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Associations of systemic inflammation markers with myocardial enzymes in pediatric adenotonsillar hypertrophy: A cross-sectional study

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ABSTRACT

Objective: The present study aimed to investigate the relationship between systemic inflammation markers and myocardial enzymes in children with adenotonsillar hypertrophy (ATH).
Methods: The levels of myocardial enzymes were detected and the systemic inflammatory biomarkers including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune inflammation index (SII) were calculated. Regression analyses were performed and a prediction model for screening myocardial injury was established by receiver operating characteristic (ROC) curve.
Results: Finally, a total of 804 children with ATH were included. After adjusting for age, BMI, fasting blood glucose and lipid profiles, both NLR and SII were significantly associated with CK-MB ($p = 0.041$ and 0.034, respectively) and LDH ($p = 0.002$ and 0.001, respectively), and PLR was associated with CK-MB ($p = 0.008$). In addition, NLR, SII were independently associated with hyper-LDH [OR = 1.447, 95%CI (1.063, 1.968); OR = 1.001, 95%CI (1.000, 1.002), respectively] and the associations were more significant in girls. A prediction model for hyper-LDH based on SII was developed with the area under the ROC curve of 0.715 (0.682, 0.746).
Conclusion: Systemic inflammation markers were only independently associated with serum hyper-LDH in children with ATH, especially in girls. Further investigation was needed to determine the relationship between systemic inflammation with myocardial enzymes in ATH children.

1. Introduction

Tonsil and adenoid are significant immune components in respiratory tract. Immunological reactions could cause pathological hypertrophy, which is called adenotonsillar hypertrophy (ATH). ATH is a common pediatric disease affecting about 34.46% of children and adolescents [1]. Upper airway obstruction caused by ATH during sleep comprises a large spectrum of adverse symptoms varying

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from snoring to the obstructive sleep apnea. Furthermore, it could lead to a series of sequelae such as otitis media [2], rhinitis [3], asthma [4], and gastroesophageal reflux disease [5]. And the hypoxia caused by ATH was also associated with dyslipidemia and transaminase elevation [6].

In addition, previous studies have well described a relationship of ATH with pulmonary and cardiovascular disorders. Mecnun et al. [7] found that the mean pulmonary arterial pressure of ATH children was significantly higher than controls. The right ventricular diastolic filling parameters and right ventricular end-diastolic diameters also changed in ATH children, and the above changes could return to normal after adenotonsilectomy [8]. Pac et al. [9] discovered a correlation between ATH and possible silent carditis. Besides, the maximum P-wave duration and P-wave dispersion on the electrocardiogram were significantly higher in ATH children [10]. In consideration of these cardiovascular risk, sufficient cardiac evaluation before operation is necessary. However, echocardiography and myocardial enzymes detection are not routine clinical examination items because of the high cost and the requirement of highly trained personnel. Therefore, developing an economic and convenient indicator for screening and early diagnosis of myocardial injury is of vital significance.

Several previous studies consistently demonstrated that inflammatory response was associated with cardiac injury [11–13]. Neutrophils are the most abundant leukocytes and act as the first-line responders in the inflammatory response. Clinical studies found that the neutrophil count was positively correlated to myocardial infarction size [12], and experimental studies also found neutrophil inhibition could reduce cardiac injury and infarct size [13]. Lymphocytes, an important cellular component of the body's immune response, could contribute to myocardial ischemia–reperfusion injury through inflammatory cytokines expression [14,15]. The hyperactive activation of platelets, which were important component of the hemostatic function, could result in occlusive thrombus formation. Recently, indices based on the above cells such as neutrophil-lymphocyte ratio (NLR), platelets-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) have been widely used as an indicator of inflammation in various disorders because of their rapid and cost-effective availability. One large-scale prospective cohort study observed positive associations of NLR, PLR and SII with seven out of 17 cancers [16]. Besides, NLR, an indicator of subclinical inflammation, was associated with psychiatric disorders [17], acute limb ischemia [18], Parkinson's disease [19], rheumatoid arthritis [20] and acromegaly [21]. PLR, an index of inflammatory balance, was also been found associated with rheumatoid arthritis [20] and acromegaly [21]. SII was associated with the exaggerated morning blood pressure surge [22] and prognosis of acute pancreatitis [23]. However, the relationship between inflammation markers (PLR, NLR and SII) and subclinical myocardial injury among ATH has not been investigated.

Therefore, we performed this large-scale cross-sectional study to investigate the relationship between inflammation markers (NLR, PLR and SII) and myocardial enzymes in order to evaluate the relationship between inflammation and early myocardial injury among ATH children.

2. Methods

2.1. Study design and participants

This retrospective study involved 1,552 children with ATH who admitted to the department of otorhinolaryngology, Qilu Hospital of Shandong University between January 2018 to June 2019. The exclusion criteria were as follows: (1) presence of immunodeficiency, myocarditis or congenital cardiovascular disease; (2) recurrent upper respiratory infections; (3) chronic diseases, such as chronic kidney disease, psychiatric disorder, or hyperparathyroidism; (4) systemic corticosteroid use in the previous 30 days; (5) history of treatment for adenoids or tonsils; and (6) missing clinical data. Ultimately, a total of 804 children with ATH were included.

Written informed parental consent was obtained from the parents or legal guardian. This study was approved by the Internal Review Board of the Institutional Ethics Committee of Qilu Hospital of Shandong University (KYLL-202008-126) and was conducted in accordance with the tenets of the Declaration of Helsinki.

2.2. Tonsil size and adenoid size

Tonsils were inspected and recorded with a size scale from 1 to 4 (1- tonsils within the tonsillar; 2- tonsils visible outside the anterior pillars; 3- tonsils extending three-quarters of the way to the midline; 4- tonsils meeting at the midline). Adenoids were scored with an adenoid grade scale from 1 to 4 (1-adenoids had no contact with torus tubarius; 2-the adenoids were in contact with the torus tubarius; 3-the adenoids were in contact with the torus tubarius and vomer; 4-the adenoids were in contact with the torus tubarius, vomer, and soft palate). ATH was assessed by two experienced otolaryngologists (YW and YL).

2.3. Blood biochemistry

A fasting blood sample between 7:00 and 8:00 a.m. was collected from each patient. Blood biochemistry including myocardial enzymes [creatine kinase (CK), isozyme of CK (CK-MB), and lactate dehydrogenase (LDH)], fasting blood glucose (FBG) and lipid profile [total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG)] were assessed in the hospital laboratory. Dyslipidemia in terms of TC, HDL-C, LDL-C and TG was defined as ≥ 5.17, <1.03, ≥ 3.33 and ≥ 1.7 mmol/l, respectively, according to the US National Cholesterol Education Program Adult Treatment Panel III (NCEPIII) [24]. According to the standards of the hospital laboratory, CK more than 174 U/L was defined as hyper-CK, CK-MB more than 4.0 ng/ml was defined as hyper-CK-MB, and LDH more than 230 U/L was defined as hyper-LDH.

Routine leukocyte, neutrophil, lymphocyte counts were simultaneously obtained. NLR, PLR, and SII were calculated as neutrophil-

to-lymphocyte ratio, platelet-to-lymphocyte ratio, and neutrophil·platelet/lymphocyte [16–23].

2.4. Statistical analysis

SPSS 25.0 were used for the statistical analysis. We described continuous data by mean ± standard deviation, and categorical data by counts and percentages. Differences between groups were identified by analysis of Mann-Whitney *U* test for nonnormality and chi-square test for categorical. Collinearity diagnostics were performed to eliminate possible multicollinearity among confounding factors, and age, sex, BMI, FBG, HDL-C, TG, and LDL-C were incorporated into the regression model. Linear regression and binary regression analysis were used to assess the relationship between inflammatory markers and myocardial injury after multivariable adjustment. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Receiver operating characteristic (ROC) curve analyses were used to assess the diagnostic accuracy. The area under the ROC curve (AUC), sensitivity and specificity were calculated to assess the performance of the prediction model. A p-value<0.05 was considered statistically significant.

3. Results

3.1. Basic characteristics of the study participants

Finally, a total of 804 children were included. They were divided into male group (n = 554) and female group (n = 250). The basic characteristics are shown in Table 1. The boys exhibited higher myocardial enzymes, including CK (99.47 ± 39.05 vs.91.04 ± 35.59), CK-MB (2.05 ± 0.96 vs. 1.73 ± 0.81), LDH (255.70 ± 39.78 vs. 247.08 ± 42.55) (allp <0.05). Besides, the percentage of hyper-LDH was higher in boys (75.45% vs. 68.00%, p = 0.027). As to inflammation markers, the PLR (100.99 ± 33.04 vs. 96.54 ± 33.61, p = 0.013) and SII (383.09 ± 238.04 vs. 343.05 ± 220.56, p = 0.012) were also higher in boys, while there was no significant difference between the two groups with regard to NLR.

3.2. Associations of inflammation markers with abnormal myocardial enzymes

As shown in Table 2, after adjusting for age, sex, BMI, FBG, HDL-C, TG and LDL-C, NLR was associated with CK-MB (β = −0.100, p = 0.041) and LDH (β = 7.226, p = 0.002); PLR was associated with CK-MB (β = −0.002, p = 0.011); SII was associated with CK-MB (β

Table 1
Basic characteristics of the study subjects.

	Total (N = 804)	Boys (N = 554)	Girls (N = 250)	P value
Characteristics				
Age, y	6.58 ± 2.85	6.51 ± 2.78	6.73 ± 2.99	0.610
Height, m	1.24 ± 0.19	1.24 ± 0.19	1.23 ± 0.20	0.454
Weight, kg	29.18 ± 14.76	29.91 ± 15.28	27.55 ± 13.43	**0.007**
BMI, kg/m^2	17.98 ± 3.77	18.40 ± 4.02	17.06 ± 2.98	< **0.001**
Dyslipidemia (n, %)	694, 86.32	480, 86.64	214, 85.60	0.690
Myocardial enzymes				
CK, U/L	96.85 ± 38.18	99.47 ± 39.05	91.04 ± 35.59	< **0.001**
CK-MB, ng/ml	1.95 ± 0.93	2.05 ± 0.96	1.73 ± 0.81	< **0.001**
LDH, U/L	253.02 ± 40.83	255.70 ± 39.78	247.08 ± 42.55	**0.003**
Hyper-CK (n, %)	25 (3.11)	17 (3.07)	8 (3.20)	0.921
Hyper-CK-MB (n, %)	35 (4.35)	29 (5.23)	6 (2.40)	0.068
Hyper- LDH (n, %)	588 (73.13)	418 (75.45)	170 (68.00)	**0.027**
Lipid profiles				
TG, mmol/L	0.93 ± 0.48	0.91 ± 0.50	0.96 ± 0.44	**0.010**
TC, mmol/L	4.05 ± 0.73	4.01 ± 0.67	4.14 ± 0.84	0.053
LDL-C, mmol/L	2.25 ± 0.58	2.21 ± 0.55	2.32 ± 0.63	**0.026**
HDL-C, mmol/L	1.34 ± 0.27	1.33 ± 0.27	1.34 ± 0.28	0.777
FBG, mmol/L	4.67 ± 0.41	4.69 ± 0.40	4.58 ± 0.41	< **0.001**
Inflammation markers				
Leukocyte, × 10^9/l	8.18 ± 2.15	8.27 ± 2.10	7.97 ± 2.26	0.013
Neutrophils, × 10^9/l	3.63 ± 1.55	3.69 ± 1.54	3.50 ± 1.57	**0.049**
Lymphocytes, × 10^9/l	3.67 ± 1.18	3.66 ± 1.16	3.70 ± 1.23	0.786
Platelet counts, × 10^9/l	337.59 ± 73.67	342.02 ± 73.12	327.75 ± 74.08	**0.005**
NLR	1.09 ± 0.61	1.11 ± 0.63	1.04 ± 0.55	0.174
PLR	99.61 ± 33.26	100.99 ± 33.04	96.54 ± 33.61	**0.013**
SII	370.64 ± 233.56	383.09 ± 238.04	343.05 ± 220.56	**0.012**

BMI, body mass index; CK, creatine kinase; CK-MB, isozyme of creatine kinase; LDH, lactic dehydrogenase; TG, triglycerides; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, neutrophil*platelet/lymphocyt.
Kolmogorov-Smirnov test showed that continuous variables were nonnormally distributed, so the differences between the two groups were identified by Mann-Whitney *U* test and chi-square test for categorical variables.

= −0.067, p = 0.034) and LDH (β = 0.114, p = 0.001). Then logistic regression models were performed to estimate the relationship between the inflammation markers (NLR, PLR and SII) and abnormal myocardial enzyme (i.e., hyper-CK, hyper-CK-MB, and hyper-LDH). The results showed that only NLR and SII were associated with hyper-LDH with ORs (95% CI) being 1.447(1.063, 1.968) and 1.001(1.000, 1.002), respectively (Table 3). The associations between all inflammation markers and hyper-CK/hyper-CK-MB were not significant.

3.3. Associations of inflammation markers with abnormal myocardial enzyme stratified by sex

To further exclude the influence of sex, the relationships were evaluated stratified by sex. As shown in Table 4, after adjusting for age, sex, BMI, FBG, HDL-C, TG and LDL-C, the studied inflammation markers (NLR, PLR and SII) were not associated with CK and CK-MB. In terms of LDH, only in girls, NLR and SII were associated with hyper-LDH with ORs (95% CI) being 2.854 (1.275, 6.389) and 1.002 (1.000, 1.004), respectively, and no significant relationship between PLR and LDH was observed.

3.4. Establishment of predictive models

Considering the relationship between inflammation markers and LDH, we performed ROC analyses to assess the diagnostic accuracy (Table 5). Furthermore, according to the result of the logistic regression analysis, one prediction model with NLR not included for hyper-LDH was generated. PRE, based on age, LDL and SII, was developed using the formula Logit(P) = −0.297*age+0.51*LDL+0.001*SII. The AUC was 0.715 (0.682, 0.746) with a sensitivity and specificity of 60.4% (95%CI, 56.3–64.4) and 72.7% (95%CI, 66.2–78.5), respectively (Fig. 1 A). And rate of positive results for blood biochemistry and PRE was shown in Fig. 1 B.

4. Discussion

The present study demonstrated that systemic inflammation markers are associated with myocardial enzymes among ATH children. After adjusting for age, sex, BMI, FBG, HDL-C, LDL-C and TG, NLR and SII were independently associated with hyper-LDH, and the associations were more significant in AHT girls. Furthermore, we developed a simple prediction model based on age, LDL and SII, which exhibited satisfactory efficiency in terms of screening hyper-LDH patients among ATH children. These findings indicated the possible role of systemic inflammation in screening abnormal myocardial enzymes in ATH children.

Clinically, pediatric myocardial injury was usually occult and the screening for myocardial injury predominantly focused on adults. However, the consequences may be more deleterious in children because of the insufficient potential for the recovery of reversibly damaged cardiomyocyte. Numerous previous studies have confirmed the associations of ATH with abnormalities in cardiovascular structure and function [7–10], and detecting myocardial risk preoperatively was of great significance for attenuating further injury, but the echocardiography and myocardial enzymes examination are not routine clinical examination items. In addition, the central and complicated role of systemic inflammation in the pathophysiology of myocardial injury has aroused much attention [11–15], and chronic inflammatory events was closely demonstrated associated with ATH [25]. Wu et al. [26] found NLR was negatively associated with CK-MB and LDH in children with COVID-19. But in children with frequent ventricular premature beat, NLR was positively correlated with the peak of cardiac troponin I [27]. Nonetheless, the association of systemic inflammation with myocardial injury among ATH children has not been investigated. In our preliminary analysis, NLR was negatively associated with CK-MB among ATH children, while the associations of NlR with hyper-CK-MB were all not significant. Notably, we found NLR was significantly associated with hyper-LDH after multiple adjustment, consistent with studies in other populations [26,27]. This finding indicated that NLR may be a predictive index of the myocardial injury in ATH children, but NLR was not included in the final prediction model for screening hyper-LDH.

SII has been reported to be associated with carotid intima-media thickness and coronary stenosis [28,29], even has been a powerful tool for predicting acute pulmonary embolism [29]. In the present study, after multiple adjustment, SII was significantly associated with hyper-LDH among ATH children, and a simple prediction model based on SII with satisfactory efficiency was established. Thus, we think that serum SII, a marker of inflammation and immune response, could be used as a sensitive indicator of hyper-LDH in ATH children. Despite SII, two recognized risk factors, age and LDL, were also combined in the model. However, LDH is not a specific marker of myocardial injury, thus the relationship between inflammation and myocardial enzymes was indeterminate.

Table 2
Associations of inflammation markers with myocardial enzymes' levels.

	CK		CK-MB		LDH	
	β	p	β	p	β	p
NLR	−4.012	0.076	**−0.100**	**0.041**	**7.226**	**0.002**
PLR	−0.014	0.736	**−0.002**	**0.011**	−0.005	0.907
SII	−0.010	0.076	**−0.067**	**0.034**	**0.114**	**0.001**

Adjusted for age, sex, BMI, FBG, HDL-C, TG, and LDL-C.
CK, creatine kinase; CK-MB, isozyme of creatine kinase; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, neutrophil*platelet/lymphocyte.

Table 3
Associations of inflammation markers with abnormal myocardial enzyme.

	Hyper-CK		Hyper-CK-MB		Hyper-LDH	
	OR	95% CI	OR	95% CI	OR	95% CI
NLR	0.932	(0.463, 1.875)	0.451	(0.175, 1.166)	**1.447**	**(1.063, 1.968)**
PLR	1.003	(0.991, 1.015)	0.989	(0.975, 1.003)	1.001	(0.995, 1.006)
SII	1.000	(0.998, 1.002)	0.997	(0.995, 1.000)	**1.001**	**(1.000, 1.002)**

Adjusted for age, sex, BMI, FBG, HDL-C, TG, and LDL-C.
CK, creatine kinase; CK-MB, isozyme of creatine kinase; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, neutrophil*platelet/lymphocyte.

Table 4
Associations of inflammation markers with abnormal myocardial enzyme stratified by sex.

	Boys		Girls	
	OR	95% CI	OR	95% CI
CK				
NLR	0.749	(0.287, 1.954)	1.500	(0.480, 4.692)
PLR	0.999	(0.983, 1.015)	1.010	(0.991, 1.029)
SII	0.999	(0.997, 1.002)	1.001	(0.998, 1.004)
CK-MB				
NLR	0.387	(0.127, 1.182)	0.819	(0.150, 4.488)
PLR	0.985	(0.973, 1.005)	0.991	(0.959, 1.024)
SII	0.997	(0.994, 1.000)	0.999	(0.994, 1.004)
LDH				
NLR	1.242	(0.886, 1.742)	**2.854**	**(1.275, 6.389)**
PLR	1.001	(0.994, 1.007)	1.002	(0.991, 1.012)
SII	1.001	(1.000, 1.002)	**1.002**	**(1.000, 1.004)**

Adjusted for age, sex, BMI, FBG, HDL-C, TG, and LDL-C.
CK, creatine kinase; CK-MB, isozyme of creatine kinase; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, neutrophil·platelet/lymphocyte.

Table 5
The efficiency of NLR, PLR, SII and the model in predicting hyper-LDH.

	AUC (95% CI)	Cut-off value	Sensitivity/Specificity (%)
NLR	0.511(0.475–0.546)	0.73	30.3/75.9
PLR	0.548(0.513–0.583)	90.8	47.8/63.0
SII	0.527(0.491–0.562)	265.1	63.6/43.1
PRE	0.715 (0.682–0.746)	−0.31	60.4/72.7

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, neutrophil·platelet/lymphocyte; PRE, prediction model.

It is worth noting that the relationship between NLR/SII and hyper-LDH was more obvious in girls than in boys. The main underlying mechanism may lie in the effect of fat distribution. Adipose tissue is considered to be an endocrine organ that promote inflammatory state and metabolic processes, which could lead to cardiovascular consequences. Garnett et al. [30] demonstrated that there exist sex differences in body composition before puberty, and girls had more total body fat and trunk fat than boys. And greater deposition of fat is a strong independent predictor of cardiometabolic risk factors in children [31]. In addition to the possible effect of fat distribution, physiological characteristics of muscle and the development of organ function may further illustrate the difference. For instance, girls' muscle strength is worse, heart volume and capacity are lower, and vital capacity are smaller, which could limit the compensation of cardiopulmonary adaptive function [32,33].

To our best knowledge, this was the first study to investigate the relationship between inflammation markers (NLR, PLR and SII) and myocardial enzymes among ATH children. The strength of the present study includes the relatively large-scale sample, and multiple confounders adjustment including age, BMI, FBG, HDL-C, TG, LDL-C, enhancing the credibility of the evidence. Meanwhile, it has some limitations. First, this study was an observational cross-sectional design, temporality was unclear, thus, causality between inflammation markers and myocardial enzymes cannot be inferred. Second, although we performed analysis with multivariable adjusted, other potentially confounding factors such as physical exercise which may affect outcomes were not adjusted. Third, LDH is not a specific marker of myocardial injury, thus the relationship between inflammation and myocardial enzymes was indeterminate and further investigation was needed. Considering these limitations, further fundamental and intervention studies are warranted to confirm the clinical significance of our findings.

In conclusion, in this large-scale cross-sectional study, we investigated the relationship between systemic inflammation markers and myocardial enzymes in ATH children. Following multivariate adjustment, we found NLR and SII were only associated with LDH,

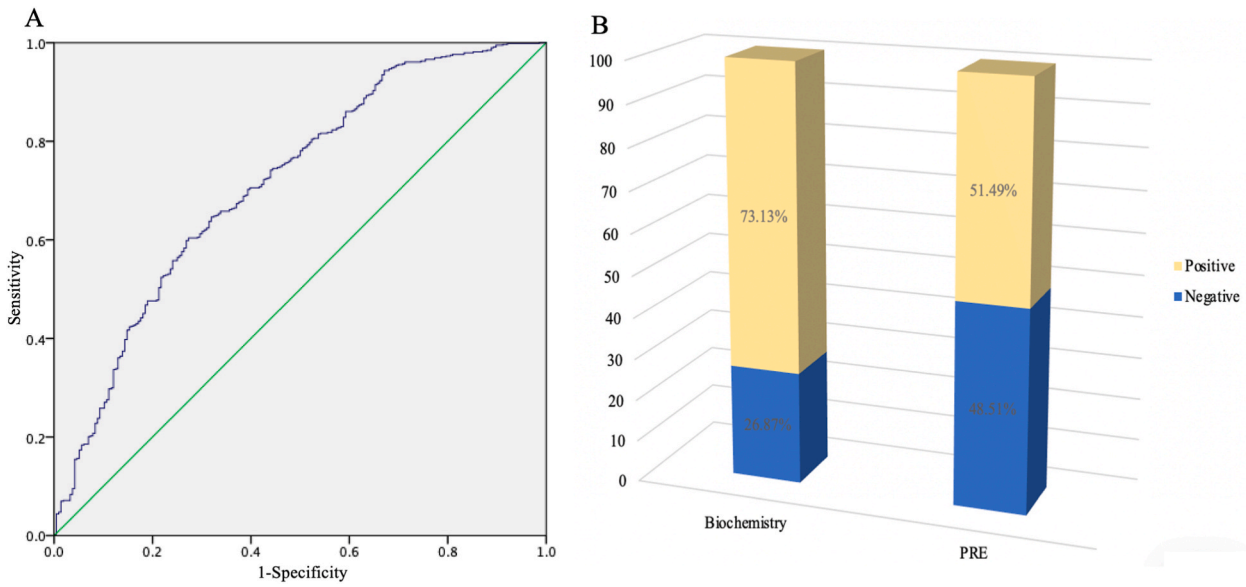

Fig. 1. Diagnostic outcomes for the model in screening hyper-LDH. (A. ROC curve for PRE. B. Rate of positive results for blood biochemistry and PRE.)
LDH, lactic dehydrogenase; PRE, prediction model.

and the associations were more significant in AHT girls. A prediction model based on SII provided a simple and practical screening tool for hyper-LDH patients among ATH children. In addition, further investigation was needed to determine the relationship between systemic inflammation with myocardial enzymes in ATH children.

Author contribution statement

Yingying Han, Ruixiang Guo: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Juanjuan Zou, Yan Wang: Conceived and designed the experiments; Wrote the paper.
Haipeng Wang, Ziyu Feng: Analysed and interpreted the data.
Yanzhong Li: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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