; 48: 418-426.

[5] Gille J, Ostermann H, Dragu A, Sablotzki A. Sablotzki, MR-proADM: a new biomarker for early diagnosis of sepsis in burned patients. J Burn Care Res 2017; 38: 290-298.

[6] Valenzuela-Sánchez F, Valenzuela-Méndez B, Rodríguez-Gutiérrez JF, Estella-García Á, González-García MÁ. New role of biomarkers: mid-regional pro-adrenomedullin, the biomarker of organ failure. Ann Transl Med 2016; 4: 329.

[7] Angeletti S, Dicuonzo G, Fioravanti M, De Cesaris M, Fogolari M, Lo Presti A, Ciccozzi M, De Florio L. MR-Proadrenomedullin, and cytokines measurement in sepsis diagnosis: advantages from test combination, Dis Markers 2015; 2015: 951532.

[8] Enguix-Armada A, Escobar-Conesa R, García-De La Torre A, De La Torre-Prados MV. Usefulness of several biomarkers in the management of septic patients: C-reactive protein, procalcitonin, presepsin and mid-regional pro-adrenomedullin. Clin Chem Lab Med 2016; 54: 163-8.

[9] Angeletti S, Spoto S, Fogolari M, Cortigiani M, Fioravanti M, De Florio L, Curcio B, Cavalieri D, Costantino S, Dicuonzo G. Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections. APMIS 2015; 123: 740-8.

[10] Akpinar S, Rollas K, Alagöz A, Seğmen F, Sipit T. Performance evaluation of MR-proadrenomedullin and other scoring systems in severe sepsis with pneumonia. J Thorac Dis 2014; 6: 921-9.

[11] Goode KM, Nicholls R, Pellicori P, Clark AL, Cleland JG. The in vitro stability of novel cardiovascular and sepsis biomarkers at ambient temperature. Clin Chem Lab Med 2014; 52: 911-8.

[12] Angeletti S, Battistoni F, Fioravanti M, Bernardini S, Dicuonzo G. Procalcitonin and mid-regional pro-adrenomedullin test combination in sepsis diagnosis. Clin Chem Lab Med 2013; 51: 1059-67.

[13] Travaglino F, De Berardinis B, Magrini L, Bongiovanni C, Candelli M, Silveri NG, Legramante J, Galante A, Salerno G, Cardelli P, Di Somma S. Utility of Procalcitonin (PCT) and Mid regional pro-Adrenomedullin (MR-proADM) in risk stratification of critically ill febrile patients in Emergency Department (ED). A comparison with APACHE II score. BMC Infect Dis 2012; 12: 184.

[14] Suberviola B, Castellanos-Ortega A, Llorca J, Ortiz F, Iglesias D, Prieto B. Prognostic value of proadrenomedullin in severe sepsis and septic shock patients with community-acquired pneumonia. Swiss Med Wkly 2012; 142: w13542.

[15] Di Somma S, Magrini L, Travaglino F, Lalle I, Fiotti N, Cervellin G, Avanzi GC, Lupia E, Maisel A, Hein F, Wagner F, Lippi G. Opinion paper on innovative approach of biomarkers for infectious diseases and sepsis management in the emergency department. Clin Chem Lab Med 2013; 51: 1167-75.

[16] Julián-Jiménez A, Timón Zapata J, Laserna Mendieta EJ, Sicilia-Bravo I, Palomo-de Los Reyes MJ, Cabezas-Martínez A, Laín-Terés N, Estebaran-Martín J, Lozano-Ancín A, Cuena-Boy R. [Diagnostic and prognostic power of biomarkers to improve the management of community acquired pneumonia in the emergency department]. Enferm Infecc Microbiol Clin 2014; 32: 225-35.

[17] Önal U, Valenzuela-Sánchez F, Vandana KE, Rello J. Pro-Adrenomedullin (MR-proADM) as a biomarker for sepsis and septic shock: narrative review. Healthcare (Basel) 2018; 6.

[18] Ara-Somohano C, Bonadona A, Carpentier F, Pavese P, Vesin A, Hamidfar-Roy R, Minet C, Vanzetto G, Schwebel C, Timsit JF. Evaluation of eight biomarkers to predict short-term mortality in patients with acute severe dyspnea. Minerva Anestesiol 2017; 83: 824-835.

[19] Lundberg OH, Bergenzaun L, Rydén J, Rosenqvist M, Melander O, Chew MS. Adrenomedullin and endothelin-1 are associated with myocardial injury and death in septic shock patients. Crit Care 2016; 20: 178.

[20] Karakike E, Adami ME, Lada M, Gkavogianni T, Koutelidakis IM, Bauer M, Giamarellos-Bourboulis EJ, Tsangaris I. Late Peaks of HMGB1 and sepsis outcome: evidence for synergy with chronic inflammatory disorders. Shock 2018.

[21] Camps J, Iftimie S, García-Heredia A, Castro A, Joven J. Paraoxonases and infectious diseases. Clin Biochem 2017; 50: 804-811.

[22] Matsumoto H, Ogura H, Shimizu K, Ikeda M, Hirose T, Matsuura H, Kang S, Takahashi K, Tanaka T, Shimazu T. The clinical importance of a cytokine network in the acute phase of sepsis. Sci Rep 2018; 8: 13995.