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ORIGINAL RESEARCH

SESN2 as a Novel Diagnostic and Prognostic Biomarker for Kawasaki Disease and Coronary Artery Lesions

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Background: Kawasaki Disease (KD), a leading cause of acquired heart disease in children, presents significant diagnostic and prognostic challenges due to its complex pathogenesis and lack of specific biomarkers, leading to potential delays in treatment and increased risk of coronary artery lesions (CALs). Sestrin2 (SESN2), a stress-inducible protein with documented cytoprotective functions and established biomarker utility in cardiovascular diseases, warrants investigation in KD.

Methods: We conducted a single-center prospective study enrolling 72 KD patients and 38 healthy controls (HCs). Serum SESN2 levels were quantified using enzyme-linked immunosorbent assay (ELISA). Participants were stratified by CAL presence and severity. We evaluated SESN2 levels in different groups, assessed its correlations with clinical parameters and inflammatory markers, and performed ROC analysis to determine its diagnostic and predictive accuracy for KD and CAL.

Results: Serum SESN2 levels were significantly elevated in KD patients compared to HCs (P=0.001), with markedly higher levels in the KD-CAL subgroup (P=0.014), escalating stepwise with lesion severity. SESN2 positively correlated with inflammatory markers and coronary artery lesions. A substantial reduction in SESN2 was observed post-IVIG therapy (P=0.012). ROC analysis revealed SESN2 as a reliable diagnostic marker for KD (AUC=0.697) and a predictive marker for CAL (AUC=0.684).

Conclusion: Serum SESN2 is a valuable biomarker for KD, capable of reflecting disease activity and predicting CAL. This dual function highlights its potential to improve risk stratification and guide clinical management in affected children.

Keywords: Kawasaki disease, Sestrin2, coronary arterial lesions

Introduction

Kawasaki disease (KD) is a pediatric systemic vasculitis of unclear origin, primarily affecting children under five years old. Its clinical presentation includes persistent fever, rash, conjunctivitis, oral mucosal changes, desquamation of the skin on the extremities, and cervical lymphadenopathy.[1–3] Epidemiologic studies reveal significant regional variations, with incidence rates in East Asian populations exceeding the US by 10- to 30-fold, where the disease affects approximately 18–25 per 100,000 children under five annually.[2] KD causes inflammation in the coronary arteries and surrounding cardiovascular tissues. Without treatment, about 25% of patients develop coronary artery lesions (CALs), which may lead to coronary artery aneurysms (CAAs), stenosis, and severe cardiovascular complications.[1,4,5] While prompt treatment with intravenous immunoglobulin (IVIG) and aspirin reduces CAA risk to approximately 5%,[1,6] KD remains the most common cause of acquired heart disease in children in high-income countries.[7,8]

Despite the availability of effective therapy, the clinical management of KD is hampered by significant diagnostic hurdles. The absence of a definitive laboratory test or pathognomonic sign means diagnosis often relies on recognizing a constellation

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of non-specific symptoms.[9] This ambiguity frequently leads to delayed treatment initiation, undermining the efficacy of IVIG and leaving patients vulnerable to suboptimal outcomes.[1,10] Consequently, there is an urgent and unmet need for novel biomarkers that can facilitate early, accurate diagnosis and predict the risk of coronary complications.

SESN2 (Sestrin2) is a highly conserved stress-responsive gene crucial for cellular homeostasis, antioxidant defense, and metabolic regulation.[11,12] As a member of the Sestrin family, it is activated under oxidative stress, hypoxia, and DNA damage, mainly through the p53, Nrf2, and HIF-1α pathways.[13,14] Once activated, SESN2 exerts protective effects as a key regulator of the mTORC1, AMPK, and Keap1/Nrf2 pathways, which reduces reactive oxygen species (ROS) and promotes autophagy.[12–15]

KD is fundamentally an acute systemic vasculitis, characterized by extensive endothelial injury and an imbalance in oxidative stress, which are the primary drivers of CAL.[6,8,16,17] Mechanistically, SESN2 has been proven to play a vital role in maintaining endothelial health; for instance, its knockdown in human umbilical vein endothelial cells (HUVECs) exacerbates inflammation, apoptosis, and ROS production.[18] Clinically, accumulating evidence has positioned SESN2 as a promising biomarker for a range of pathological conditions. Its role is specifically prominent in cardiovascular diseases, where elevated levels are associated with conditions like coronary atherosclerosis, a pathology sharing similar critical features of vascular damage with KD.[19,20] Therefore, combining these mechanistic insights with clinical precedents, it is biologically plausible to hypothesize that SESN2 functions as a critical counter-regulatory mechanism in the pathogenesis of KD. Specifically, the intense oxidative and inflammatory milieu of KD may trigger the upregulation of SESN2 as a protective response. Based on this link, we propose that serum SESN2 levels could serve as a potential biomarker for the diagnosis of KD and the prediction of CAL formation. In this way, it can contribute to the early diagnosis and prognosis prediction of KD in the future. To the best of our knowledge, no existing literature has explored the association between serum SESN2 levels and KD. Consequently, our study is uniquely designed to systematically evaluate its diagnostic and predictive utility in this context.

Method

Subjects

Our study consecutively enrolled subjects from the Children's Hospital of Chongqing Medical University between February 2025 and May 2025. Participants were prospectively categorized into KD and healthy control (HC) groups according to diagnostic criteria. KD diagnosis followed criteria from the Scientific Committee of the Japanese Circulation Society.[21,22] HC subjects were selected during routine physical examinations.

The criteria for inclusion of the KD cohort in this study were as follows: (1) Patients meeting the diagnostic criteria for KD; (2) Individuals with complete clinical documentation, including results from blood biochemical analyses and echocardiographic evaluations; (3) Participants who received standard therapy consisting of 2 g/kg IVIG and aspirin immediately after diagnosis. Exclusion criteria for the KD cohort included: (1) Cases complicated by congenital malformations or genetic metabolic disorders; (2) Recurrent KD; (3) Patients who had received IVIG, glucocorticoids, immunosuppressants, biologics, or aspirin within the prior three months before the acute phase of KD; (4) Subjects with incomplete medical records or insufficient diagnostic data; (5) Blood specimens showing signs of hemolysis.

For the HC cohort, inclusion criteria were: (1) No febrile manifestations, respiratory distress, gastrointestinal symptoms, or other acute infectious manifestations within one week around enrollment, with normal hematological indices; (2) Definite exclusion of KD diagnosis through clinical assessment; (3) Normal physical examination findings without any clinically significant abnormalities affecting overall health. Exclusion criteria for the HC cohort were: (1) Individuals with congenital anomalies or genetic metabolic diseases; (2) Participants who had received glucocorticoids, IVIG, immunosuppressants, biologics or aspirin in the three months preceding the study; (3) Cases with unclear medical history or inadequate diagnostic information; (4) Blood samples demonstrating hemolytic characteristics.

All pediatric patients with confirmed KD diagnosis received immediate echocardiographic assessment prior to anticoagulant therapy and IVIG administration for coronary artery evaluation. Patient stratification was based on established coronary artery Z-score criteria. Coronary artery Z-scores were calculated using the regression equations proposed by Kobayashi et al.[23] For the definition of CALs, we followed the "Recommendations for clinical management

of Kawasaki disease coronary artery lesions (2020)" issued by the Subspecialty Group of Cardiology, the Society of Pediatrics, Chinese Medical Association.[24] According to this guideline (consistent with the 2017 AHA Scientific Statement[1]), CAL was defined as a coronary artery Z-score ≥ 2.0 and NCAL was defined as Z-score < 2.0. To further elucidate the predictive value of SESN2 for the severity of coronary injury, the KD-CAL subgroup was further stratified. Lesions with a Z-score ≥ 2.0 but < 2.5 were defined as non-aneurysmal coronary artery lesions (NACAL), whereas those with a Z-score ≥ 2.5 were defined as coronary artery aneurysms (CAA). Finally, for an analysis based on aneurysm burden, patients were classified according to the number of aneurysms into three groups: No coronary artery aneurysms (NCAA; Z-score < 2.5), a single CAA (1CAA), and two CAAs (2CAA). Our study complied with international ethical standards of the Declaration of Helsinki (as revised in 2024)[25] and received ethical approval from the Ethics Committee of the Children's Hospital of Chongqing Medical University. Written informed consent was acquired from legal guardians of all enrolled subjects prior to study participation.

Sample Collection and Measurement of Serum SESN2 Levels

Serum samples were collected immediately before the initiation of anticoagulants and IVIG treatment. The median time of sample collection was 5 days (IQR: 4–6 days) after the onset of fever. As shown in Table 1, there was no significant

Table 1 Demographic and Clinical Characteristics of the KD-CAL and KD-NCAL Subgroups

Variable	KD-CAL (n=23)	KD-NCAL (n=49)	P-value
Age (months)	24(8, 46)	30(14.5, 61)	0.109
Male (n, %)	7(30.4)	27(55.1)	0.051
iKD (n, %)	5(21.7)	9(18.4)	0.756
Days of pre-IVIG fever	4.93±2.50	5(4, 6.5)	0.460
WBC (10^9/L)	15.05±4.91	14.38±5.16	0.604
N (10^9/L)	10.52±4.98	9.96±5.04	0.668
N (%)	66.82(54.88, 80.18)	70.69(61.29, 83.24)	0.510
L (10^9/L)	3.34(2.45, 4.3)	2.42(1.71, 3.64)	0.148
L (%)	27.07(13.48, 32.78)	20.47(11.31, 31.18)	0.210
NLR	2.43(1.88, 5.29)	3.39(1.76, 8.49)	0.313
ESR (mm/h)	73.64±25.51	63.91±29.57	0.285
CRP (mg/L)	85.26±51.88	59.41±38.74	0.022*
Hb (g/L)	106.14±13.30	109.17±12.48	0.361
PLT (10^9/L)	363(264.5, 458)	328(287.5, 385)	0.285
ALT (U/L)	37.5(19.5, 107.25)	32(18.25, 61.75)	0.617
AST (U/L)	33(23, 50.75)	32(25, 63.75)	0.690
ALB (g/L)	37.85(34.81, 39.6)	41.2(38.05, 43.4)	0.002**
TT (s)	15.6(15.1, 16.3)	15.7(15.2, 16.53)	0.323
PT (s)	12.6(11.9, 13.4)	12.2(11.48, 13.03)	0.143
APTT (s)	29.2(26.1, 31)	27.7(26.7, 28.8)	0.207
PCT (ng/mL)	0.56(0.26, 0.82)	0.56(0.23, 1.57)	0.966
FIB (g/L)	7.33(6.01, 7.82)	6.12(4.74, 7.56)	0.134
CK-MB (ug/L)	0.48(0.18, 1.4)	0.48(0.18, 1.17)	0.951
BNP (pg/mL)	49.93(27.84, 153.73)	25.91(14.70, 98.45)	0.242
SESN2 (ng/mL)	6.26(4.63, 9.01)	4.51(3.79, 6.41)	0.014*

Note: *P< 0.05, **P<0.01.

Abbreviations: KD, Kawasaki disease; CAL, coronary artery lesions; NCAL, non-CAL; iKD, incomplete KD; Days of pre-IVIG fever, Days of fever before intravenous immunoglobulin treatment; WBC, white blood cell counts; N, neutrophil counts; N%, percentage of neutrophils; L, leukomonocyte counts; L%, percentage of leukomonocytes; NLR, neutrophil-to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; PLT, platelet counts; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, Albumin; TT, thrombin time; PT, prothrombin time; APTT, activated partial thrombo plastin time; PCT, procalcitonin; FIB, plasma fibrinogen; CK-MB, creatine kinase-MB.

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difference in the sampling timing between the CAL and NCAL groups, ensuring comparability. Venous blood samples were collected into sterile tubes without anticoagulant. Samples were allowed to clot for 30 minutes at room temperature and then centrifuged at 3000 rpm for 10 minutes. The separated serum was immediately stored at −80°C. All samples (including the HC group) were analyzed within 3 months of collection. Serum SESN2 concentrations were quantified using enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp., Wuhan, China) in strict accordance with the manufacturer's instructions.

Clinical Parameters

Demographic and Clinical Characteristics

Demographic parameters including age and sex were methodically archived for all study subjects. Extensive clinical information was systematically documented for KD cases. This information included the diagnostic subtype (incomplete Kawasaki disease [iKD]), the duration of fever before the administration of IVIG and Z-score, defined as the maximum of four coronary arteries in multiple echocardiography results throughout the acute phase of KD.

Laboratory Assessments

Blood samples were collected following standardized protocols to assess the subsequent parameters: (1) Hematological indices: White blood cell (WBC) count, hemoglobin (Hb), platelet (PLT) count, neutrophil count (N), neutrophil percentage (N%), lymphocyte count (L), lymphocyte percentage (L%) and neutrophil-to-lymphocyte ratio (NLR), defined as the ratio of neutrophil count to lymphocyte count. (2) Inflammatory markers: C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR). (3) Liver function parameters: Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin. (4) Coagulation indices: Thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen (FIB) concentrations. (5) Cardiac biomarkers: Myocardial injury markers including creatine kinase-MB (CK-MB) and B-type natriuretic peptide (BNP) levels. (6) Inflammatory cytokine panel: Multiplex analysis of interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), IL-17A, IL-1β, IL-12P70, IL-5 and IL-8.

Statistical Analysis

The statistical evaluation of clinical and laboratory parameters was conducted with SPSS software version 25.0 (IBM, Chicago, IL, USA). Data distribution normality was verified through the Shapiro–Wilk test. Continuous variables were expressed as mean ± SD if all compared groups followed a normal distribution; otherwise, to ensure consistency and statistical rigor, these variables were expressed as median with interquartile range (IQR; 25th–75th percentiles) for all groups. Accordingly, independent t-tests or one-way ANOVA were used for normally distributed data, while the Mann–Whitney *U*-test or Kruskal–Wallis test was employed for non-normally distributed data. For paired comparisons of samples before and after IVIG treatment, the Wilcoxon signed-rank test was utilized. Categorical variables were assessed using χ^2-tests or Fisher's exact tests. Correlations were assessed using Spearman's rank correlation for non-normally distributed data and Pearson's correlation for normally distributed data. Diagnostic accuracy of SESN2 for KD identification and subgroup differentiation was evaluated through receiver operating characteristic (ROC) curve analysis, with area under the curve calculations. Statistical significance was defined as two-tailed $p < 0.05$. Data visualization employed R software (version 4.3.2) for correlation heatmaps and GraphPad Prism software (version 8.2.1; GraphPad Inc., San Diego, CA, USA) for ROC curves and scatter dot plots generation.

Results

Characteristics of Participants

The final study cohort consisted of 72 eligible patients with KD (34 males, 38 females; median age: 30 months) and 38 matched healthy controls (HC; 22 males, 16 females; median age: 35 months). As detailed in the study flow diagram (Figure 1), the patient group was stratified by coronary artery status into subgroups with (KD-CAL, n=23) or without (KD-NCAL, n=49) coronary artery lesions.

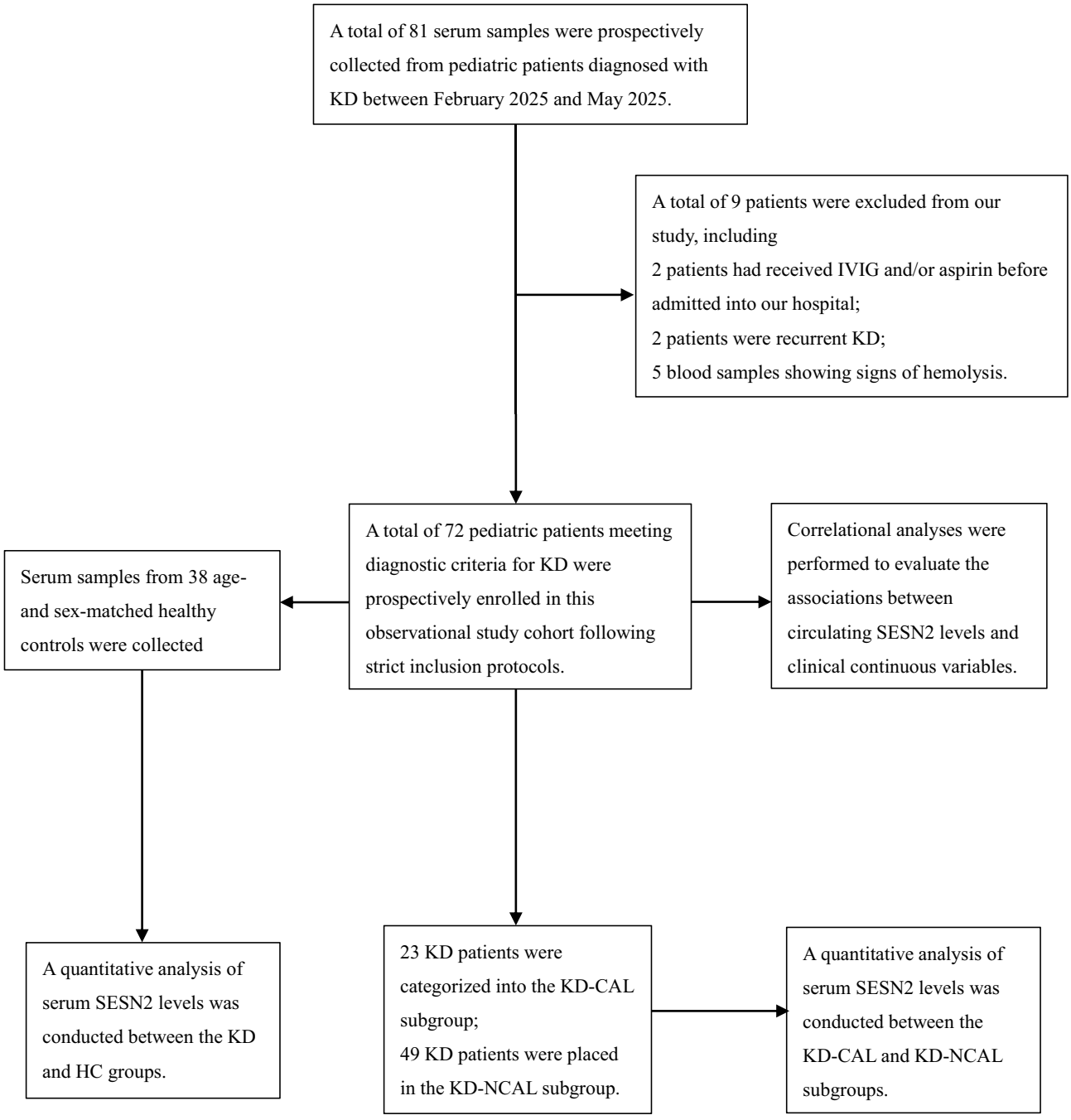

Figure 1 Study flow chart.
Abbreviations: KD, Kawasaki disease; IVIG, intravenous immunoglobulin; CAL, coronary artery lesion; NCAL, non-CAL; HC, healthy control.

Baseline Comparison of Laboratory Parameters

The KD and HC groups were well-matched in terms of age and sex distribution ($P > 0.05$). Compared to the HC group, patients with KD presented with a distinct laboratory profile, characterized by significantly elevated levels of WBC, N, N%, NLR, ALT, PT, APTT, and FIB. Concurrently, levels of L, L%, Hb, ALB, and TT were markedly diminished in the KD cohort (Table 2).

The Levels of Serum SESN2 in KD Group and HC Group

Serum SESN2 levels were higher in the KD group (5.17 [3.90–7.91] ng/mL) than in the HC group (3.49 [2.98–6.14] ng/mL; $P = 0.001$; Figure 2A and Table 2).

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Table 2 Demographic and Clinical Characteristics of the KD and HC Group

Variable	KD (n=72)	HC (n=38)	P-value
Age (months)	30(12, 54)	35(12, 50)	0.823
Male (n, %)	34(47.2)	22(52.8)	0.387
WBC (10^9/L)	14.68±4.73	9.08±2.91	<0.001**
N (10^9/L)	8.83(6.85, 13.30)	2.79(1.74, 3.81)	<0.001**
N (%)	70.69(58.83, 82.50)	33.3(23, 44.35)	<0.001**
L (10^9/L)	2.92(1.94, 3.95)	4.74(3.42, 6.34)	<0.001**
L (%)	21.32(11.61, 30.88)	55.2(44.05, 67.5)	<0.001**
NLR	3.39(1.90, 7.46)	0.66(0.32, 0.98)	<0.001**
Hb (g/L)	108.57±12.93	123.03±10.05	<0.001**
PLT (10^9/L)	343(280, 409)	331(281, 408.5)	0.858
ALT (U/L)	30(18, 58)	19(16.5, 26)	<0.001**
AST (U/L)	32(25, 44)	34(29, 39.5)	0.675
ALB (g/L)	40.8(37.5, 42.7)	43.4(42, 46.1)	<0.001**
TT (s)	15.7(15.2, 16.5)	17.9(17.25, 18.55)	<0.001**
PT (s)	12.2(11.5, 12.9)	10.8(10.5, 11.2)	<0.001**
APTT (s)	27.90±3.02	26.77±2.87	0.042*
FIB (g/L)	6.68(4.88, 7.56)	2.05(1.86, 2.33)	<0.001**
SESN2 (ng/mL)	5.17(3.90, 7.91)	3.49(2.98, 6.14)	0.001**

Note: *P< 0.05, **P<0.01.

Abbreviations: KD, Kawasaki disease; HC, healthy control; WBC, white blood cell counts; N, neutrophil counts; N%, percentage of neutrophils; L, leukomonocyte counts; L%, percentage of leukomonocytes; NLR, neutrophil-to lymphocyte ratio; Hb, hemoglobin; PLT, platelet counts; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, Albumin; TT, thrombin time; PT, prothrombin time; APTT, activated partial thrombo plastin time; FIB, plasma fibrinogen;

The Baseline Comparation Between KD-CAL Subgroup and KD-NCAL Subgroup

The KD-CAL and KD-NCAL subgroups were comparable in age, sex, and rates of iKD ($P > 0.05$). However, patients in the KD-CAL group exhibited substantially higher CRP and lower ALB levels than those in the KD-NCAL group ($P < 0.05$; Table 1). Furthermore, in a subset of 20 patients with available data, no significant differences in cytokine profiles were observed between the subgroups (Table 3).

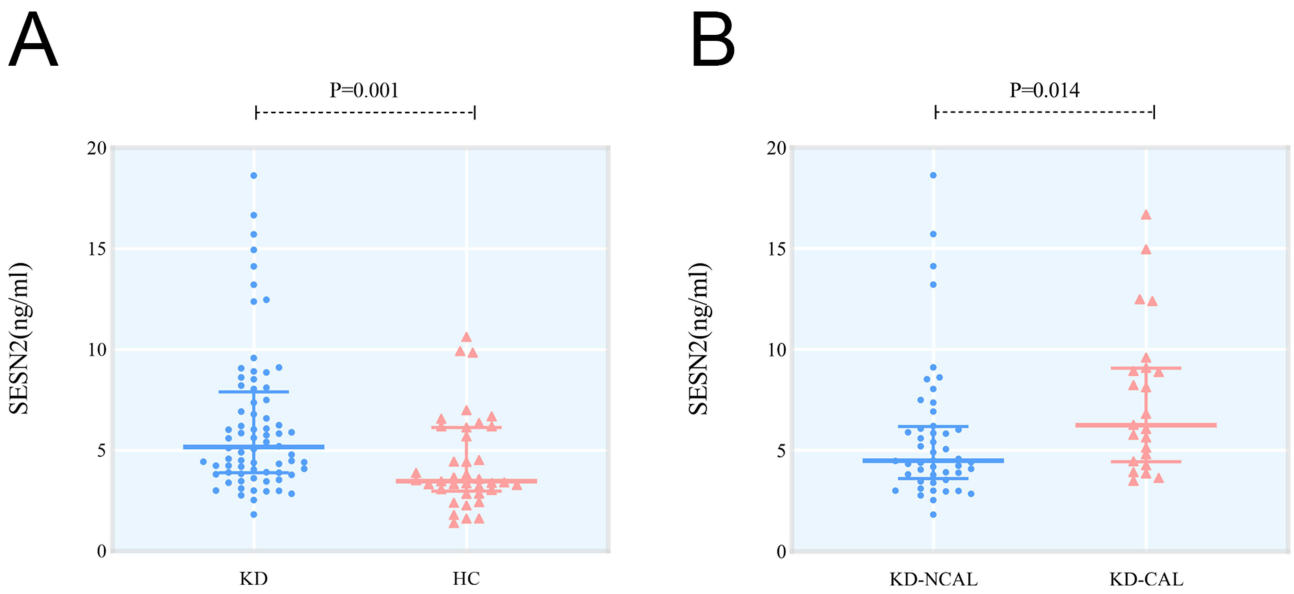

Figure 2 Serum SESN2 levels in all subjects. (**A**) The levels of SESN2 in KD and HC groups. (**B**) The levels of SESN2 in KD-NCAL and KD-CAL subgroups.
Abbreviations: KD, Kawasaki disease; HC, healthy control; CAL, coronary artery lesion; NCAL, non-CAL.

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Table 3 Inflammatory Cytokines Levels in KD-CAL and KD-NCAL

Variable	KD-CAL (n=4)	KD-NCAL (n=16)	P-value
IL-2	2.00±1.35	1.10±0.85	0.110
IL-4	1.68±0.32	1.19±0.85	0.281
IL-6	111.88±86.54	71.33±51.85	0.235
IL-10	16.29(5.01, 99.22)	6.7(3.9, 13.02)	0.395
TNF-α	2.42±0.66	1.78±1.27	0.347
IFN-γ	2.47(0.85, 5.32)	1.23(1.03, 2.05)	0.682
IL-17A	0.56(0.02, 3.48)	3.21(0, 7.70)	0.437
IL-1β	2.01(1.52, 3.06)	2.27(1.45, 2.91)	0.963
IL-5	3.45(0.45, 6.14)	0.42(0.30, 0.92)	0.170
IL-12P70	1.3(0.65, 1.31)	1.09(0.15, 1.68)	1.000
IL-8	31.78(17.86, 47.02)	26.44(18.73, 34.99)	0.705

Abbreviations: IL, interleukin; TNF, tumor necrosis factor; INF, interferon.

The Levels of Serum SESN2 in KD-CAL Subgroup and KD-NCAL Subgroup

Serum SESN2 concentrations were also elevated in the KD-CAL subgroup (6.26 [4.63–9.01] ng/mL) compared to the KD-NCAL subgroup (4.51 [3.79–6.41] ng/mL; P = 0.014). This finding underscored a direct association between higher SESN2 levels and the presence of coronary artery lesions (Figure 2B and Table 1).

Serum SESN2 Levels Correlate with the Severity of Coronary Artery Lesions

The association between serum SESN2 and the severity of coronary artery pathology was further investigated. A stepwise increase in SESN2 levels was evident when patients were stratified by lesion severity into subgroups with no coronary artery lesions (NCAL), non-aneurysmal coronary artery lesions (NACAL), or coronary artery aneurysms (CAA) (P = 0.047; Figure 3A and Table 4). This dose-dependent relationship was corroborated by an analysis based on the number of aneurysms, which indicated that SESN2 concentrations progressively increased from patients with no aneurysms to those with one or two (P = 0.033; Figure 3B and Table 5).

Reduction of Serum SESN2 Following IVIG Therapy

A paired analysis of eight patients revealed a significant reduction in serum SESN2 levels following IVIG therapy. SESN2 concentrations decreased from a pre-treatment median (IQR) of 5.83 (4.40–8.38) ng/mL to a post-treatment median (IQR) of 4.51 (4.10–5.55) ng/mL (P=0.012; Figure 4 and Table 6), suggesting that SESN2 levels are responsive to effective anti-inflammatory intervention.

Correlation of SESN2 Levels with Clinical Parameters

Correlation analysis indicated that SESN2 levels were significantly positively associated with key inflammatory markers (CRP, IL-6, IL-10, IL-8), CK-MB, and Z-score. Conversely, a significantly negative correlation with Hb was observed. No significant correlations were found with any other tested parameters (P > 0.05) (Table 7 and Figure 5).

The Effect of SESN2 in Predicting KD and KD-CAL

As shown in Table 8 and Figure 6A, several conventional inflammatory biomarkers demonstrated high performance in distinguishing KD patients from HCs. Notably, neutrophil count (N) exhibited the highest discriminative power (AUC = 0.916), followed by NLR (AUC = 0.899) and WBC (AUC = 0.833). Although SESN2 showed a statistically significant ability to identify KD (AUC = 0.697, P=0.001), its performance was modest compared to these top-performing conventional markers.

In the more challenging task of predicting CALs within the KD population (Table 9 and Figure 6B), the majority of biomarkers lost their predictive ability. Traditional indices, including WBC, N, NLR, BNP, and pro-inflammatory

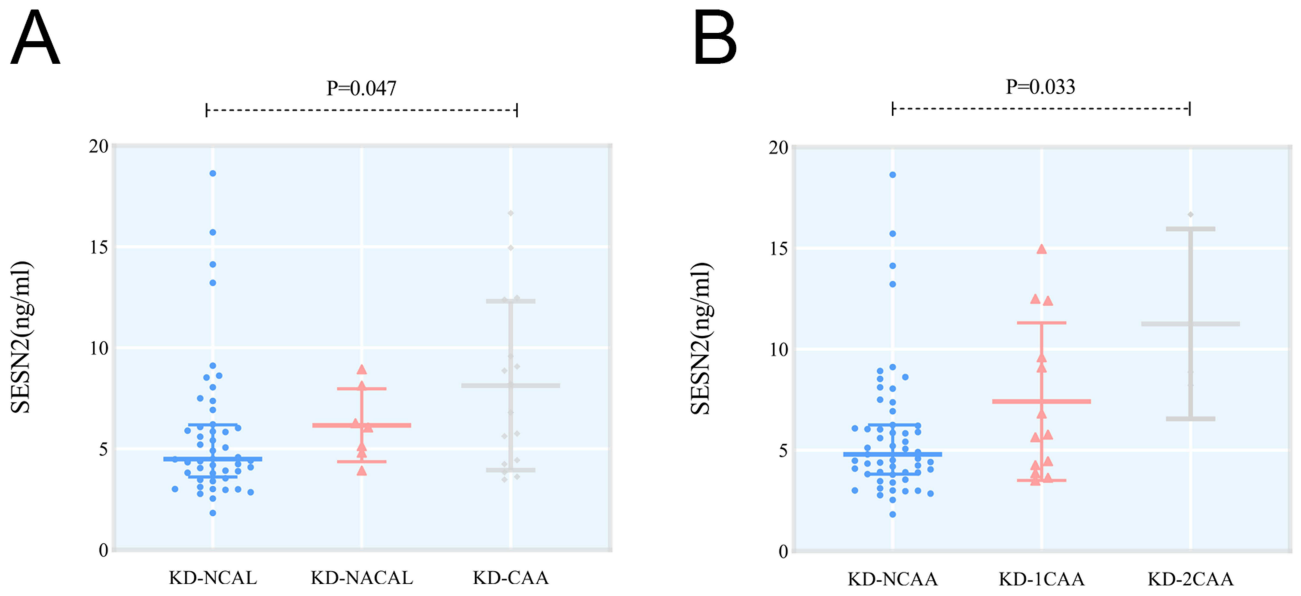

Figure 3 Serum SESN2 levels in KD subjects. (**A**) The levels of SESN2 in KD-NCAL, KD-NACAL and KD-CAA subgroups. (**B**) The levels of SESN2 in KD-NCAA, KD-1CAA and KD-2CAA subgroups.
Abbreviations: KD, Kawasaki disease; NCAL, non-coronary artery lesion; NACAL, Non-aneurysmal coronary artery lesions; CAA, coronary artery aneurysm; NCAA, no coronary artery aneurysms; 1CAA, a single coronary artery aneurysm; 2CAA, two coronary artery aneurysms.

cytokines (IL-6 and TNF-α), failed to significantly distinguish CAL from NCAL patients (all P>0.05). In our head-to-head comparison, SESN2 emerged as a significant predictor with the highest statistical significance (AUC = 0.684, P=0.013). While CRP also demonstrated significant predictive value (AUC = 0.647, P=0.048), SESN2 provided a more balanced performance in terms of sensitivity and specificity (65.2% and 64.6%, respectively) compared to CRP, which exhibited high specificity (87.0%) but notably low sensitivity (47.8%).

Discussion

This study explored the clinical utility of serum SESN2 as a circulating biomarker in KD. We identified significantly elevated SESN2 levels in KD patients compared to HCs. SESN2 levels were also notably higher in KD-CAL subgroup, showing a stepwise increase with lesion severity. It correlated positively with inflammatory and coronary artery lesions. A significant reduction in SESN2 was observed post-IVIG therapy. ROC analysis confirmed SESN2 as a reliable

Table 4 Comparison of Serum SESN2 Levels in Children with Kawasaki Disease with NCAL, NACAL and CAA Subgroups

	KD-NCAL (n=49)	KD-NACAL (n=7)	KD-CAA (n=16)	P-value
SESN2 (ng/mL)	4.51(3.79, 6.22)	6.05(4.80, 8.12)	7.51(4.30, 11.69)	0.047*

Note: *P< 0.05.
Abbreviations: KD, Kawasaki disease; NCAL, No coronary artery lesions; NACAL, Non-aneurysmal coronary artery lesions; CAA, coronary artery aneurysm.

Table 5 Comparison of Serum SESN2 Levels in Children with Kawasaki Disease with No, Single, or Two Coronary Artery Aneurysms

	KD-NCAA (n=56)	KD-1CAA (n=13)	KD-2CAA (n=3)	P-value
SESN2 (ng/mL)	4.86 (3.86, 6.43)	5.76(4.05, 10.99)	8.88(8.55, 12.78)	0.033*

Note: *P< 0.05.
Abbreviations: KD, Kawasaki disease; NCAA, no coronary artery aneurysms; 1CAA, a single coronary artery aneurysm; 2CAA, two coronary artery aneurysms.

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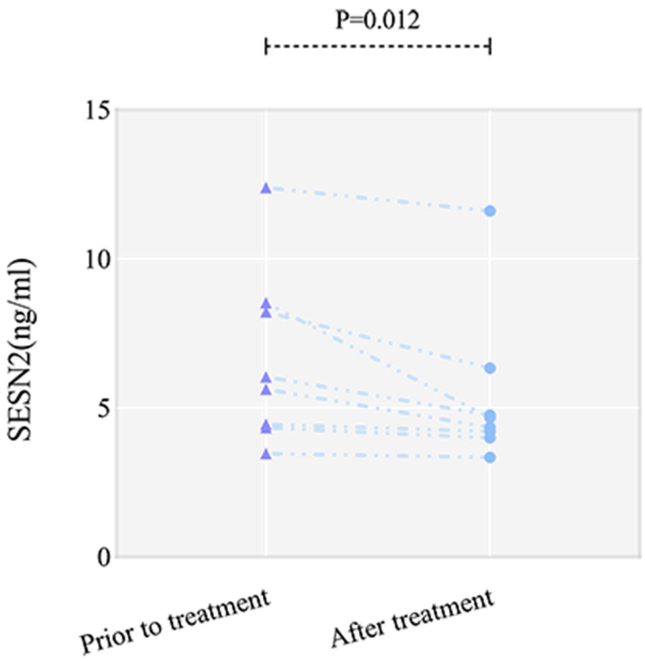

Figure 4 Comparison of serum SESN2 levels before and after intravenous immunoglobulin (IVIG) treatment in children with Kawasaki disease. (n=8).

diagnostic biomarker for KD and a predictive marker for CAL. These findings suggest SESN2 is a valuable circulating biomarker reflecting KD disease activity and coronary involvement, offering insights into inflammatory processes.

Sestrin2 (SESN2), first identified by Budanov et al in 2002,[26] is a stress-inducible protein, whose transcription is upregulated in response to various stressors like DNA damage, hypoxia, and oxidative stress, mediated by p53, HIF-1α, and NRF2, respectively, with NRF2 forming a positive feedback circuit with SESN2.[11,13,27] Functionally, its primary mechanism of action involves the activation of AMPK and the subsequent inhibition of the mTOR. This signaling cascade triggers autophagy and suppresses the generation of ROS, ultimately conferring cellular protection.[27,28]

Given its pivotal function in maintaining cellular homeostasis under stress, it is therefore unsurprising that a reactive upregulation of SESN2 is a common feature of a wide spectrum of pathologies.[27] Accordingly, SESN2 has emerged as an important biomarker across a range of diseases,[29–32] a role particularly well-established in the context of coronary artery disease. Indeed, a pioneering study by Ye et al in 2017 was the first to report elevated plasma SESN2 levels in patients with coronary artery disease (CAD).[20] This finding was corroborated by Kishimoto et al in 2020, who not only confirmed increased circulating SESN2 in CAD but also revealed a positive correlation between SESN2 levels and the number of coronary vessels with >50% stenosis.[19] This observation provided strong evidence that circulating SESN2 levels reflect the severity of CAD.

Beyond its biomarker potential, SESN2 has also been shown to exert substantial protective effects on a variety of tissue cells,[33–35] particularly within vascular endothelial cells. Yi et al reported in 2014 that angiotensin II (AngII) stimulated a compensatory upregulation of SESN2 in vascular endothelial cells, and that SESN2 knockdown exacerbated AngII-induced cytotoxicity, thus underscoring SESN2's protective role in vascular endothelial cells.[36] Building upon

Table 6 Comparison of Serum SESN2 Levels Before and After Intravenous Immunoglobulin (IVIG) Treatment in Children with Kawasaki Disease. (n=8)

	Before IVIG	After IVIG	P-value
SESN2 (ng/mL)	5.83(4.40, 8.38)	4.51(4.10, 5.55)	0.012*

Note: *P< 0.05.
Abbreviation: KD, Kawasaki disease.

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Table 7 Correlations Between Serum SESN2 Levels and Clinical Parameters in the KD Group

Variable	r	P-value
Days of pre-IVIG fever	−0.057	0.637
WBC (10^9/L)	−0.153	0.200
N (10^9/L)	−0.220	0.073
N (%)	−0.157	0.187
L (10^9/L)	0.175	0.164
L (%)	0.224	0.062
NLR	−0.206	0.117
ESR (mm/h)	0.072	0.621
CRP (mg/L)	0.251	0.036*
Hb (g/L)	−0.306	0.011*
PLT (10^9/L)	0.081	0.510
ALT (U/L)	0.098	0.418
AST (U/L)	0.059	0.629
ALB (g/L)	−0.220	0.067
TT (s)	0.043	0.737
PT (s)	0.081	0.520
APTT (s)	−0.158	0.181
PCT (ng/mL)	0.103	0.416
FIB (g/L)	−0.134	0.282
CK-MB (ug/L)	0.341	0.006**
BNP (pg/mL)	0.224	0.130
IL-2	0.430	0.059
IL-4	0.415	0.069
IL-6	0.520	0.019*
IL-10	0.481	0.032*
TNF-α	0.315	0.176
IFN-γ	0.422	0.064
IL-17A	0.340	0.142
IL-1β	0.171	0.472
IL-5	0.361	0.118
IL-12P70	0.175	0.460
IL-8	0.451	0.046*
Z-score	0.311	0.008**

Note: *P< 0.05, **P<0.01.

Abbreviations: KD, Kawasaki disease; Days of pre-IVIG fever, Days of fever before intravenous immunoglobulin treatment; WBC, white blood cell counts; N, neutrophil counts; N%, percentage of neutrophils; L, leukomonocyte counts; L%, percentage of leukomonocytes; NLR, neutrophil-to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; PLT, platelet counts; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, Albumin; TT, thrombin time; PT, prothrombin time; APTT, activated partial thrombo plastin time; PCT, procalcitonin; FIB, plasma fibrinogen; CK-MB, creatine kinase-MB;IL, interleukin; TNF, tumor necrosis factor; INF, interferon; Z-score, the maximum Z-score of any coronary artery segment measured by echocardiography during hospitalization.

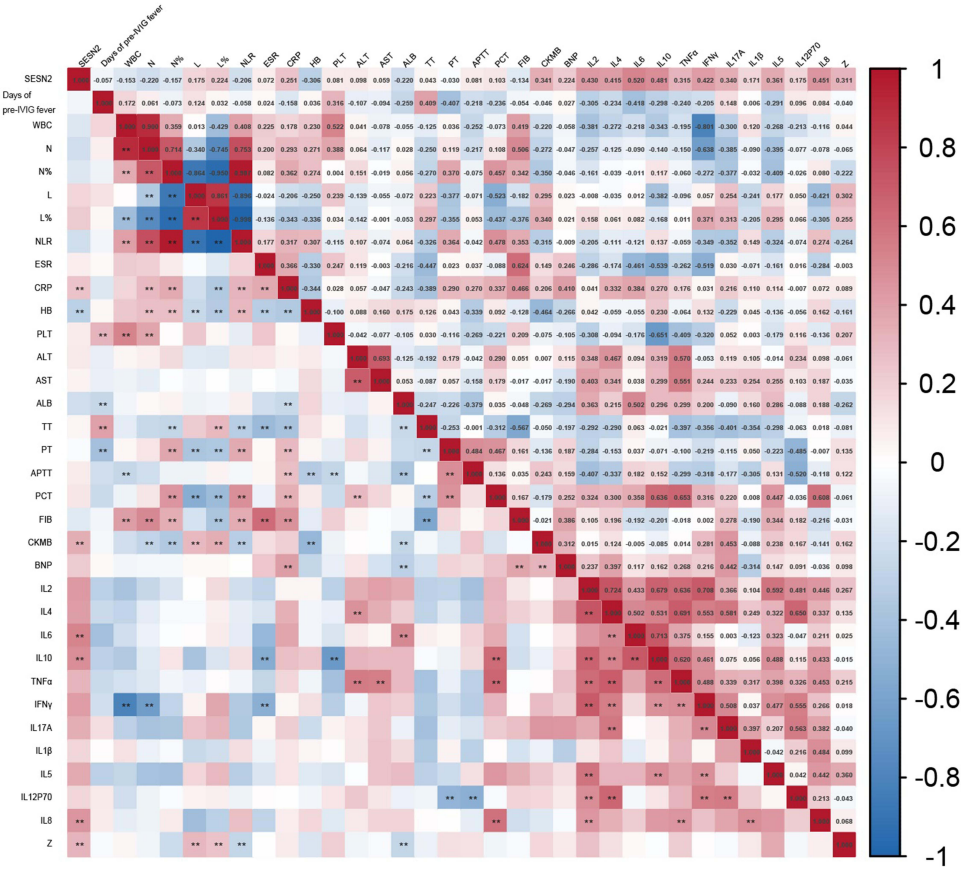

Figure 5 Correlations between serum SESN2 levels and clinical parameters in the KD group. **P<0.05.

Abbreviations: KD, Kawasaki disease; CAL, coronary artery lesion; NCAL, non-CAL; iKD, incomplete KD; Days of pre-IVIG fever, Days of fever before intravenous immunoglobulin treatment; WBC, white blood cell counts; N, neutrophil counts; N%, percentage of neutrophils; L, leukomonocyte counts; L%, percentage of leukomonocytes; NLR, neutrophil-to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hb, hemoglobin; PLT, platelet counts; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, Albumin; TT, thrombin time; PT, prothrombin time; APTT, activated partial thrombo plastin time; PCT, procalcitonin; FIB, plasma fibrinogen; CK-MB, creatine kinase-MB; IL, interleukin; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma.

this, Li et al further elucidated SESN2's protective role, demonstrating it mitigates LPS-induced inflammation and cellular stress in endothelial cells via AMPK activation. SESN2 suppresses NF-κB phosphorylation, limits adhesion molecules and inflammatory cytokines, and reduces ROS production, endoplasmic reticulum (ER) stress, and cell death, thereby protecting vascular integrity.[18] This cytoprotective action of SESN2 in endothelial cells has since been repeatedly substantiated by extensive research,[37–40] gaining widespread acknowledgment.

Against this backdrop of SESN2's recognized utility as a biomarker across various diseases and its well-documented cytoprotective functions, especially in CAD where heightened circulating SESN2 levels track with disease severity and the extent of vessel stenosis, its role in KD warrants investigation. KD is a severe systemic vasculitis characterized by

Table 8 Predictive Ability of Biomarkers to Distinguish KD and HC

Variable	P-value	AUC	95% CI	Cut-Off Value	SE	SP	+LR	-LR	Youden Index
SESN2	0.001*	0.697	0.590–0.805	3.81	79.2%	60.5%	2.01	0.34	0.397
WBC	0.001*	0.833	0.757–0.910	9.97	80.6%	73%	2.99	0.27	0.536
N	0.001*	0.916	0.854–0.977	4.06	95.5%	82.9%	5.58	0.05	0.784
NLR	0.001*	0.899	0.832–0.966	1.39	84.7%	85.7%	5.92	0.18	0.704

Note: *P< 0.05.

Abbreviations: KD, Kawasaki disease; HC, healthy controls; AUC, Area under the curve;95% CI, 95% Confidence interval; SE, Sensitivity; SP, Specificity; +LR, Positive likelihood ratio; -LR, Negative likelihood ratio; WBC, white blood cell counts; N, neutrophil counts; NLR, neutrophil-to lymphocyte ratio.

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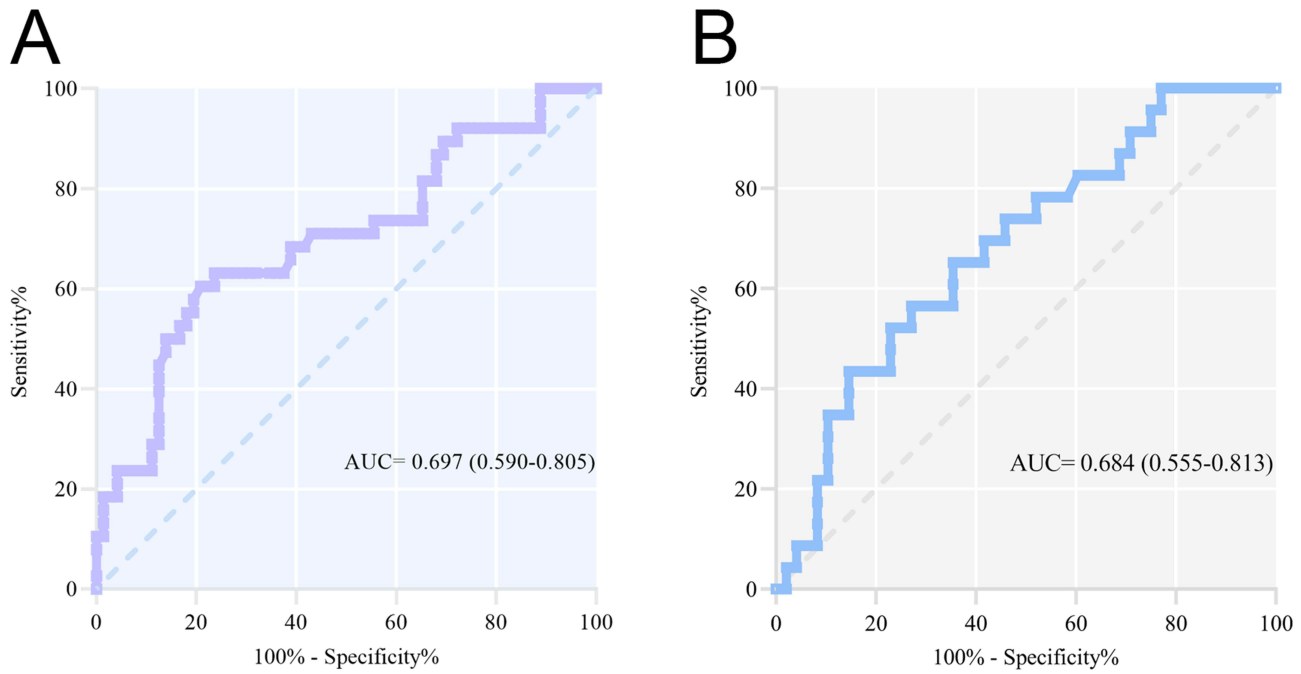

Figure 6 Evaluation of serum SESN2 for the diagnosis of KD and prediction of KD-CAL. (**A**) The ROC curve of SESN2 in the KD group; (**B**) The ROC curve of SESN2 in the KD-CAL subgroup.
Abbreviations: KD, Kawasaki disease; CAL, coronary artery lesion; ROC, receiver-operating characteristic.

inflammation, oxidative stress, and endothelial damage, which constitute a sustained assault on vascular endothelial cells.[6,8,16,17] In line with its role as a stress-inducible protein, activating AMPK and suppressing inflammation, ROS, and ER stress, SESN2's elevation in KD patients is thus a reactive and compensatory response aimed at protecting the injured vasculature.

Our study directly addresses this critical area. We observed markedly elevated SESN2 levels in KD patients relative to HCs. These elevations were notably pronounced in the KD-CAL subgroup, escalating with lesion severity. Additionally, SESN2 positively correlated positively with inflammatory and coronary artery lesions. This robust induction of a protective factor like SESN2, while beneficial in principle, paradoxically serves as a crucial quantitative indicator of the magnitude of the underlying pathological burden and the severity of cellular stress. Therefore, the high

Table 9 Predictive Ability of Biomarkers to Distinguish KD-CAL and KD-NCAL

Variable	P-value	AUC	95% CI	Cut-Off Value	SE	SP	+LR	-LR	Youden Index
SESN2	0.013*	0.684	0.555–0.813	5.62	65.2%	64.6%	1.84	0.54	0.298
WBC	0.676	0.531	0.386–0.676	13.81	60.9%	52.1%	1.27	0.75	0.13
N	0.605	0.539	0.392–0.686	6.96	81.8%	31.8%	1.20	0.57	0.136
NLR	0.310	0.418	0.268–0.569	0.56	100%	7.9%	1.09	0	0.079
ESR	0.238	0.609	0.429–0.790	81	50%	79.4%	2.43	0.63	0.294
CRP	0.048*	0.647	0.503–0.791	98.72	47.8%	87%	3.68	0.60	0.348
PCT	0.896	0.510	0.361–0.660	0.235	85%	27.3%	1.17	0.55	0.123
BNP	0.193	0.627	0.452–0.802	32.5	75%	55.9%	1.70	0.45	0.309
IL-6	0.299	0.672	0.347–0.996	77.71	75%	68.7%	2.40	0.36	0.437
TNF-α	0.257	0.688	0.464–0.911	1.595	100%	56.2%	2.28	0	0.562

Note: *P< 0.05.
Abbreviations: KD, Kawasaki disease; CAL, coronary artery lesion; NCAL, non-CAL; AUC, Area under the curve;95% CI, 95% Confidence interval; SE, Sensitivity; SP, Specificity; +LR, Positive likelihood ratio; -LR, Negative likelihood ratio; WBC, white blood cell counts; N, neutrophil counts; NLR, neutrophil-to lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin; BNP, B-type natriuretic peptide; IL, interleukin; TNF-α, tumor necrosis factor-alpha; NA, not applicable.

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circulating SESN2 levels in KD patients, despite SESN2's protective attributes, signal that the inflammatory and damaging processes are profoundly active, increasing the likelihood of significant coronary artery involvement. Its substantial reduction post-IVIG therapy and reliable performance as both a diagnostic and predictive biomarker in ROC analysis further affirm its utility in reflecting KD disease activity and the risk of coronary artery lesions.

To further evaluate the clinical position of SESN2, we compared its performance with established biomarkers. Regarding initial KD diagnosis, SESN2 (AUC = 0.697) was outperformed by neutrophil counts and NLR (AUC > 0.85). This suggests that for the primary screening of KD against a healthy state, traditional inflammatory indices, which reflect the massive systemic neutrophil activation, remain the more robust tools. This relatively modest diagnostic power may be partly attributed to the absence of a febrile control group and potential selection bias inherent in our single-center retrospective cohort. The primary advantage of SESN2 lies in its prognostic value for coronary complications. In our cohort, most traditional markers, including WBC, NLR, BNP, and even pro-inflammatory cytokines (IL-6 and TNF-α), lost their predictive power for CAL ($P > 0.05$). While CRP showed significance, its clinical utility was hampered by a notably low sensitivity (47.8%), potentially leading to a high rate of missed CAL cases. In contrast, SESN2 demonstrated a more balanced performance with significantly higher sensitivity (65.2%, $P = 0.013$). Ultimately, since a definitive gold-standard biomarker for KD remains elusive, identifying SESN2 provides a novel pathophysiological dimension. We believe it serves as a critical "piece of the puzzle" for future multi-marker predictive models, potentially enhancing diagnostic precision beyond what single parameters can offer.

While these findings are promising, our study presents several limitations. First, the absence of a febrile control group is a significant constraint, which prevents us from evaluating the specific capability of SESN2 to differentiate KD from other febrile conditions in clinical practice. Second, as a standalone biomarker, SESN2 exhibited relatively modest performance, particularly in the initial diagnosis of KD itself, suggesting its diagnostic utility may be more effective when integrated into multi-marker predictive models rather than as a primary screening tool. Third, although this was a prospective observational study, certain laboratory parameters, including D-dimer, serum ferritin, and soluble IL-2 receptor, were not included in the original study protocol. The unavailability of these data limited our ability to further cross-validate the association between SESN2 and the extent of vascular injury or inflammatory response. Furthermore, our study is constrained by its single-center, retrospective design and relatively small sample size, which may introduce selection bias and limit the generalizability of the results. Therefore, further large-scale, multi-center studies incorporating febrile control groups are warranted to rigorously validate the diagnostic and predictive capacity of SESN2 and confirm its clinical utility in real-world practice.

Conclusion

In conclusion, SESN2 serves as a dual-role biomarker in KD. From a physiological standpoint, its elevation reflects the systemic stress response during the acute phase. More significantly, from a pathophysiological perspective, SESN2 exhibits unique value in predicting CAL, outperforming most traditional markers, including WBC, NLR, BNP and cytokines, which failed to reach statistical significance for CAL prediction in our cohort. Compared to CRP, SESN2 offers superior sensitivity and more balanced performance. Therefore, SESN2 is not merely a general stress responder but a specialized indicator of vascular injury, providing a critical new dimension for risk stratification in KD.

Data Sharing Statement

The clinical data in this study was obtained in Children's Hospital of Chongqing Medical University. Data will be made available on request from the corresponding authors.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University on February 25, 2025, with approval number 2025-085, and complied with the Declaration of Helsinki. Written informed consent was obtained from a parent and/or legal guardian of all participants.

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Author Contributions

Chang Liu: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing -original draft; Yi Wei: data curation, investigation, methodology, project administration, resources; Fengchuan Jing: Conceptualization, data curation, investigation, methodology, project administration, resources; Qijian Yi: Conceptualization, methodology, project administration, resources, supervision, writing - review and editing. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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