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Correlations of Changes in Brain Natriuretic Peptide (BNP) and Cardiac Troponin I (cTnI) with Levels of C-Reactive Protein (CRP) and TNF-α in Pediatric Patients with Sepsis

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Statistical Analysis C
Data Interpretation D
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Background: This study investigated the changes in plasma brain natriuretic peptide (BNP) and cardiac troponin I (cTnI) levels in pediatric patients with sepsis, and explored their relationships with serum inflammatory factors in pediatric patients.

Material/Methods: A total of 120 pediatric patients with sepsis admitted to and treated at our hospital from 2013 to 2017 were divided into 4 groups: a systemic inflammatory response syndrome (SIRS) group (n=28), a sepsis group (n=35), a severe sepsis group (n=27), and a septic shock group (n=30). Plasma BNP, cTnI, and creatine kinase-MB (CK-MB) levels in pediatric patients in the 4 groups were measured, and the correlations of BNP and cTnI with plasma inflammatory factors C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) were investigated.

Results: The plasma BNP and cTnI levels in pediatric patients with sepsis were significantly higher than those in the SIRS group ($p<0.05$). After hospitalization and treatment, levels of BNP and cTnI in pediatric patients were decreased. The concentrations of BNP and cTnI were correlated with CRP level ($r=0.88$ and 0.88, respectively). The associations (r value) of BNP and cTnI with TNF-α levels were 0.35 and 0.48, respectively.

Conclusions: The levels of plasma BNP and cTnI are associated with the severity of sepsis in pediatric patients, and were positively correlated with CRP and TNF-α levels, which provides a novel strategy for the early diagnosis and evaluation of sepsis in pediatric patients.

MeSH Keywords: Natriuretic Peptide, Brain • Sepsis • Systemic Inflammatory Response Syndrome

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Background

Sepsis is an infection- and non-infection-induced systemic inflammatory response syndrome (SIRS) [1]. Infectious factors are predominantly involved in bacterial infections, while non-infectious factors refer to nonspecific inflammations including trauma and burn. The deteriorated SIRS may develop in different phases, from sepsis, to inflammatory sepsis, to septic shock. Sepsis is characterized by rapid progression, which may easily cause multiple organ dysfunction syndrome (MODS), leading to high mortality [2,3]. Previous evidence indicated that most pediatric patients with sepsis are prone to MODS, of which 40–50% suffer from cardiac insufficiency or heart failure [4]. Since the kidneys are relatively sensitive to toxins, renal failure occurs first, which results in accumulation of toxins and disturbance of the water-electrolyte balance in the body of pediatric patients. The increasing volume load of the heart and detoxification of the liver give rise to the failures of other organs. Therefore, early diagnosis is of great importance for preventing the progression of sepsis in patients. Brain natriuretic peptide (BNP) is a type of prohormone secreted by cardiomyocytes. Previous reports found that the plasma level of BNP was increased in patients with myocardial dysfunction and was also considered as a potential marker of unfavorable prognosis in patients with severe sepsis and septic shock [5,6]. Increased levels of cardiac troponin I (cTnI) are associated with adverse clinical outcomes of heart disease patients, indicating it may be a sensitive and specific biomarker for use in diagnosing and stratifying patients with heart failure [7]. This study aimed to determine the roles of BNP and cTnI in the occurrence and progression of sepsis in pediatric patients to define the specific molecular targeting indicators for the early diagnosis of sepsis in pediatric patients.

Material and Methods

Basic data

A total of 120 pediatric patients with sepsis admitted to and treated at our hospital from 2013 to 2017 were retrospectively analyzed. The study was approved by the Ethics Committee of the Second People's Hospital of Kashgar. The informed consent form was signed by the patients' guardians. There were no statistically significant differences in basic data of pediatric patients, such as gender, age, and basic medical history, among the 4 groups ($p>0.05$) (Table 1).

Criteria for grouping

According to the diagnostic criteria for pediatric sepsis [8] published in the New England Journal of Medicine in 2015, the 120 patients enrolled in this study were divided into 4 groups: a systemic inflammatory response syndrome (SIRS) group (n=28), a sepsis group (n=35), a severe sepsis group (n=27), and a septic shock group (n=30). Pediatric patients with autoimmune diseases, immunodeficiencies, previous severe organ dysfunctions, or other diseases such as tumors were excluded. Pediatric patients were enrolled if they had a positive (blood) culture by bacteriological examination in our hospital or had an infectious focus on imaging and computed tomography (CT) results.

Examination methods

Venous blood was collected from all pediatric patients at 1, 3, and 7 days after admission and centrifuged to collect the supernatant. Then, BNP, cTnI, and procalcitonin (PCT) were

Table 1. Comparisons of general data among the 4 groups of pediatric patients.

Group	SIRS group (n=28)	Sepsis group (n=35)	Severe sepsis group (n=27)	Septic shock group (n=30)	P value
Age (years old)	4.7±2.8	5.4±1.7	5.9±2.5	5.7±2.4	0.2474
Sex					
Male	16	24	16	18	0.9376
Female	12	21	11	12	
Infection site respiratory system	11	12	11	13	0.8972
Abdomen	4	7	5	6	0.9345
Hematological system	4	6	4	3	0.8749
Urinary system	4	4	2	3	0.8713
Chest	3	3	3	3	0.9877
Other parts	2	3	2	2	0.9926

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Table 2. Comparisons of BNP, cTnI, and CK-MB levels at 1 day after admission among the 4 groups of pediatric patients (x±s).

Item	SIRS group	Sepsis group	Severe sepsis group	Septic shock group
BNP (pg/mL)	610.6±154.2	896.3±178.9*	1467±278.6*	2980.7±365.8*
cTnI (mg/L)	42.2±19.8	150.3±90.2*	321.4±140.3*	573.6±124.8*
CK-MB (U/L)	18.92±3.26	29.7±4.53*	39.3±4.89*	52.3±4.65*

Compared with SIRS group, * $p<0.05$.

detected by electrochemiluminescence, and immunoturbidimetry was applied to measure C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α). All procedures were strictly conducted by professionals.

Statistical analyses

Statistical Product and Service Solutions (SPSS) 17.0 was employed for statistical analyses. The *t* test was used for the intergroup comparison and the chi-square test was used for enumeration data. Continuous data from multiple groups were analyzed by using one-way ANOVA with Tukey's post hoc test. Correlations were analyzed using Pearson analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of general data of pediatric patients with sepsis among four groups

The age range of the 120 patients was 1.9 years old to 8.4 years old. Data on patient sex, abdomen infections, and blood, chest, and urinary systems were also recorded. The no statistically significant differences in patient characteristics were observed among the 4 groups ($p>0.05$) (Table 1).

Comparisons of BNP, creatine kinase-MB (CK-MB,) and cTnI levels among the 4 groups of pediatric patients with sepsis

The plasma BNP and cTnI levels in the 4 groups of pediatric patients were clearly elevated, and were higher than those in normal children (BNP, 75.48 (42.38–115.86) pg/mL) (cTnI, 38.52 (27.51–45.85) pg/mL) (Table 2). In addition, the levels of BNP and cTnI were significantly up-regulated at day 1 post admission, which is in agreement with the severity of sepsis in pediatric patients, displaying statistically significant differences ($p<0.05$). Our data suggest that BNP and cTnI can be used as potential molecular markers to evaluate the severity of sepsis (Table 2).

Comparisons of serum BNP and cTnI concentrations at different time points among the 4 groups of pediatric patients

Serological detection in the 4 groups of pediatric patients was further performed at 1, 3, and 7 days after admission. The levels of BNP and cTnI among patients present a reducing trend at day 3 and 7 after admission. Notably, the treatment significantly decreased the levels of BNP and cTnI in pediatric patients at day 7 after admission from each group, compared to that at day 1, correspondingly ($p<0.05$) (Figure 1A, 1B).

Comparisons of serum inflammatory factors and health evaluation scores of pediatric patients among the 4 groups

Serological detection, SOFA scoring and APACHE II scoring were carried out at 1 day after admission in the 4 groups of pediatric patients. We observed that the values of CRP, TNF-α, IL-6, PCT, WBC, SOFA, APACHE II serum inflammatory factors CRP, TNF-α, interleukin-6 (IL-6), white blood cell (WBC), and PCT were to some extent elevated as the severity of the disease enhanced. Compared with those in the SIRS group, the levels of inflammatory factors TNF-α, CRP, PCT, and IL-6 were significantly increased in the sepsis group, severe sepsis group, and septic shock group ($p<0.05$). No statistically significant difference was detected in WBC between the SIRS group and sepsis group, but WBC in the severe sepsis group and septic shock group were significantly higher ($p<0.05$) (Table 3).

Correlation analyses of plasma BNP, cTnI, and inflammatory factors in the 4 groups of pediatric patients with sepsis

Hierarchical correlation analysis was applied to calculate the correlations of serum BNP and cTnI with plasma inflammatory factors CRP and TNF-α at 1 day after hospitalization in the 4 groups of pediatric patients. The results indicated that BNP was positively related to CRP ($r=0.88$) and TNF-α ($r=0.35$), and cTnI was also positively associated with CRP ($r=0.88$) and TNF-α ($r=0.48$) (Figure 2).

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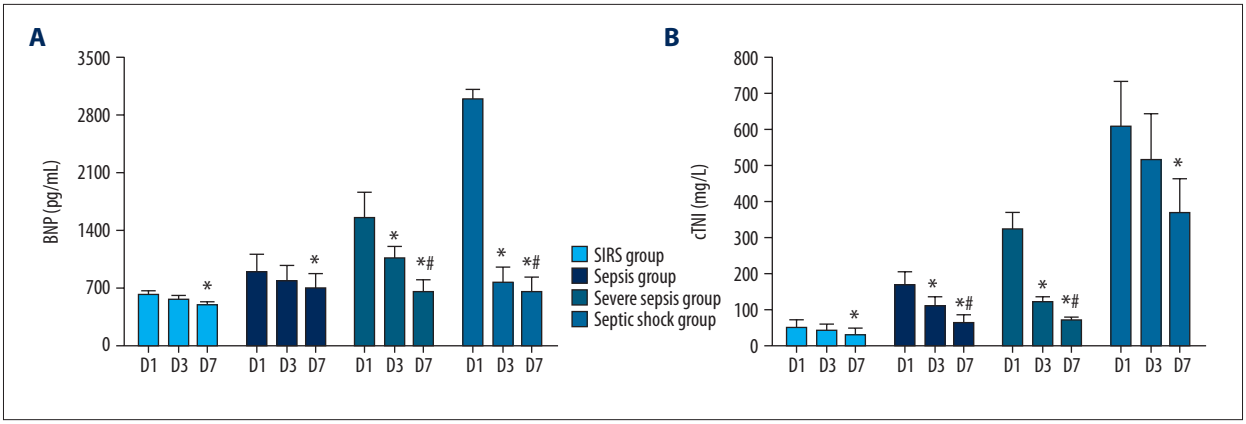

Figure 1. The levels of BNP and cTnI in patients at different time points. (**A**) Serum BNP content at day 1, 3, and 7 days after admission. (**B**) Serum cTnI content at days 1, 3, and 7 after admission. Systemic inflammatory response syndrome (SIRS) group (n=28), sepsis group (n=35), severe sepsis group (n=27), and septic shock group (n=30). The *t* test was used for intergroup comparison. Continuous data from multiple groups were analyzed using one-way ANOVA with Tukey's post hoc test. * p<0.05, compared with D1. # p<0.05, compared with D3.

Table 3. Comparisons of serum inflammatory factor levels and health evaluation scores among the 4 groups of pediatric patients (x±s).

Item	SIRS group	Sepsis group	Severe sepsis group	Septic shock group
CRP (mg/L)	9.88±6.43	17.26±5.96*	25.84±14.76*	35.89±17.42*
TNF-α (ng/mL)	189.5±84.3	365.4±114.6*	415.6±158.9*	514.7±153.2*
IL-6 (pg/L)	106.8±17.9	346.2±187.4*	452.4±203.6*	554.3±198.5**
PCT (ng/mL)	2.74±1.43	5.57±2.24	10.93±3.62*	15.87±6.74*
WBC (×10^9/L)	10.7±2.14	10.9±1.86	14.9±1.54	19.7±3.25*
SOFA	–	6.2±1.57	10.3±1.43	11.6±2.85
APACHE II	9.5±3.7	14.7±6.3	20.5±4.8*	29.4±8.7*

Compared with SIRS group, * *p*<0.05, APACHE II – acute physiology and chronic health evaluation II, SOFA – sequential organ failure assessment.

Discussion

Various infectious and non-infectious factors can easily induce uncontrolled and nonspecific systemic inflammatory responses (also known as SIRS [9]) in children due to their underdeveloped immune system and weak resistance to external stimuli [10]. SIRS is able to stimulate the immune system of children, leading to the activation and release of a variety of inflammatory factors, including CRP, TNF-α, and interleukin-6. The response of the body's immune defense cascades is thus abnormally enhanced and excessive cytokines are released into the blood. As a result, systemic organs are damaged and destroyed, and MODS occurs [11,12]. Sepsis, severe sepsis, and septic shock are characterized according to the systemic inflammatory response [13]. Sepsis is potentially life-threatening, especially for pediatric patients, because it progresses rapidly and has become a major cause for the growth in mortality rates of critically ill patients [14,15]. In recent years, the importance of early diagnosis of SIRS has deepened understanding and awareness of the pathogeneses of SIRS and sepsis. Early diagnosis and treatment are key to reducing the mortality rate of patients with sepsis and to improve clinical treatment efficacy [16,17]. Currently, the differentiated identification on patients with SIRS, potential patients with sepsis, and even high-risk patients with severe sepsis in early stage is a tremendous challenge for clinicians. Diagnosis of clinical diseases is often accompanied by relevant biological indicators such as cytokines and molecular markers. For instance, serum interleukin-6 level serves as an indicator of aseptic meningitis among children with enterovirus 71-induced hand, foot, and mouth disease [18]. Plasma gelsolin level has been used as an indicator to evaluate the severity of disease in HIV-1-infected patients [19]. It was suggested that use of cTnI in triage of patients with unstable coronary disease may identify those at greater risk for adverse cardiac events [20]. Also, early elevated B-type natriuretic peptide levels are associated with cardiac

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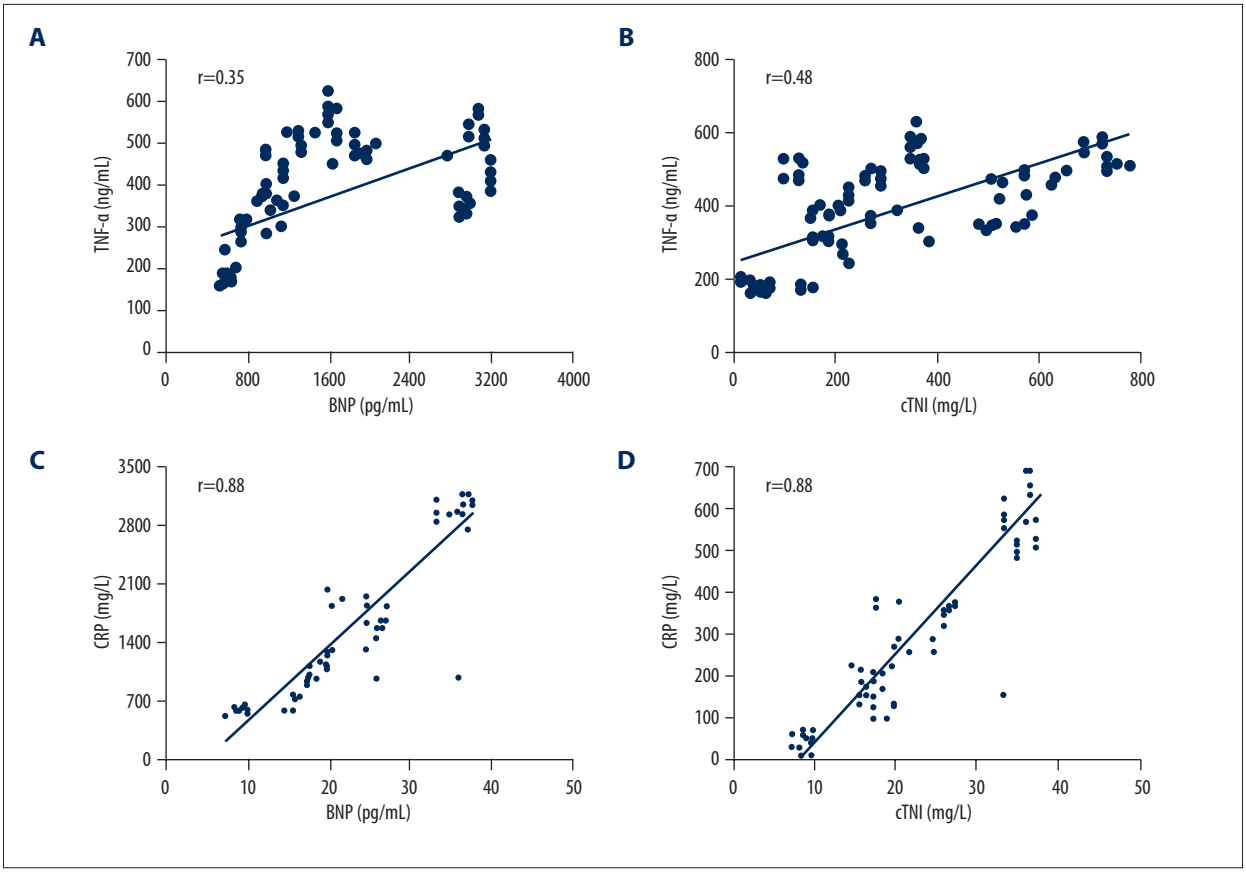

Figure 2. Correlation analysis among the 4 groups of pediatric patients by using Pearson analysis. (**A**) Relationship between serum BNP and TNF-α. (**B**) Correlation between serum cTnI and TNF-α. (**C**) Association between serum BNP and CRP. (**D**) Relationship between serum cTnI and CRP. Total number of patients was 120.

dysfunction and poor clinical outcome in pediatric septic patients, and serum BNP shows potential value for diagnosis of intracranial injury in minor head trauma [21,22]. Clinical indicators commonly used in the diagnosis of sepsis include interleukins and D-dimer. However, it has been reported that these indicators cannot predict SIRS due to their low specificity or sensitivity in the early diagnosis of sepsis [23].

BNP is mainly synthesized and secreted by the ventricles. BNP maintains the dynamic balance of electrolytes in the body by promoting the expansion of blood vessels and natriuretic and diuretic effects [24]. Elevated plasma BNP is correlated with the severity and mortality of patients with sepsis [25]. It has been demonstrated that the prognostic value of initial plasma NT-proBNP can help improve clinical outcomes of children with septic shock [26]. This may be because the release of bacterial toxins and inflammatory factors results in myocardial damage and overproduction of BNP. Simultaneously, the excessive release of inflammatory factors in sepsis impairs the function of the kidneys, causing renal insufficiency or kidney failure. It further causes blockage of water and sodium excretion and accumulation of various metabolic products in the body, thereby increasing the cardiac volume load as well as stimulating the ventricles to produce and release more natriuretic and diuretic BNP to maintain electrolyte balance in the body. At the same time, impaired renal function reduces the production of endogenous enzymes degrading BNP, thus leading to accumulation of BNP in the plasma, which is validated by previous finding of high gene expression of BNP in sepsis at the gene level [27,28]. CTnI is an ideal marker for the assessment of myocardial damage during sepsis [29]. Myocardial damage caused by inflammatory factors and bacterial toxins in patients with sepsis lead to increasing release of cTnI, and cTnI can very specifically and sensitively reflect the degree of myocardial damage [30]. Some studies have reported the roles of CK-MB and PCT in the early diagnosis of sepsis, but the specificity is unsatisfactory. Therefore, BNP and cTnI are promisingly biological indicators to determine the risk of patients with sepsis.

Conclusions

Taken together, our data demonstrate that the levels of plasma BNP and cTnI are correlated with the severity of sepsis in

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pediatric patients and are positively related to the levels of inflammatory factors CRP and TNF-α, which may help in early diagnosis and evaluation of sepsis.

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Conflict interest

None.

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