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Early Clinical Predictive Value of Serum Amyloid A and C Reactive Protein Changes in Children with Acute Upper Respiratory Tract Infection

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YZ and DS conducted the experiments in this study. JB, FL and YD contributed to the design and interpretation of the current study and wrote the article.

Key words
Serum amyloid A, C-reactive protein, Acute upper respiratory tract infection (ARTI), Early prediction

ABSTRACT

The objective of this study was to investigate the early diagnosis effect and clinical predictive value of serum amyloid A and C reactive protein in children with acute upper respiratory tract infection. A total of 324 children with acute upper respiratory tract infection (ARTI) who were treated in our hospital from October 2020 to April 2022 were selected as the research subjects. The variation of C-reactive protein concentration was tested by sphericity hypothesis, and the Greenhouse-Geisser method was used for in-depth analysis. The Receiver-Operating Characteristic (ROC) curve was drawn to evaluate the early predictive value of serum amyloid A and C reactive protein in children with acute upper respiratory tract. The concentrations of serum amyloid A and C reactive protein in children with ARTI changed significantly, with the increase of time, the concentration decreased, and the difference was statistically significant (P<0.05). The concentrations of amyloid A and C-reactive protein were significantly different, and the difference was statistically significant (P<0.05). Finally, the predictive effect of serum amyloid A and C reactive protein changes in children with ARTI was analyzed. From the ROC curve, it can be known that for both viral and bacterial upper respiratory tract infections, serum amyloid A and C reactive protein Proteins all have higher area under the line, and the ratio of the two is larger than the area under the line, both above 0.8. The serum amyloid A and C-reactive protein in the blood routine test of children with ARTI showed a changing trend. It was concluded that the changes of serum amyloid A and C-reactive protein can be used for early prediction of children with ARTI. It is of great value to improve the clinical treatment of ARTI.

INTRODUCTION

In the process of growing up, children are affected by their own immunity, and are very susceptible to various infectious diseases. Among them, acute upper respiratory tract infection (ARTI) has a high clinical prevalence. In long-term medical work, children acutely The incidence of respiratory infections is difficult to control. ARTI in children are caused by viruses and bacteria, among which viral infections are the main ones. For viral ARTI, antiviral drugs and immune-enhancing drugs are mainly used to inhibit the development of infection (Bolivar *et al*., 2020; Siddiqui *et al*., 2018). In the current clinical treatment, the cure rate of ARTI in children is low. exacerbated. In order to effectively prevent and treat ARTI in children, a large number of medical researchers are looking for a method that can rapidly detect ARTI in early childhood, so as to realize the early diagnosis of ARTI in children (Xia and Shi, 2012; Giannini *et al*., 2019). So far, the commonly used detection method in clinical practice is serum sample detection, which can effectively analyze individual serum indicators and provide early effective treatment. For ARTI in children, recent studies have shown that serum amyloid A can produce a more significant response to acute inflammation and its sensitivity is significantly higher than traditional positive indicators, so it can be used in the diagnosis of acute respiratory tract infection in children. High effectiveness (Zhang *et al*., 2020; Chou *et al*., 2016). In addition, some studies have suggested that C-reactive protein can also effectively detect the inflammatory response of individuals, and it has been found from clinical practice that C-reactive protein combined with other serum protein indicators can more effectively detect ARTI in children (Zhou *et al*., 2018). In this study, in order to treat ARTI in children, a detection strategy combining the changes of serum amyloid A and C-reactive protein was

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proposed, and the changes of the two indicators in serum detection were analyzed to make early prediction of ARTI in children.

MATERIALS AND METHODS

General information

A total of 324 children with ARTI who were treated in our hospital from October 2020 to April 2022 were selected as the research subjects, including 163 boys and 161 girls, with an average age of 5.69 years. Inclusion criteria for viral infection: (1) increased lymphocytes, normal or low white blood cells, and normal C-reactive protein; (2) upper respiratory tract infection; (3) positive respiratory virus test; (4) no significant infection lesions; (5) Conventional symptomatic treatment showed obvious curative effect. Inclusion criteria for bacterial infection: (1) increased neutrophils, increased white blood cells, and increased C-reactive cells; (2) upper respiratory tract infection; (3) negative respiratory virus test; (4) obvious infection foci; (5) Conventional symptomatic treatment has no obvious effect, and antibiotic treatment shows significant effect. Exclusion criteria: (1) children with secondary fever after diagnosis and treatment; (2) lower respiratory tract infection; (3) children with septic shock, sepsis and other symptoms; (4) children with congenital immune dysfunction; (5) Children with fever due to recent surgery, drug treatment, etc. All the children participating in the experiment and their parents were informed about the content and steps of the experiment, and signed the informed consent. The study was carried out after obtaining the approval of the ethics committee of our hospital.

Research methods

All children participating in the experiment were instructed to fast for 6-8 h, and then serum samples were collected. 2-4 ml of venous blood was collected from all children, stored at room temperature, and sent for inspection in time. When hemolysis occurred, serum samples should be tested before testing. Shake until serum is clear and clear. During the detection process, first check the batch number, prepare the items required for the experimental detection, store all the reagents in an environment of 2~8°C, and place them in a non-illuminated area, and equilibrate their temperature to room temperature before use. Next, add samples and buffers according to the instructions, shake well and incubate at room temperature. Then add antiserum, antiserum adopts goat anti-human IgG latex particles, shake well, and start the instrument in time to obtain the test results through the instrument.

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Excel was used to collect general information of all children, including age, gender, and parental status. The evaluation standard for serum amyloid A detection is that when its value is less than 10 mg/L, it is negative; when the serum amyloid A detection value is greater than 10 mg/L, it is marked as positive. The evaluation standard for C-reactive protein detection is that when its value is less than 10mg/L, it is negative; when the value of C-reactive protein is greater than 10 mg/L, it is marked as positive (Lin and Ying, 2011; Sun *et al*., 2018).

Statistical methods

All data were statistically analyzed by SPSS26.0, and the count data such as gender were expressed as cases or percentages, and x^2 was used to test. For measurement data such as serum protein detection value, if it conforms to normal distribution, it is $\bar{x}\pm s$ expressed as mean±standard deviation. The detection results of serum amyloid A and C-reactive protein were tested by sphericity hypothesis test and Greenhouse-Geisser analysis, and the prediction effect of serum amyloid A and C-reactive protein was evaluated by receiver operating characteristic (ROC) curve. A P value less than 0.05 indicated that the data difference was statistically significant.

RESULTS

Comparative analysis of the types of ARTI in children with ARTI in the study, the results are shown in Table I. It compares and analyzes the differences in age, gender, and parental medical history of children with viral ARTI and bacterial ARTI. There was no significant difference between the indicators, and the test results showed that the P value was greater than 0.05.

The study collected the serum amyloid A and C reactive protein test results of all children with ARTI, and the results are shown in Table II. As shown in Table

II, the study analyzed the differential detection values of serum amyloid A and C reactive protein in the serum detection of children with different types of ARTI and the ratio of the two indicators. It can be known that serum amyloid A and C reactive protein The protein follows a normal distribution. Comparing the differences in various indicators of children with viral ARTI and bacterial upper respiratory tract infection, the results showed that the indicators of the two types of children were significantly different, and the differences were statistically significant (P<0.05).

The change trend of serum amyloid A concentration in children with different types of acute upper respiratory tract is shown in Table III. As can be seen from Table III, the study analyzed the difference of serum amyloid A concentration with time. First, the spherical hypothesis test was performed on the changes of serum amyloid A concentration in children with bacterial ARTI. The results showed that the differences in serum amyloid A concentrations were statistically significant (P<0.05). Therefore, the Greenhouse-Geisser method was used to analyze the change of serum amyloid A concentration. During the calculation process, the significance test of the concentration change was less than 0.05, and the F value was 1783.265, indicating that under the influence of time change, the serum amyloid A concentration was obtained. significantly reduced. The changes in serum amyloid A concentration in children with viral ARTI showed that the differences in serum amyloid A concentrations were statistically significant under the influence of time (P<0.05). The Greenhouse-Geisser method was used to analyze, and the concentration difference test under the influence of time showed that P'<0.05, and the F value was 43.231. Comparing the differences in serum amyloid A concentration between bacterial and viral infections of two different types, statistical tests showed that the differences in serum amyloid a concentration at different time points were significant, and the difference was statistically significant (P<0.05).

Table I. Types of ARTI in children.

		Viral-type of ARTI (104)	Bacterial-type infection of ARTI (220)	t/ χ^2	P
Age		5.71±2.73	5.92±2.62	0.643	0.552
Gender	Male	53	112	0.961	0.323
	Female	51	108		
Medical history of parents	Yes	58	117	1.571	0.104
	No	46	103		

Table II. Detection of serum amyloid A and C-reactive protein in children with ARTI.

Group		Example number	Detection value	t	P
Serum amyloid A	Virus type	104	124.98±100.29	-8.572	0.000
	Bacterial-type	220	54.22±42.45		
C-reactive protein	Virus type	104	7.51±2.66	13.642	0.000
	Bacterial-type	220	12.82±3.40		
Serum amyloid A/C-reactive protein	Virus type	104	19.41±17.99	-11.448	0.000
	Bacterial-type	220	4.26±3.68		

Table III. Changes of serum amyloid a concentration in different types of children with ARTI.

	24h	48h	72h	96h	F	P'	P
Virus type	144.69±20.54	178.77±17.74	171.38±28.88	88.03±16.58	43.231	0.000	0.000
Bacterial-type	109.17±11.73	99.23±7.44	32.10±6.16	23.93±5.09	1783.256	0.000	0.000
t	-2.38	-6.34	-5.86	-5.49	90.24	0.000	0.000
P	0.020	0.000	0.000	0.000			

The trend of C-reactive protein concentration in children with different types of ARTI is shown in Figure 1. It can be seen from Figure 1 that with the change of time, the concentration of C-reactive protein in children with viral ARTI first decreased and then decreased. The trend of increasing and then decreasing, the overall trend shows a downward trend. In children with bacterial ARTI, the concentration of C-reactive protein increased first and then decreased with time.

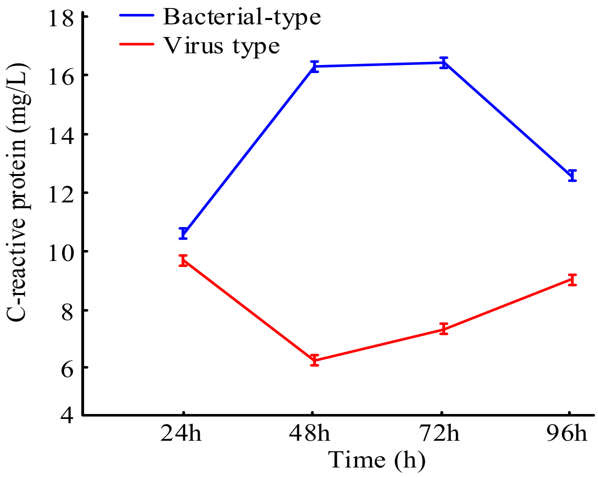

Fig. 1. Changes of C-reactive protein concentration in different types of children with ARTI.

The differences in C-reactive protein concentration changes in children with ARTI of different infection types within 24-96 h of infection were analyzed, as shown in Table IV. As shown in Table IV, firstly, the before-and-after differences of C-reactive protein concentration in children with bacterial ARTI over time were analyzed, and the spherical hypothesis was tested, and the results were shown as $P<0.05$. The Greenhouse-Geisser method was further used to analyze the difference in C-reactive protein concentration at different times, and the calculated F value was 337.68, and the P value was less than 0.05. The differences of C-reactive protein concentration over time in children with viral ARTI were analyzed. The results show that the P'value under the spherical hypothesis test is greater than 0.05. The difference in protein concentration was statistically significant ($P'<0.05$, F=15.12). Comparing the differences in C-reactive protein concentrations of different types of infections at the same time point, the results showed that the differences in C-reactive protein concentrations in children with bacterial and viral ARTI were significant and statistically significant ($P<0.05$).

First, the differences in serum amyloid A and C-reactive protein changes over time in children with ARTI of non-single virus type were analyzed, as shown in Table V. Non-isolated viral infections include influenza A and B viruses and respiratory syncytial virus. As can be seen from Table I, with time changes, the detection values of serum amyloid A in children with ARTI infected by the two virus types are presented as a whole. The trend gradually decreased, and the preliminary test showed that the difference produced by the change was statistically significant ($P<0.05$). Further analysis showed that there were significant differences in serum amyloid A in children with influenza A and B viruses and respiratory syncytial virus caused by time changes ($P'<0.05$, F=86.27; $P'<0.05$, F=768.56). The analysis of the detection results of C-reactive protein in children with two virus types showed that the detection value showed a decreasing trend with the change of time. The spherical hypothesis test was used to show that P *was* less than 0.05. Further analysis by Greenhouse-Geisser method showed that the difference of C-reactive protein under the time difference was statistically significant ($P'<0.05$, F=126.38; $P'<0.05$, F=97.42).

Serum amyloid A and C-reactive protein in children with ARTI with different non-isotype bacterial infection were analyzed over time, as shown in Table VI. It shows that the bacterial types involved in the comparison are divided into four types, namely Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. The A and C reactive proteins showed a decreasing trend, and the spherical hypothesis test was used, and the results showed that the P value was less than 0.05. Using the Greenhouse-Geisser method, the F values of serum amyloid A under the infection of Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Staphylococcus aureus were

Table IV. Difference test results of C-reactive protein in different infection types.

	24h	48h	72h	96h	F	P'	P
Virus type	9.69±0.30	6.17±0.41	7.25±0.41	5.39±0.68	15.12	0.000	0.219
Bacterial-type	10.50±0.94	16.27±0.95	12.55±1.30	8.37±1.58	337.68	0.000	0.004
t	2.73	28.09	22.44	7.71	44.62	0.000	0.000
P	0.008	0.000	0.000	0.000			

Table V. Changes of serum amyloid A and C-reactive protein in children with non-isolated virus infection.

		24h	48h	72h	96h	F	P'	P
Influenza A and B virus	Serum amyloid A	226.37±51.93	252.95±32.55	297.14±7.23	160.13±7.28	86.27	0.000	0.219
	C-reactive protein	12.15±0.61	12.36±0.49	12.18±0.55	7.03±0.21	126.38	0.000	0.000
Respiratory syncytial virus	Serum amyloid A	61.77±8.27	104.59±2.18	45.61±5.26	15.93±1.91	768.56	0.000	0.004
	C-reactive protein	8.65±0.22	8.37±0.36	7.94±0.63	6.08±0.25	97.42	0.000	0.052

Table VI. Changes of serum amyloid A and C-reactive protein in children with non-isolated bacterial infection.

		24h	48h	72h	96h	F	P'	P
Streptococcus pneumoniae	Serum amyloid A	109.97±12.87	201.51±6.81	30.72±7.22	27.13±5.92	401.86	0.000	0.000
	C-reactive protein	10.31±0.54	12.66±0.37	10.07±0.33	7.19±0.34	102.65	0.000	0.000
Haemophilus influenzae	Serum amyloid A	108.37±11.71	102.26±4.99	428.90±4.68	19.71±5.15	592.35	0.000	0.000
	C-reactive protein	10.63±0.22	11.12±0.27	9.37±0.53	6.01±0.28	119.37	0.000	0.000
Moraxella mucositis	Serum amyloid A	106.82±11.75	95.49±8.64	33.53±5.59	24.47±3.69	463.60	0.000	0.000
	C-reactive protein	10.19±0.28	12.08±0.41	9.51±0.42	6.19±0.33	184.29	0.000	0.000
Staphylococcus aureus	Serum amyloid A	111.51±11.91	97.64±7.71	35.22±5.69	24.42±2.28	427.49	0.000	0.000
	C-reactive protein	10.38±0.38	11.37±0.39	9.27±0.46	6.22±0.38	155.38	0.000	0.000

401.86, 592.35, 463.60, 427.49, C-reactive protein The F values were 102.65, 119.37, 184.29, and 155.38, respectively, and the test results showed that the differences in time changes were significant (P'<0.05).

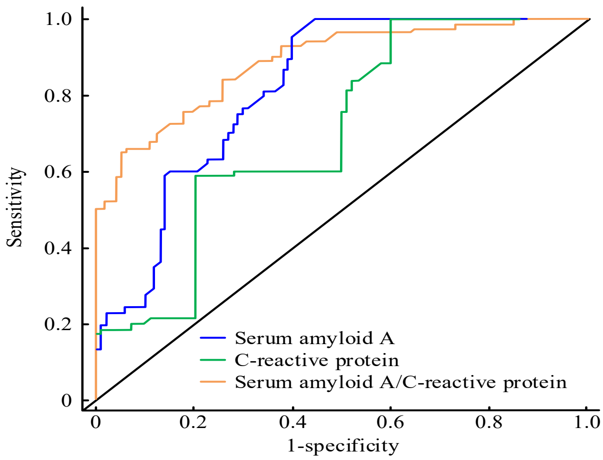

Fig. 2. Prediction performance analysis of serum amyloid A and C-reactive protein in viral infection.

The ROC curve was used to evaluate the predictive value of serum amyloid A and C-reactive protein in children with ARTI. The clinical diagnostic value of ARTI is shown in Figure 2. Figure 2 shows that in the prediction of viral ARTI, the area under the ROC curve of the three evaluation indicators are all greater than 0.7. The area under the line of the ratio of the two ratios is the largest, reaching 0.886, with a sensitivity of 97.5% and a specificity of 95.0%; the area under the ROC curve of the detection value of C-reactive protein is the smallest, at 0.704, with a sensitivity of 65.5% and a specificity of 95.0%. The degree is 59.0%.

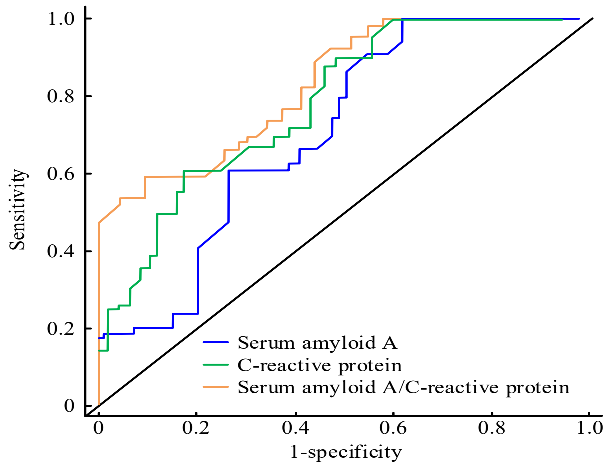

Fig. 3. Prediction of serum amyloid A and C-reactive protein in bacterial infection.

Figure 3 is an analysis of the predictive value of serum amyloid A and C reactive protein in children with bacterial ARTI on children with ARTI. Similarly, the detection values of serum amyloid A and C reactive protein and the difference between the two The ratio is used as an evaluation index. As shown in Figure 3, for bacterial ARTI, it can be seen that the area under the curve of all indicators is above 0.7, among which the ratio of serum amyloid A to C-reactive protein shows the largest area under the line, it reached 0.832, with a sensitivity of 97.5% and a specificity of 94.5%. In addition, the smallest area under the curve appeared on the serum amyloid A index, which was 0.712, with a sensitivity of 66.5% and a specificity of 60.5%.

DISCUSSION

ARTI in children is a common infectious disease in children's growth and development, and its types are divided into viral and bacterial types. The treatment of children is complex, so its early diagnosis is of great value (Choi *et al*., 2020; Costa *et al*., 2021). There are various methods for diagnosing ARTI in children, among which routine blood test is the most widely used method to distinguish infection types. In recent years, with the medical practice proving the importance of inflammatory markers in serum samples, serum amyloid A and C-reactive protein have gradually become the early diagnostic criteria for infectious diseases (Chen and Yan-Jundepartment, 2011). Serum amyloid A can significantly reflect the individual's inflammatory status. During the acute reaction phase, the serum amyloid A concentration will increase rapidly, and its response to infectious diseases is more significant. C-reactive protein is a protein that promotes the repair of damaged immune systems, and its concentration increases when the body faces inflammation to protect the body (Spletstoser *et al*., 2019; Lee *et al*., 2020; Wang *et al*., 2021). It can be known from a large number of studies that serum amyloid A and C-reactive protein can evaluate the body's inflammation and tissue immune damage to a certain extent (Rodriguez-Fernandez *et al*., 2021). Therefore, in this study, aiming at children with ARTI, in order to improve the clinical treatment effect of children with ARTI, it is proposed to analyze the change trend of serum amyloid A and C-reactive protein for early prediction and diagnosis.

In the study, we first analyzed the changes and differences of serum amyloid A and C-reactive protein in children with ARTI with different types. C-reactive protein concentration showed a decreasing trend. And it can be known from the research results that there are significant differences in serum amyloid A and C-reactive protein concentrations in viral and bacterial ARTI. Among them, the serum amyloid A in children with viral ARTI was significantly higher than that in children with bacterial ARTI, and the C-reactive protein in children with viral ARTI was significantly lower than that in children with bacterial ARTI, the difference is statistically significant. A large number of studies have pointed out that in the early stage of viral infection, serum amyloid A increases rapidly, which is a sensitive indicator for predicting viral infection (Ramdhan *et al*., 2019; Gottman and Glass, 1978). At the same time, some studies believe that bacterial secretions can change the structure of the infected cell extracellular mold, thereby exposing the contact binding site of C-reactive protein to promote the synthesis of C-reactive protein. Under virus infection, the sensitivity of C-reactive protein is not high (Arslan *et al*., 2018; Patel *et al*., 2019; Montoro *et al*., 2020; Yuen *et al*., 2021). The detection and analysis of serum samples of children with ARTI of non-isolated viral and bacterial types showed that the serum amyloid A and C-reactive protein concentrations of children with ARTI of different infection types showed a gradual decrease trend with time, and Through the difference comparison, it is shown that the difference of the detection index under different time is statistically significant. Previous studies have pointed out that children with ARTI with different types of infection have significant differences in protein expression in their bodies, and with the change of infection degree, the protein content will further change, which is consistent with the current research results (Wittmann *et al*., 1985; Sudaryatma *et al*., 2019).

In the analysis of the predictive diagnostic effect of serum amyloid A and C-reactive protein on ARTI in children, it is shown that serum amyloid A and C-reactive protein have high predictive value for viral upper respiratory tract infection, and both of them have high predictive value. The sensitivity and specificity of the ratio in prediction were both over 95%. In the analysis of the predictive value of serum amyloid A and C-reactive protein for bacterial upper respiratory tract infection, both serum tests have high predictive performance, the area under the ROC curve is above 0.7, and the two serum tests have high predictive performance. The prediction effect shown by the ratio is better, and the offline area reaches 0.832. The above results show that the use of serum amyloid A and C-reactive protein to achieve early prediction of ARTI is effective, and the type of infection in children can be determined by analyzing the difference in serum amyloid A and C-reactive protein concentrations. Previous studies have shown that changes in the concentrations of serum amyloid A and C-reactive protein are affected by the inflammatory response in the body, and many studies have pointed out that serum amyloid A and C-reactive protein can effectively judge the degree of upper respiratory tract infection (Hayashi *et al*., 2013; Ishimaru *et al*., 2019; Mei *et al*., 2021).

CONCLUSION

In conclusion, the changes of serum amyloid A and C-reactive protein can be effective in the early diagnosis of ARTI in children, and the ratio between the two can be more effective in early prediction of the disease. It plays an important role in the early prevention of ARTI in clinical children. However, it can still be found from the current experiments that in the early prediction of ARTI in children, the markers in the serum samples are less selected, and there is the possibility that some other markers may be affected. Therefore, in the follow-up study, the value of other serum markers in the early prediction of ARTI in children will be further explored, and the current research content will be expanded.

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IRB approval

This research was carried out with the approval of Research Guidance Workshop Committee (Affiliated Hospital of Hebei University).

Ethical statement

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Statement of conflict of interest

The authors have declared no conflict of interest.

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