ORIGINAL ARTICLE

Serum levels of sirtuin 6 are associated with severe community acquired pneumonia in children: An observational study

Los niveles séricos de sirtuin 6 se asocian con neumonía adquirida en la comunidad grave en niños: Un estudio observacional

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Abstract

Objective: *The objective of this study was to investigate the role of sirtuin 6 (SIRT6) in severe community acquired pneumonia (CAP) in child patients.* **Methods:** *This prospective observational research enrolled a total of 75 severe child CAP patients who went to our hospital during April 2016 to December 2020, and 75 mild/moderate CAP child patients were included as control. SIRT6 and inflammatory factors C-reactive protein (CRP), interleukin (IL)-6, and procalcitonin (PCT) were tested by the enzyme linked immunosorbent assay (ELISA). Demographic data including age, sex, as well as clinical symptoms, duration of ICU stay, duration of mechanical ventilation were collected. The routine blood test was conducted for all patients and WBC amount and neutrophil ratio were recorded. The pediatric critical illness score (PCIS) and 1-month mortality were collected.* **Results:** *Levels of SIRT6 were remarkably lower in severe CAP patients or deceased patients compared with mild/moderate or survival patients, respectively. Levels of CRP, PCT, and interleukin-6 (IL-6) were markedly higher in severe patients than mild/moderate patients. However, only levels of CRP were significantly higher in deceased CAP patients and serum levels of SIRT6 were negatively correlated with serum levels of CRP, PCT, and IL-6. The higher levels of CRP, PCT and IL-6, as well as higher mortality rate and lower levels of PCIS were found in patients with lower SIRT6 compared with parents with higher SIRT6. SIRT6 had the potential for diagnosis of severe CAP and patients with lower SIRT1 showed shorter 1-month survival. Further, logistic regression showed that only age and CRP were independent risk factors for 1-month mortality of CAP child parents.* **Conclusion:** *Down-regulated SIRT6 in severe CAP child patients predicted higher expression of inflammatory factors, severer clinical outcomes and poor prognosis.*

Keywords: *SIRT6. Community acquired pneumonia. Children. Prognosis. Observational study.*

Resumen

Objetivo: *Investigar el papel de sirtuin 6 (SIRT6) en la neumonía adquirida en la comunidad (NAC) grave en pacientes infantiles.* **Métodos:** *Esta investigación observacional prospectiva inscribió a un total de 459 pacientes con NAC infantil grave que acudieron a nuestro hospital entre abril de 2016 y diciembre de 2020, y se incluyeron como control 459 pacientes con NAC infantil leve/moderada.* **Resultados:** *Los niveles de SIRT6 fueron notablemente más bajos en pacientes con NAC grave o pacientes fallecidos en comparación con los pacientes leves/moderados o con supervivencia, respectivamente. Todos los niveles de PCR, PCT e Interleukin-6 (IL-6) fueron significativamente más altos en pacientes con CAP fallecidos y los niveles séricos de SIRT6 se correlacionaron negativamente con los niveles séricos de CRP, PCT e IL-6. Los niveles más altos de PRISM, CRP, PCT e IL-6, así como una mayor tasa de mortalidad y niveles más bajos de PCIS se encontraron en pacientes con menor SIRT6 en comparación con los padres con mayor SIRT6. SIRT6 tenía potencial para el diagnóstico de NAC grave.*

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Conclusión: *La SIRT6 regulada a la baja en pacientes infantiles con NAC grave predijo una mayor expresión de factores inflamatorios, resultados clínicos más graves y mal pronóstico.*

Palabras clave: *SIRT6. Neumonía adquirida en la comunidad. Niños. Pronóstico. Estudio observacional.*

Introduction

Community acquired pneumonia (CAP) is a common respiratory disease accounting for more than 3 million deaths every year worldwide[1-3]. In children, pneumonia is also a leading cause of morbidity and mortality worldwide, with an estimated of 120 million new cases every year and the mortality rate in severe patients is about 8.7%, especially for young infants[4,5]. Due to the high mortality for severe CAP in children, the early diagnosis and treatment are very important for child patients[6].

Sirtuin 6 (SIRT6) is a member in sirtuin family, which shows multiple bioactivities in many diseases, such as diabetes[7], cancer[8], and cardiovascular diseases[9]. Besides, SIRT6 was also found to be associated with inflammation response. It was found the deficiency of SIRT6 might be related to activated inflammation[10]. However, up to now, no study reported the clinical role of SIRT6 in CAP patients.

In the present study, we aimed to investigate the role of SIRT6 in severe CAP child patients, especially for its relationship with clinical outcomes and prognosis. This study might provide clinical evidence for SIRT6 in CAP.

Materials and methods

This cross-sectional research enrolled a total of 75 severe child CAP patients who went to our hospital during January 2018 to December 2020. All patients who met the following inclusion criteria during the study period were consecutively enrolled. The diagnosis of child CAP and severe CAP was according to the criteria of Chinese Medical Association (2013 version)[11]. Briefly, the diagnosis criteria for CAP were: (1) patients with cough, expectoration, or aggravation of the original respiratory symptoms, purulent sputum, with or without chest pain; (2) fever; (3) signs of lung consolidation and/or auscultation of wet rales; (4) WBC > 10×10^9/L or < 4.0×10^9/L, with or without left shift of neutrophils' nucleus; and (5) imaging examination showing patchy or patchy infiltration shadow or interstitial changes, with or without pleural effusion. Patients who were with any one of (1)~(4) and (5) were diagnosed as CAP. The diagnosis criteria of severe CAP were: (1) patients with temperature ≥ 38.5°C; (2) patients with respiratory rate ≥ 70/min for 0~3 years old child or respiratory rate ≥ 50/min for 4~14 years old child; (3) patients with inspiratory depression of chest wall; (4) patients with nasal fan, cyanosis, intermittent apnea, and breathing moan; (5) patients with dehydration sign; and (6) patients with severe complications including heart failure, respiratory failure, shock, microcirculation disturbance, toxic encephalopathy, sepsis, toxic intestinal paralysis (or) empyema, and pneumothorax. Patients with (1) and (2) and any of 3~6) were diagnosed as severe CAP. Other patients were defined as mild-moderate CAP. The following patients were excluded: (1) patients had taken antibiotics, antiviral drugs, or anti-inflammatory drugs within 3 months before the study; (2) patients with chronic inflammatory diseases such as asthma; and (3) patients with congenital diseases such as congenital heart disease and congenital hypothyroidism. Besides, this study also included 75 mild/moderate CAP child patients as control. Written informed consent was obtained from all the parents of the patients. The present study was approved by the Ethic Committee of Henan Children's Hospital, Children's Hospital of Zhengzhou University.

Measurement of serum SIRT6 and inflammatory factors

Briefly, 5 mL peripheral venous blood were collected in EDTA tubes from all child within 24 h after admission. After centrifugation at 1500 g for 20 min, serum levels of SIRT6, interleukin (IL)-6, and procalcitonin (PCT) were tested by the enzyme linked immunosorbent assay (ELISA) using commercial kits (SIRT6 cat no. MBS2705672, MYBio Source; interleukin-6 (IL-6) cat no. EK0410, BOSTERBio; PCT cat no. ab221828, Abcam). The serum levels of C reactive protein (CRP) were detected using an automatic biochemical analyzer (Hitachi 7600, Hitachi Corporation, Japan).

Data collection

Demographic data including age, sex, as well as clinical symptoms, duration of ICU stay, and duration of mechanical ventilation were collected. The routine blood test was conducted for all patients and WBC amount and neutrophil ratio were recorded. For 1-month survival analysis, the pediatric critical illness score

(PCIS) was collected. All course death for patients was considered for 1-month mortality and the mortality time was defined from the admission time to the death.

Statistical analysis

The distribution of the data was analyzed by Kolmogorov–Smirnov method. Normally distributed data were expressed by mean ± SD. Chi-square test was used to compare the rates. Comparison between two groups was analyzed by Student t-test. Pearman's analysis was conducted for correlation analysis. Kaplan–Meier (K-M) curve was performed for survival analysis. The receiver operating characteristic (ROC) curve was used for diagnostic analysis. Logistic regression analysis was conducted for 1-month mortality using binary regression analysis by a step back method. $p < 0.05$ was considered as statistically different. All calculations were made using SPSS 21.0 (SPSS Inc., Chicago, USA).

Results

Basic characteristics in all child patients

A total of 75 severe CAP child patients, as well as 75 mild/moderate CAP child patients were included in this study. As shown in table 1, severe CAP patients showed markedly higher ratios of fever, cough, shortness of breath, dyspnea, nasal fan/cyanosis, and severe complications ($p < 0.05$). Besides, the levels of CRP, PCT, IL-6, and WBC were all significantly higher, while levels of PCIS were remarkably lower in severe CAP patients ($p < 0.05$). Besides, the 1-month mortality rate was also significantly higher in severe patients ($p < 0.05$). No other significant difference was found.

Table 1. Characteristics of all patients

Variable	Mild/moderate, (n = 75)	Severe CAP patients (n = 75)	p*
Mean age, years	5.17 ± 3.85	4.56 ± 3.29	0.297
Age range, n (%)			0.572
0~4	36 (48.0)	39 (52.0)	
5~14	39 (52.0)	36 (48.0)	
Sex, male: female	42: 33	47: 28	0.337
Symptoms, n (%)			
Fever	43 (57.33)	75 (100.00)	< 0.001
Cough	62 (82.67)	69 (92.00)	0.047
Sputum	59 (78.67)	64 (85.33)	0.220
Shortness of breath	23 (30.67)	50 (66.67)	< 0.001
Dyspnea	5 (6.67)	21 (28.00)	< 0.001
Nasal fan/cyanosis	2 (2.67)	20 (26.67)	< 0.001
Severe complications	0 (0.00)	11 (14.67)	< 0.001
PCIS	85.54 ± 5.90	75.34 ± 6.39	< 0.001
CRP, mg/L	26.48 ± 14.67	68.00 ± 29.59	< 0.001
PCT, μg/mL	50.67 ± 23.70	122.99 ± 58.32	< 0.001
IL-6, pg/mL	85.93 ± 38.29	210.62 ± 93.15	< 0.001
WBC, 10^9/mL	17.58 ± 4.55	22.31 ± 5.48	< 0.001
Neutrophil ratio (%)	58.51 ± 7.30	72.40 ± 8.91	< 0.001
1-month mortality (%)	2 (2.67)	12 (16.00)	0.001

*Comparison between severe and mild/moderate patients. Chi-square test was used to compare the rates. Comparison between two groups was analyzed by Student t-test.
CAP: community acquired pneumonia; PCIS: pediatric critical illness score;
CRP: c-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; WBC: white blood cells.

Serum levels of SIRT6 were decreased in severe and deceased child CAP patients and were correlated with inflammatory factors

Then, the serum levels of SIRT6 were measured in different CAP patients. It was found that levels of SIRT6 were remarkably lower in severe CAP patients or deceased patients compared with mild/moderate or survival patients, respectively ($p < 0.05$) (Fig. 1). The inflammatory factors of CRP, PCT, and IL-6 were also measured. Results showed that only levels of CRP were significantly higher in deceased CAP patients ($p < 0.05$). Further, Pearson's analysis showed that serum levels of SIRT6 were negatively correlated with serum levels of CRP, PCT, and IL-6 (all $p < 0.05$) (Table 2).

Serum levels of SIRT6 were associated with clinical outcomes of severe child CAP patients

To further reveal the role of SIRT6 in severe CAP parents, patients were divided into high SIRT6 group and low SIRT6 group according to the mean serum level of SIRT6 (9.32 ng/mL). As shown in table 3, the higher levels of CRP, PCT and IL-6, as well as higher mortality rate and lower levels of PCIS, as well as younger age were found in patients with lower SIRT6 compared with parents with higher SIRT6 ($p < 0.05$). besides, higher percentage of patients with fever, shortness of breath, nasal fan/cyanosis, and severe complications were also observed in patients with lower SIRT6 ($p < 0.05$). No other significant difference was observed. These results indicated that

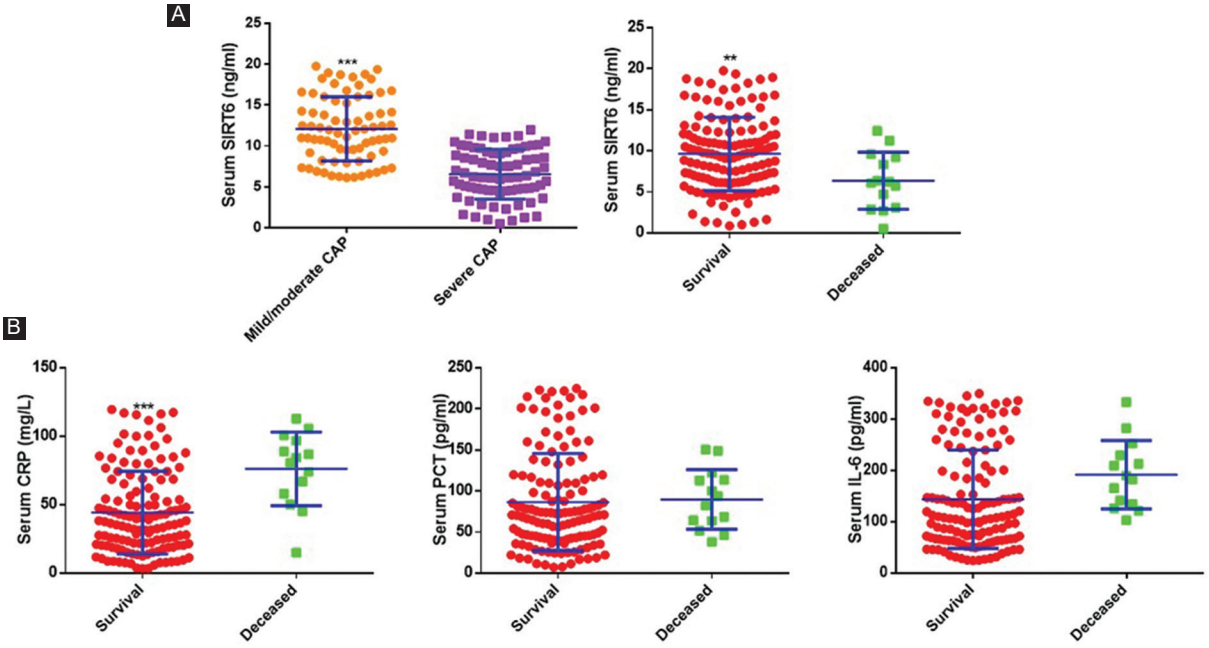

Figure 1. A: *serum levels of SIRT6 in severe/mild-moderate and deceased/survival child CAP patients.* **B:** *serum levels of CRP, PCT and IL-6 in deceased/survival child CAP patients. ***p < 0.001, **p < 0.01. SIRT6: sirtuin 6; CAP: community acquired pneumonia; CRP: c-reactive protein; PCT: procalcitonin; IL-6: interleukin-6.*

Table 2. Pearson's correlation for SIRT6 and inflammatory factors

	SIRT6	CRP	PCT	IL-6
SIRT6				
Pearson's correlation	-	–0.381	–0.319	–0.388
p value	-	< 0.001	< 0.001	< 0.001
CRP				
Pearson's correlation	–0.381	-	0.454	0.507
p value	< 0.001	-	< 0.001	< 0.001
PCT				
Pearson's correlation	–0.319	0.454	-	0.489
p value	< 0.001	< 0.001	-	< 0.001
IL-6				
Pearson's correlation	–0.388	0.507	0.489	-
p value	< 0.001	< 0.001	< 0.001	-

SIRT6: sirtuin 6; CRP: c-reactive protein; PCT: procalcitonin; IL-6: interleukin-6.

lower levels of SIRT6 might be associated with higher expression of inflammatory factors and poor prognosis in severe CAP child parents.

Diagnostic value of SIRT6 for severe child CAP and its association with 1-month mortality

The diagnostic value of SIRT6 for severe child CAP was then determined using ROC curve. It was found that SIRT6 had the potential for diagnosis of severe CAP in child parents with cutoff value 8.68 ng/mL, AUC0.863 (95% CI = 0.808-0.919), sensitivity 77.3%, and specificity 70.7% (Fig. 2). The K-M curve showed that patients with higher SIRT6 had significantly longer 1-month survival compared with parents with lower SIRT6 ($p < 0.05$) (Fig. 3). However, further logistic regression showed that only age and CRP were independent risk factors for 1-month mortality of severe CAP child parents (Table 4).

Discussion

Severe pneumonia is one of the main causes for death of children, especially for children under 5 years with higher mortality rate. Thus, the early diagnosis is of great significance for its treatment. In the present study, we demonstrated the role of a new inflammation-related factor, SIRT6, in severe CAP child parents. We found that SIRT6 is down-regulated in severe CAP parents, and lower SIRT6 expression was associated with the patients' severity and poor prognosis.

It is well-known that inflammation is a key factor for CAP development. CAP can activate inflammation response and enhance the release of cytokines[12,13]. Inflammatory factors such as CRP, PCT, and IL-6 are all found to be associated with clinical severity scores and can predict treatment failure, guide acute

Table 3. Comparison of clinical outcomes between CAP child patients with high/low SIRT6 expression

Variable	High SIRT6, (n = 73)	Low SIRT6 (n = 77)	p*
Mean age, years	5.58 ± 3.93	4.18 ± 3.09	0.016
Age range, n (%)			
0~4	31 (42.47)	44 (57.14)	0.038
5~14	42 (57.53)	33 (42.86)	
Sex, male: female	40: 33	49: 28	0.203
Symptoms, n (%)			
Fever	50 (68.49)	68 (88.31)	0.001
Cough	66 (90.41)	65 (84.41)	0.201
Sputum	61 (83.56)	62 (80.51)	0.575
Shortness of breath	25 (34.25)	48 (62.34)	< 0.001
Dyspnea	11 (15.07)	15 (19.48)	0.409
Nasal fan/cyanosis	6 (8.22)	16 (20.78)	0.012
Severe complications	2 (2.74)	9 (11.69)	0.014
PCIS	83.20 ± 7.75	77.83 ± 7.33	< 0.001
CRP, mg/L	37.02 ± 25.88	56.93 ± 32.90	< 0.001
PCT, μg/mL	71.30 ± 48.02	101.56 ± 61.67	0.001
IL-6, pg/mL	120.01 ± 87.74	175.07 ± 93.59	< 0.001
WBC, 10^9/mL	19.03 ± 5.17	20.82 ± 5.79	0.049
Neutrophil ratio (%)	62.55 ± 10.18	68.21 ± 10.50	0.001
1-month mortality (%)	3 (4.11)	11 (14.29)	0.013

*Comparison between severe and mild/moderate patients. Chi-square test was used to compare the rates. Comparison between two groups was analyzed by Student t-test.
SIRT6: sirtuin 6; CAP: community acquired pneumonia; PCIS: pediatric critical illness score; CRP: c-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; WBC: white blood cells.

Table 4. Logistic regression for risk factors of 1-month mortality in severe CAP child parents

Variables	Wald	Odds ratio	95% CI	P
Age	5.511	0.686	0.500-0.940	0.019
PCIS	3.159	0.902	0.804-1.011	0.076
SIRT6	0.459	0.932	0.759-1.143	0.498
CRP	4.332	1.028	1.002-1.054	0.038
PCT	0.647	0.994	0.979-1.009	0.421
IL-6	0.060	0.999	0.990-1.008	0.807
WBC	1.289	0.923	0.804.1.060	0.256
Neutrophil ratio	0.237	1.017	0.951-1.086	0.626

SIRT6: sirtuin 6; CAP: community acquired pneumonia; PCIS: pediatric critical illness score; CRP: c-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; WBC: white blood cells; CI: confidence interval.

in-hospital or ICU admission, as well as mortality[14]. Even in COVID-19, CRP, PCT, and IL-6 are elevated in serum, however might be lower than CAP patients[15].

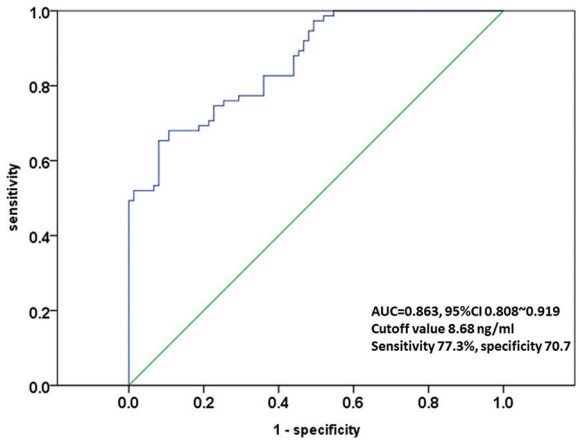

Figure 2. *ROC curve for diagnostic value of SIRT6 for child severe CAP. ROC: receiver operating characteristic; SIRT6: sirtuin 6; CAP: community acquired pneumonia.*

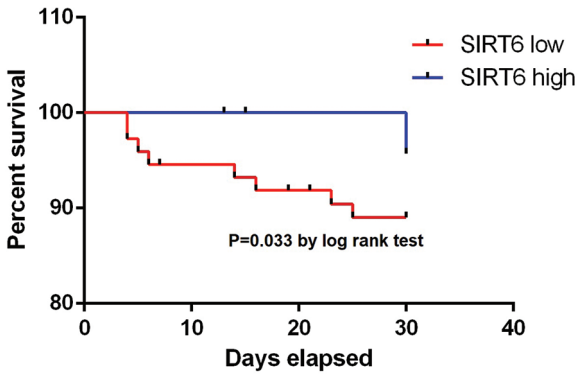

Figure 3. *K-M curve for 1-mon mortality in SIRT6 high/low severe child CAP parents. SIRT6: sirtuin 6; CAP: community acquired pneumonia.*

In our research, we also showed that CRP, PCT, and IL-6 were increased in severe CAP child patients. Besides, we also found that SIRT6 was negatively correlated with these inflammatory factors, suggesting that SIRT6 might influence CAP through regulation of inflammatory response in CAP.

The relationship between SIRT6 and inflammation has been demonstrated in several researches. Chen et al. demonstrated that overexpression of SIRT6 could suppress inflammation, oxidative stress, and cell apoptosis in spinal cord injury[16]. In other studies, SIRT6 was found to inhibit TNF-α-induced inflammation in vascular adventitial fibroblasts through ROS and Akt pathways[17,18]. Besides, hydroxytyrosol acetate was also observed to protect against inflammation of vascular endothelial cells through the activation of SIRT6[19]. In a recent study, SIRT6 was found to be down-regulated

in pre-diabetic overweight patients and was associated with increased levels of inflammatory factors[20]. All these results indicate that SIRT6 is an anti-inflammation factor which is decreased in inflammation and can protect against inflammation-related process. However, up to now, no research focused on role of SIRT6 in CAP, especially in child patients. In our research, we demonstrated for the first time that SIRT6 was decreased in severe CAP patients and lower SIRT6 was associated with increased inflammatory factors, poorer clinical outcomes, and higher 1-month mortality rate.

This study also has some limitations. The sample size is small and the underlying molecular mechanism for SIRT6 in CAP is unclear. All these need more studies to reveal.

Conclusion

This observational study showed that SIRT6 was downregulated in severe CAP child patients, and lower SIRT6 levels were correlated with higher expression of inflammatory factors, severer clinical outcomes, and poor prognosis. This study might provide a novel research target and potential biomarker for CAP in child patients.

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Conflicts of interest

All authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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