sST2 in Child with Kawasaki Disease

Subjects: Immunology
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sST2 belongs to the interleukin-1 receptor family, it is believed that sST2 is a myocardial protein produced by myocardial cells under the action of biomechanical forces. After comparison, we noticed that in the acute stage of Kawasaki disease (KD) in children, the increase of ST2 was significantly associated with IVIG-R KD and multi-organ damage, and had more predictive value than PRO-NT BNP. The higher the ST2 is, the more severe the patient is.

Kawasaki disease children sST2 coronary artery damage myocardial damage multi-organ damage

1.The Age and Gender Distribution of Children with KD

Table 1. General information.

	groups	age（year）	male（%）	*Page*	P_{gender}
MD	A（17）	2.0（0.6~3.0）	9(52.94)	0.061	0.464
	B（270）	2.5（1.5~4.0）	167(61.85)		
CAL	C（48）	1.9（0.8~2.7）	40(83.33)	0.003	<0.001
	D（239）	2.5（1.5~4.0）	136(56.90)		
MOD	E（58）	2.7（1.0~4.0）	36(62.07)	0.849	0.896
	F（229）	2.4（1.4~4.0）	140(61.14)		
IVIG-R KD	G（24）	2.8（1.8~5.0）	17(70.83)	0.109	0.318

	H（263）	2.4（1.4~4.0）	159(60.46)	

2. Comparison of sST2 Levels among Different Groups

Table 2. Comparison of sST2 levels among different groups

	groups	sST2（ng/mL）	*Z*	*P*
MD	A（17）	55.53(41.97~120.58)	-3.150	0.002
	B（270）	38.28(27.25~57.60)		
CAL	C（48）	42.82(32.24~71.78)	-2.086	0.037
	D（239）	38.35(27.14~57.46)		
MOD	E（58）	59.58(37.47~96.14)	-5.380	<0.001
	F（229）	37.49(26.33~51.83)		
IVIG-R KD	G（24）	65.67(43.96~183.66)	-4.214	<0.001
	H（263）	37.73(27.29~55.62)		

3. Comparison of Other Indicators among Different Groups

The level of CRP、NT-pro BNP and D-dimer in group A、C、E, and G were respectively higher than those in groups B, D, F, and H (P<0.05).

Table 3. Comparison of other indicators among different groups.

	P_{WBC}	P_{HB}	P_{PLT}	P_{CRP}	P_{IL-6}	P_{ESR}	P_{BNP}	$P_{D-dimer}$	P_{ALB}
A vs B	0.001	0.134	0.046	0.018	0.002	0.348	<0.001	0.003	0.072
C vs D	0.37	0.001	0.011	0.039	0.076	0.933	0.037	0.005	0.032
E vs F	0.002	<0.001	0.002	<0.001	<0.001	0.772	<0.001	<0.001	<0.001
G vs H	0.032	<0.001	0.05	<0.001	0.001	0.288	0.009	0.002	<0.001

4. Correlation Analysis between sST2 and Other Indicators

The correlation coefficient r was calculated using Spearman correlation analysis. A correlation was considered weak when $0.3 \leq |r| < 0.5$. sST2 had a weak positive correlation with WBC, CRP, IL-6, NT-pro BNP, and D-dimer, and a weak negative correlation with HB and ALB. There was no correlation between sST2 and ESR or PLT.

Table 4. Correlation analysis between sST2 and other indexs.

	Indexs	r	Sig.	95% confidence interval (CI)	
				lower limit	upper limit
sST2	WBC	0.301	<0.001	0.188	0.405
	HB	-0.333	<0.001	-0.434	-0.222
	PLT	0.196	<0.001	0.079	0.308
	CRP	0.412	<0.001	0.308	0.506
	IL-6	0.456	<0.001	0.352	0.548

ESR	0.105	0.08	-0.016	0.223
NT-pro BNP	0.419	<0.001	0.315	0.514
D-dimer	0.367	<0.001	0.258	0.467
ALB	-0.403	<0.001	-0.499	-0.299

5. KD Combined with MD

According to the differences between Group A and Group B in Table 3, sST2, WBC, PLT, CRP, IL-6, D-dimer, and NT-proBNP were included as independent variables in the univariate binary Logistic regression analysis. The increases in sST2, WBC, and CRP were promoting factors for KD complicated with MD(P<0.05).

Table 5. Univariate logistic regression analysis of KD combined with MD.

Influence factor	B	SE	Wald	*P*	OR	95%CI	
						lower limit	upper limit
sST2	0.011	0.004	7.043	0.008	1.011	1.003	1.020
WBC	0.099	0.035	7.788	0.005	1.104	1.030	1.183
CRP	0.012	0.004	10.034	0.002	1.012	1.004	1.019

Further perform the receiver operating characteristic (ROC) curve analysis. The areas under the curve (AUC) of sST2, WBC, CRP are 0.728, 0.738, and 0.686 respectively; The optimal cut-off value of sST_2 for predicting MD is 44.247 ng/ml.

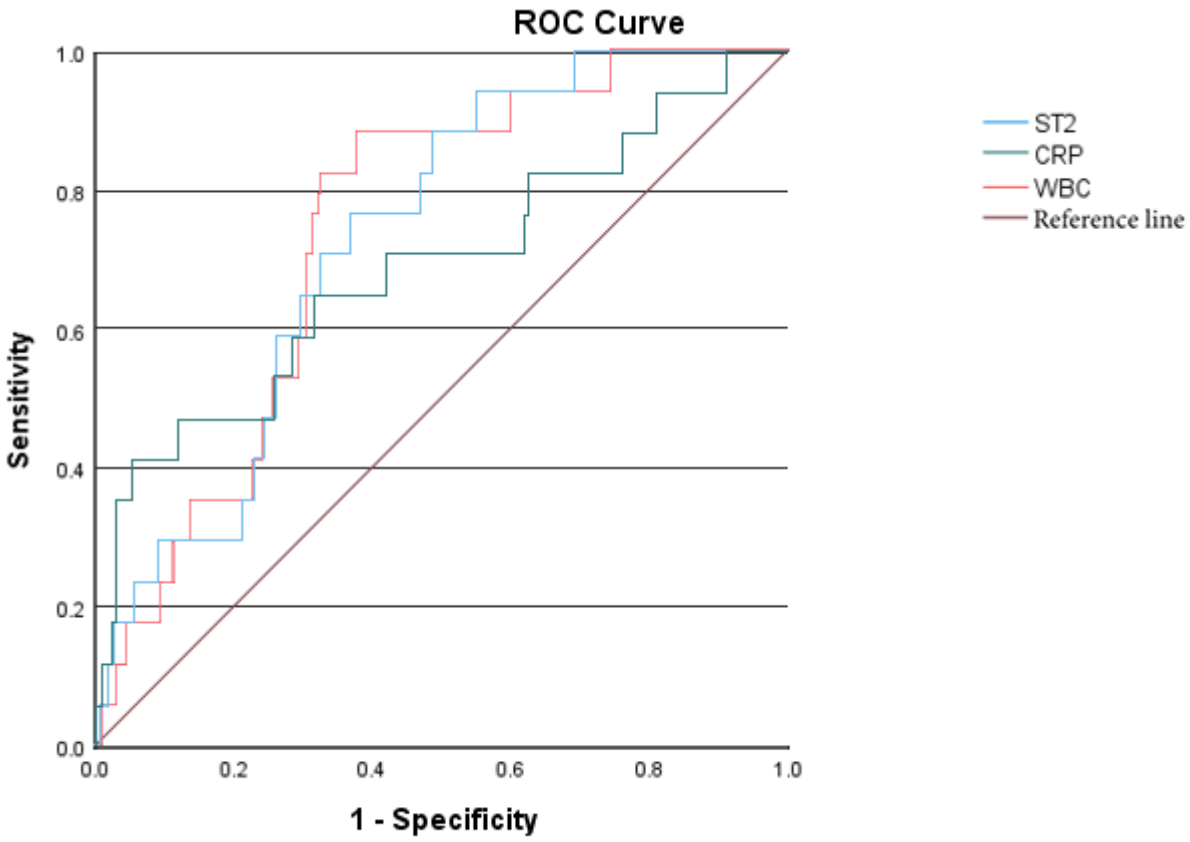

Figure 1. ROC curves of sST2, WBC, and CRP predicting KD combined with MD.

6. KD Combined with MOD

According to the differences between Group E and Group F in Table 3, sST2, WBC, HB, PLT, CRP, IL-6, NT-pro BNP, D-dimer, and ALB were included as independent variables in the univariate binary Logistic regression analysis. The results showed that the models constructed with sST2, WBC, HB, PLT, IL-6, and D-dimer were successful and had a good goodness of fit. These above independent variables were further included in the multivariate binary Logistic regression analysis, which showed that the increases in sST2 and IL-6 and the decrease in HB were independent risk factors for multiple organ involvement (P<0.05).

Table 6. Logistic regression analysis of KD combined with MOD.

factor	influence factor	B	SE	Wald	P	OR	95%CI	
							lower limit	upper limit
single	sST2	0.025	0.005	24.92	<0.001	1.025	1.015	1.035

	WBC	0.078	0.026	8.91	0.003	1.081	1.027	1.137
	HB	-0.085	0.016	28.99	<0.001	0.918	0.890	0.947
	PLT	0.002	0.001	7.97	0.005	1.002	1.001	1.004
	IL-6	0.005	0.001	22.39	<0.001	1.005	1.003	1.008
	D-dimer	0.001	0.000	16.44	<0.001	1.001	1.001	1.002
	sST2	0.013	0.005	6.01	0.014	1.013	1.003	1.024
	HB	-0.067	0.021	10.65	0.001	0.935	0.898	0.974
multi	IL-6	0.003	0.001	5.79	0.016	1.003	1.001	1.006
	WBC	-0.021	0.040	0.28	0.600	0.979	0.905	1.059
	PLT	0.001	0.001	0.51	0.477	1.001	0.998	1.003

Further perform the receiver operating characteristic (ROC) curve analysis. The AUC of sST2, IL-6,HB are 0.735、0.728、0.756 respectively; The combined AUC of the three is 0.823. The optimal cut-off value of sST2 for predicting MOD is 51.264ng/ml.

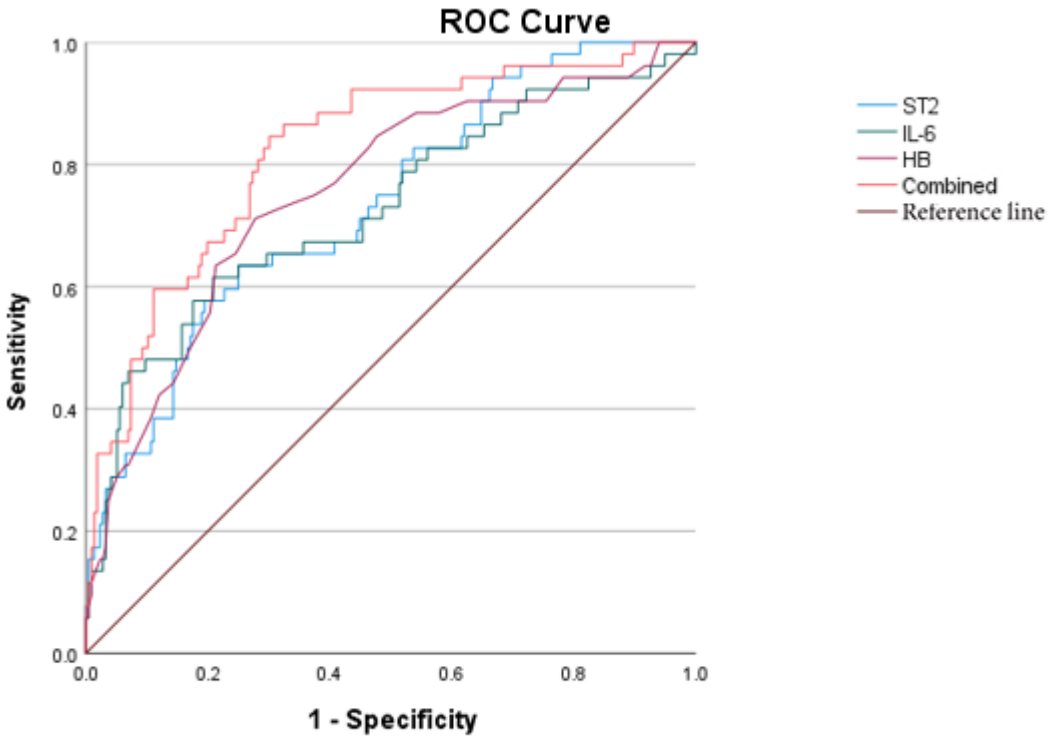

Figure 2. ROC curves of sST2, IL-6, HB, and the combined diagnosis for KD with MOD.

7. IVIG-R KD

Binary logistic regression analysis showed that sST2, HB, CRP, IL-6, ALB and IVIG-R KD models were successfully constructed with good fit; sST2 and HB were independent risk factors for IVIG-R KD (P<0.05).

Table 7. Logistic regression analysis of IVIG-R KD.

factor	influence factor	B	SE	Wald	P	OR	95%CI	
							lower limit	upper limit
single	sST2	0.026	0.005	24.142	<0.001	1.025	1.016	1.037
	HB	-0.107	0.022	23.786	<0.001	0.899	0.861	0.938
	CRP	0.017	0.003	24.584	<0.001	1.017	1.010	1.024

	IL-6	0.003	0.001	6.239	0.013	1.003	1.001	1.005
	ALB	-0.243	0.069	12.369	<0.001	0.785	0.685	0.898
	sST2	0.017	0.006	7.987	0.005	1.017	1.005	1.029
	HB	-0.062	0.027	5.354	0.021	0.940	0.892	0.991
multi	CRP	0.006	0.005	1.143	0.285	1.006	0.995	1.016
	IL-6	0.000	0.001	0.416	0.519	1.000	0.999	1.002
	ALB	0.059	0.086	0.477	0.490	1.061	0.897	1.256

Further perform the receiver operating characteristic (ROC) curve analysis. The AUC of sST2, HB are 0.760、0.783 respectively; The combined AUC of them is 0.835. sST2 increases earlier than HB decreases. The optimal cut-off value of sST2 for predicting IVIG-R KD is 43.412ng/ml.

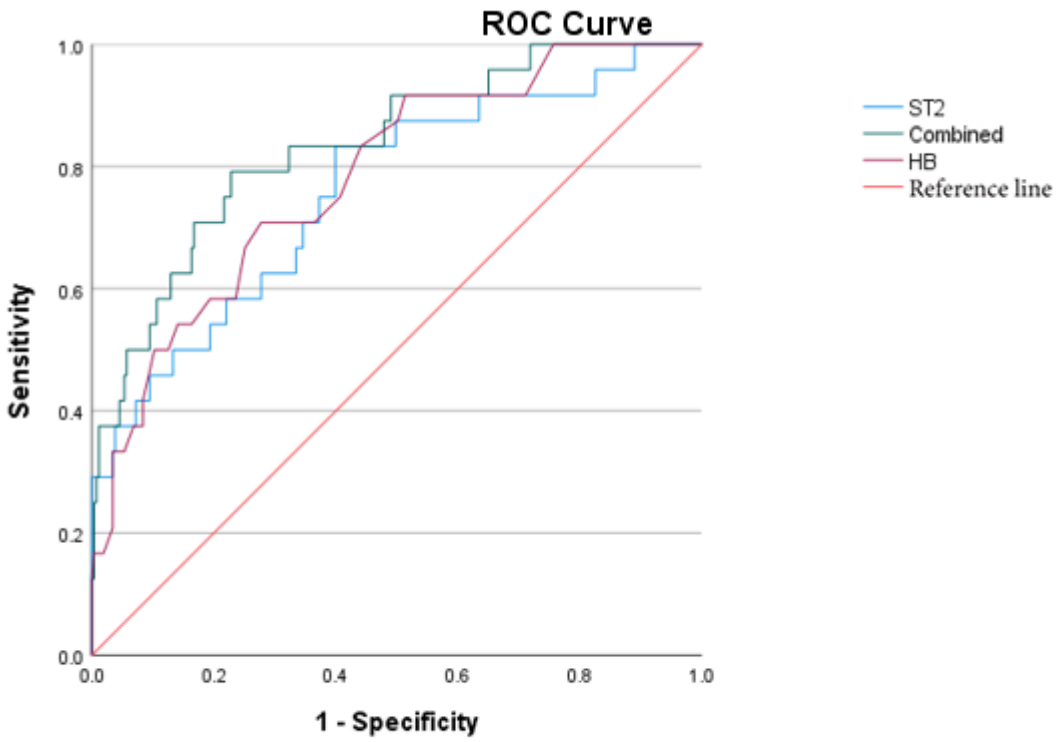

Figure 3. ROC curves of sST2, HB, and the combined prediction of IVIG-R KD.

8. Clinical Data of Four Cases with ST2>200ng/ml

Table 8. Clinical data of four cases with ST2>200.

Case	Gender	Age	ST2 (ng/ml)	Fever	Treatment	MOD
1# 19kg	F	3.5y	>200	Admission 7d Regressive10d	IVIG 4g/kg Dex5mg* 2d Methyl methicone： 2mg/kg*7d 1.5mg/kg*7d	Cardiogenic shock, Acute heart failure, Hypoproteinemia(27.1g/L), Hypokalemia, hyponatremia, Pneumonia,

					1mg/kg*1d Prednisone Po 14d ALB IV 40g	Aseptic encephalitis (EEG 2-3Hz), Localized peritonitis, Thrombocytopenia
2# 13.5 kg 102 cm	M	3y	>200	Admission 9d Regressive20d	IVIG 2g/kg Methyl methicone：20mg/kg*3d 2mg/kg*3d 1mg/kg*1d Prednisone Po 7d ALB IV 10g	CAA: LM4.7mm,Z=6.07, 3m recvered Liver damage（ALT95U/L) Hypoproteinemia(24g/L) Leukemoid reaction Aseptic encephalitis (EEG 5-7Hz) Pneumonia,
3# 9.3kg 82cm	M	23m	285.4	Admission 5d Regressive27d	IVIG 4g/kg Methyl methicone 20mg/kg*3d 10mg/kg*3d 2mg/kg*4d 1mg/kg*10d Prednisone Po 10d TNF inhibitor 5mg/kg	CAA: LM5.6mm(Z=11.1) RCA6.5mm(Z=12) Liver damage (ALT 434U/L) Hypoproteinemia (24.2g/L) Aseptic encephalitis (CSF:WBC66, Pro 0.56) Pleural effusion Moderate anemia(HGB=76g/L)

					ALBI V 70g	
4# 29kg 130cm	F	9y	287.2	Admission 6d Regressive22d	IVIG 3g/kg Methyl methicone： 2mg/kg*6d 1mg/kg*7d 0.7md/kg*3d Prednison Po 10d ALBIV 60g CTX 2mg/kg IV	CAA: LAD 6.9mm(Z= 7.63) persist RCA7.7mm(Z=10.63) persist Hypoproteinemia(20.6g/L) Aseptic encephalitis (EEG 4-7Hz) Knee joint effusion Granulocytopenia Hyponatremia, Moderate anemia(HGB=86g/L)

9. Discussion

When the physiological state of sST2 concentration is low, it can inhibit myocardial cell hypertrophy and cardiac fibrosis, thereby exerting a cardio protective effect [1].

Compared with NT-Pro BNP, the concentration of sST2 is not affected by renal function [2].

The mechanism may be that the IL-33/sST2 signaling pathway is involved in the pathophysiological processes of various inflammatory diseases and is related to inflammation and immune tolerance [3].

The more severe the condition, the higher the serum sST2 levels of patients [4].

The IL-33/sST2 axis may be a target for KD therapy [5].

References

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