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*Original Article*

# Relationship between serum plasminogen activator and D-dimer levels and the severity of Kawasaki disease in children as well as their predictive value for coronary artery lesion

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**Abstract:** Objective: To evaluate the relationships between serum plasminogen activator (PA) and D-dimer levels, the severity of Kawasaki disease (KD) in children, and their ability to predict coronary artery lesions (CAL). Methods: This retrospective study analyzed the clinical data of 102 children diagnosed with KD at the Affiliated Hospital of Jiangnan University from January 2020 to September 2023. The cohort was divided into two groups: 31 children with CAL in the CAL group and 71 without it in the non-CAL group. The study assessed the incidence of CAL and investigated the correlations between serum PA and D-dimer levels and various inflammatory markers (white blood cell (WBC) count, platelet count, and erythrocyte sedimentation rate (ESR)). Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of these biomarkers for CAL. Results: CAL was present in 30.04% of the children. Pearson correlation analysis revealed that serum PA levels were inversely correlated with WBC count ($P = 0.0187$), platelet count ($P = 0.0116$), and ESR ($P = 0.0041$), while D-dimer levels were positively correlated with these markers ($P < 0.001$). A negative correlation between PA and D-dimer levels was also observed ($P < 0.001$). The combined use of PA and D-dimer levels to predict CAL achieved an area under the curve of 0.871. Conclusion: Serum PA levels were negatively associated with the severity of KD, whereas D-dimer levels were positively associated. Together, these markers showed significant predictive value for CAL, highlighting their utility in assessing disease severity and guiding management in children with KD.

**Keywords:** Serum PA, D-dimer, Kawasaki disease, coronary artery lesion, predictive efficacy

## Introduction

Kawasaki disease (KD), also referred to as mucocutaneous lymph node syndrome, primarily affects preschool-aged children and is more prevalent in boys [1]. This condition is marked by systemic inflammation with symptoms including fever, skin rash, conjunctival congestion, oral mucosal lesions, and extremity swelling [2]. KD generally has a favorable prognosis with early diagnosis and prompt treatment, allowing most affected children to fully recover [3]. The disease is characterized by systemic vasculitis, and while many children experience complete recovery, some develop coronary artery lesions (CAL). As KD progresses, there is an increased risk of severe complications such as myocarditis, which can extend to multiple organ systems, potentially endangering the child's life [4-6]. Although the precise causes and mechanisms of KD remain unclear, it is believed to be influenced by factors including infections, immune system abnormalities, and genetic predisposition. Understanding these complex dynamics is crucial for identifying predictive factors and for managing the disease's progression and associated risks.

Serum plasminogen activator (PA), not to be confused with prealbumin, is involved in the breakdown of blood clots, whereas D-dimer, a fibrin degradation product, serves as a marker

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of coagulation and fibrinolysis activity. Elevated D-dimer levels can indicate increased blood clotting and breakdown, common in various pathological conditions [8]. The relationship between these biomarkers and their correlation with the severity of KD in children, as well as their predictive value for CAL, warrants further exploration.

This study thus analyzed serum PA and D-dimer levels in children diagnosed with KD to explore their associations with disease severity and the predictive efficacy of these markers for CAL. A key innovative aspect of this study is its focus on the dual utility of serum PA and D-dimer levels in assessing KD severity and forecasting the risk of CAL, offering valuable insights for managing and monitoring KD in pediatric populations.

## Materials and methods

### *Sample source*

This retrospective study was approved by the Medical Ethics Committee of the Affiliated Hospital of Jiangnan University. Clinical data from 102 children diagnosed with KD treated at the Affiliated Hospital of Jiangnan University between January 2020 and September 2023 were selected from an initial pool of 130 patients based on specific inclusion and exclusion criteria.

Inclusion criteria: (1) Age between 6 months and 7 years. (2) Diagnosis of KD according to the "Diagnosis, Treatment, and Long-term Management of Kawasaki Disease" guidelines [9], requiring a persistent fever of at least five days duration and at least four of the following symptoms: extremity changes (redness, swelling, or peeling of skin on hands and feet), rash (widespread, often on the trunk), conjunctivitis (bilateral non-exudative), mucous membrane changes (in the lips and oral cavity, such as redness, dryness, or cracking), and cervical lymphadenopathy (lymph nodes in the neck larger than 1.5 cm). (3) First occurrence of the disease. (4) Availability of comprehensive clinical data including age, sex, disease duration, residence, serum plasminogen activator (PA) levels, D-dimer levels, white blood cell (WBC) count, platelet count, erythrocyte sedimentation rate (ESR), and CAL status.

Exclusion criteria: (1) Prior treatment with anti-inflammatory or anticoagulant medications. (2) Presence of immune system disorders or other cardiovascular diseases. (3) Congenital heart structural abnormalities. (4) Existence of severe underlying medical conditions. (5) Liver diseases or other conditions that might influence D-dimer levels.

### *Grouping of children*

Among the 102 children assessed using the inclusion and exclusion criteria, 31 patients who developed CAL were categorized into the CAL group, while the remaining 71 patients were placed in the non-CAL group.

### *Criteria for CAL determination*

For CAL determination, the following criteria were applied: in children under 5 years old, a coronary artery main trunk diameter greater than 3 mm; in children over 5 years old, a diameter greater than 4 mm; or localized inner diameter enlargement exceeding 1.5 times that of the adjacent segment [8]. Coronary artery diameters were typically measured via echocardiography, involving proper patient positioning, use of an ultrasound probe to locate the heart area, acquisition of a coronary artery image through an optimal echocardiographic window, and diameter measurement with ultrasound software, repeated thrice to ensure accuracy.

### *Data collection and processing*

Data on age, sex, disease duration, residence, serum PA levels, D-dimer levels, WBC count, platelet count, ESR, and CAL status were collected via the hospital information system. This study explored CAL incidence and the relationships between serum PA and D-dimer levels and inflammatory markers (WBC count, platelet count, ESR). Receiver operating characteristic (ROC) curves were generated to evaluate the predictive value of serum PA and D-dimer levels, individually and combined, for CAL in KD patients.

### *Statistical analyses*

Statistical analyses were conducted using SPSS version 20.0 (IBM Corp, Armonk, NY, USA), and graphs were plotted using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Count data were presented as n (%) and analyzed using chi-square tests for intergroup comparisons. Measurement data were described as mean ± standard deviation and

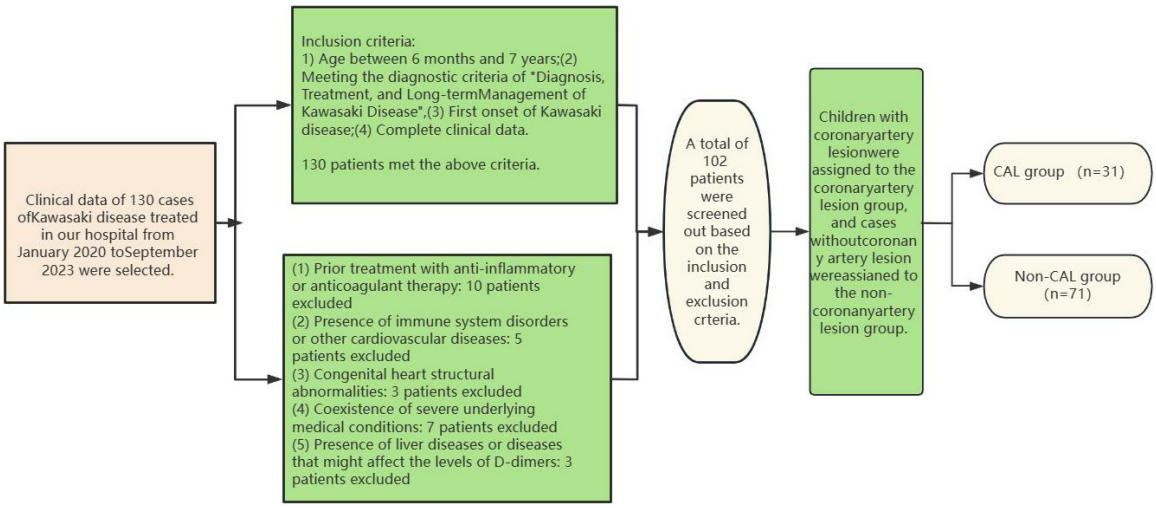


**Figure 1.** Screening and grouping process. CAL, coronary artery lesion.

**Table 1.** Comparison of clinical data

| Factor | CAL group (n = 31) | Non-CAL group (n = 71) | *P* value |
|---|---|---|---|
| Age | | | 0.0717 |
| < 5 years old | 28 | 53 | |
| ≥ 5 years old | 3 | 18 | |
| Sex | | | 0.0993 |
| Male | 20 | 53 | |
| Female | 14 | 18 | |
| Course of disease | | | 0.7693 |
| < 3 days | 13 | 32 | |
| ≥ 3 days | 18 | 39 | |
| Rash | | | 0.3810 |
| Yes | 25 | 62 | |
| No | 6 | 9 | |
| Conjunctivitis | | | 0.9352 |
| Yes | 26 | 60 | |
| No | 5 | 11 | |
| Cervical lymph nodes enlargement | | | 0.6591 |
| Yes | 16 | 40 | |
| No | 15 | 31 | |
| Place of residence | | | 0.7380 |
| Rural area | 19 | 41 | |
| Urban area | 12 | 30 | |

CAL, coronary artery lesion.

analyzed with t-tests for inter-group comparisons. The predictive performance of serum PA and D-dimer levels, both separately and combined, for CAL was assessed using ROC curves. The area under the curve (AUC) among different indicators was compared using the DeLong test [10]. A *p*-value < 0.05 was considered statistically significant.

## Results

### *Comparison of baseline data*

Following the application of inclusion and exclusion criteria, 102 children were enrolled in the study. Based on the occurrence of CAL, patients were categorized into the CAL group and the non-CAL group. The process of screening and grouping is detailed in **Figure 1**. The baseline characteristics of both groups were statistically similar, ensuring comparability (**Table 1**).

### *Comparison of incidence of CAL among included patients*

In the included patients, the incidence of CAL was 30.04%, with 31 out of 102 cases showing CAL.

### *Comparison of associations of serum PA levels with WBC count, platelet count, and ESR in KD children*

Pearson correlation analysis uncovered negative associations between serum PA levels and

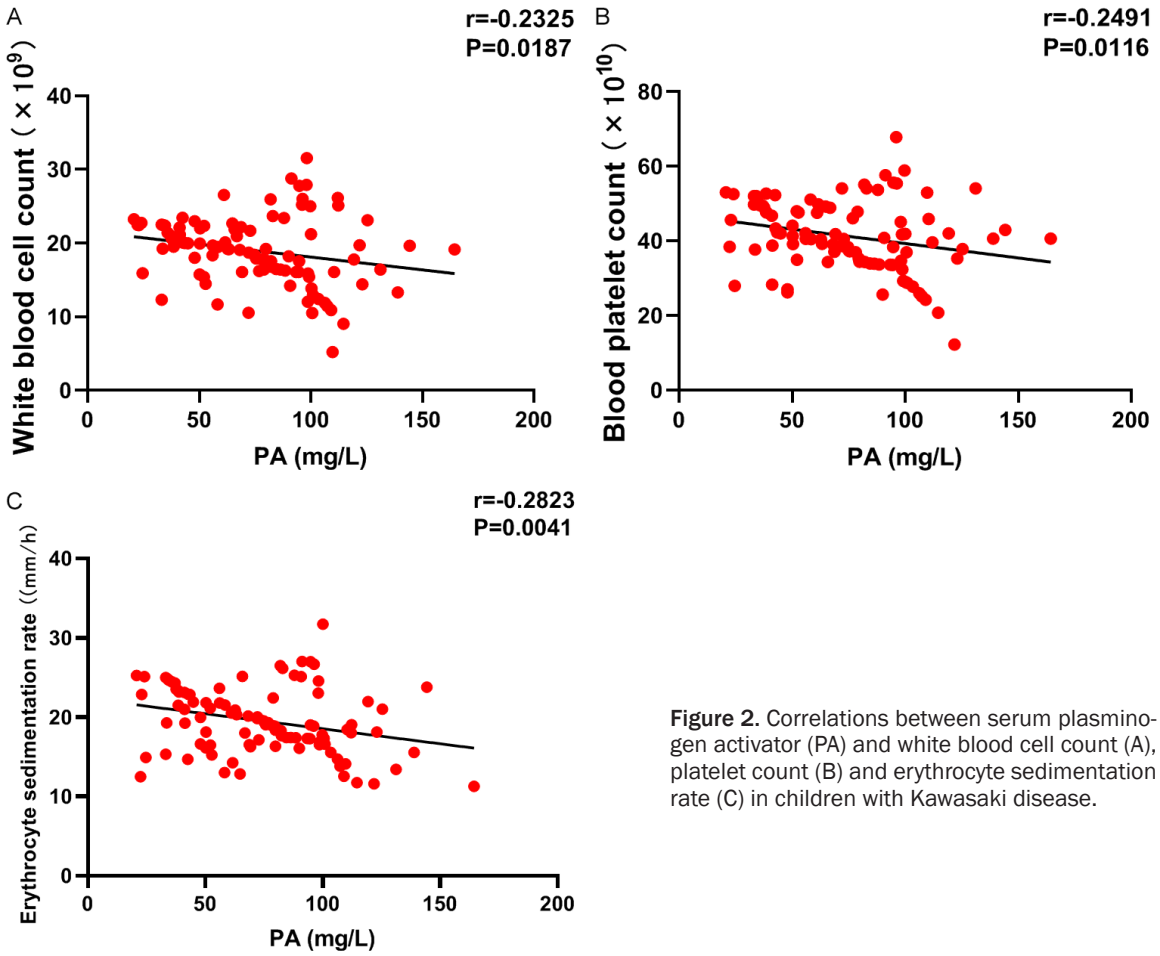


**Figure 2.** Correlations between serum plasminogen activator (PA) and white blood cell count (A), platelet count (B) and erythrocyte sedimentation rate (C) in children with Kawasaki disease.

WBC count (P = 0.0187), platelet count (P = 0.0116), and ESR in children with KD (P = 0.0041) (**Figure 2**).

*Comparison of correlations of D-dimer with WBC count, platelet count and ESR in KD children*

Pearson correlation analysis identified positive associations between D-dimer levels and WBC count, platelet count, and ESR in KD children (P < 0.001, **Figure 3**).

*Comparison of correlation between PA and D-dimers in KD children*

Pearson correlation analysis uncovered negative association between PA and D-dimers in KD children (P < 0.001, **Figure 4**).

*Predictive efficacy of serum PA and D-dimer levels for CAL in children with KD*

The ROC curve analysis (**Figure 5**) demonstrated that the combined use of serum PA and D-dimer levels resulted in an AUC of 0.871. This was higher than the AUCs for serum PA alone (0.823) and D-dimer alone (0.782). The accuracy of predicting CAL in KD children was enhanced when using the combined measurements of serum PA and D-dimer levels compared to using either biomarker alone (**Tables 2** and **3**).

## Discussion

KD is an acute febrile rash illness predominantly affecting children. The early diagnosis of KD largely relies on clinical signs and is supported by laboratory tests, although these diagnostic criteria often lack high specificity [11, 12]. In severe cases, KD may lead to CAL [13], making it crucial to identify markers closely associated with KD severity and the risk of CAL.

KD can induce inflammation and lesions in the coronary arteries, potentially leading to narrowing, dilation, or aneurysm formation if not

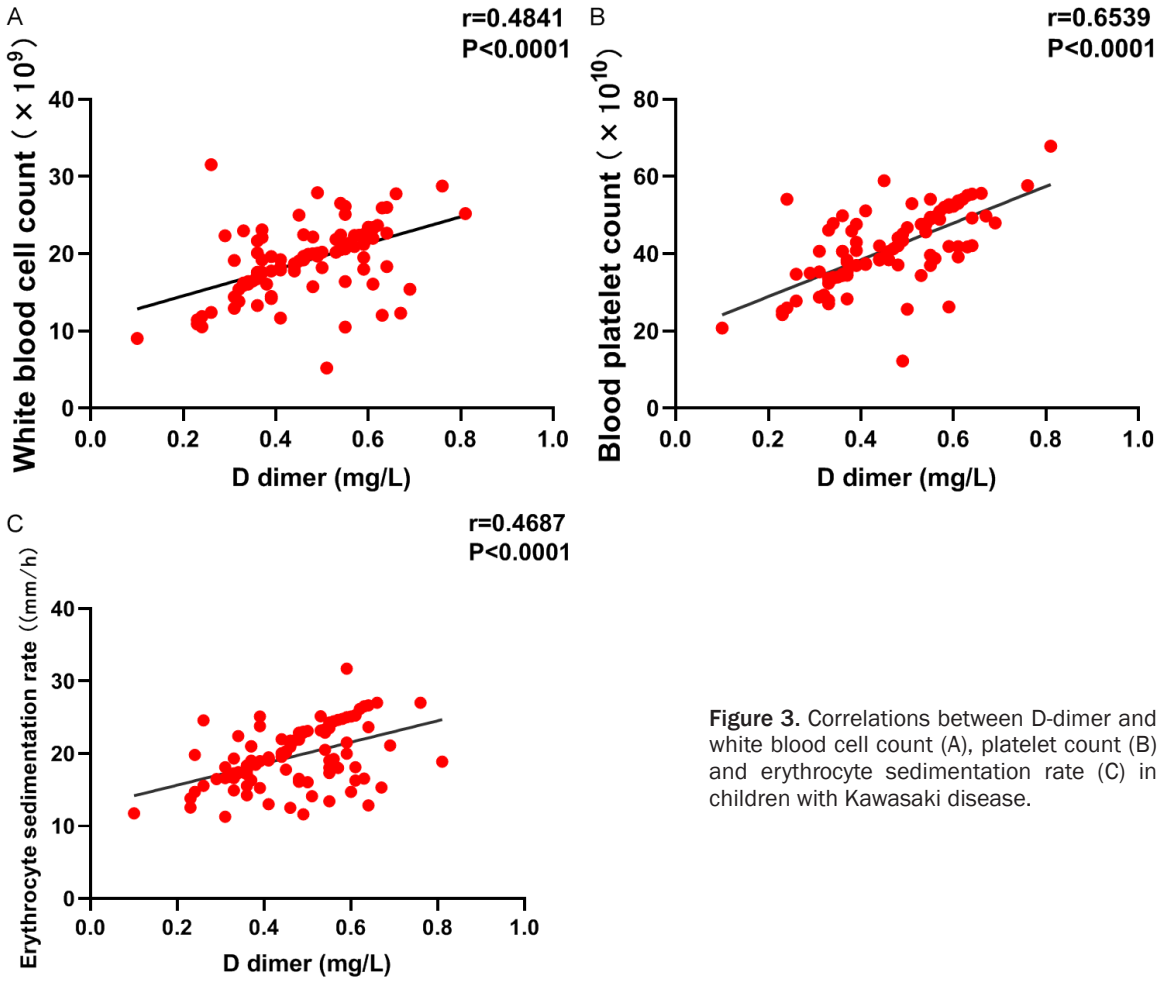


**Figure 3.** Correlations between D-dimer and white blood cell count (A), platelet count (B) and erythrocyte sedimentation rate (C) in children with Kawasaki disease.

promptly or adequately treated [13]. The incidence of CAL in this study was 30.04%, a figure that might reflect the limited sample size. This rate underscores the commonality of CAL in KD patients and highlights the importance of monitoring these complications.

Regarding biomarkers, serum PA, a plasma protein with a relatively short half-life of about two days, can indicate recent changes in the body's nutritional and inflammatory status [14-17]. D-dimer, a fibrin degradation product, results from fibrinolysis and is useful in assessing the activity of the body's coagulation and fibrinolytic systems [18].

In normal physiological conditions, the body maintains a balance among coagulation, anticoagulation, and fibrinolysis systems. However, when these systems are disrupted by various stimuli, leading to hypercoagulability, fibrinolysis, and thrombosis, substantial amounts of D-dimer are produced. D-dimer serves as a critical marker for assessing the status of blood coagulation and fibrinolysis [19].

Commonly used in the diagnosis and severity assessment of KD in children, WBC count, platelet count, and ESR are indispensable diagnostic tools [20, 21]. WBC count measures the number of WBCs in the blood, which typically increases in KD due to inflammatory responses [22]. Platelet count, indicative of the number of platelets, often rises in KD, likely due to vascular inflammation and platelet activation [23]. ESR, which gauges the rate at which red blood cells settle, is generally elevated in KD, reflecting an ongoing inflammatory process [24].

This study's Pearson correlation analysis revealed that serum PA levels negatively correlate with WBC count, platelet count, and ESR in children with KD, while D-dimer levels show a positive correlation with these markers. These

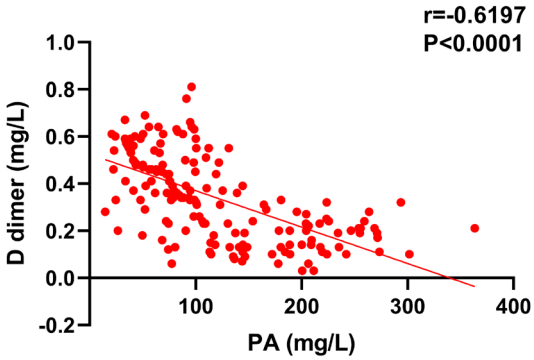


**Figure 4.** Correlation between plasminogen activator (PA) and D-dimers in Kawasaki disease children.

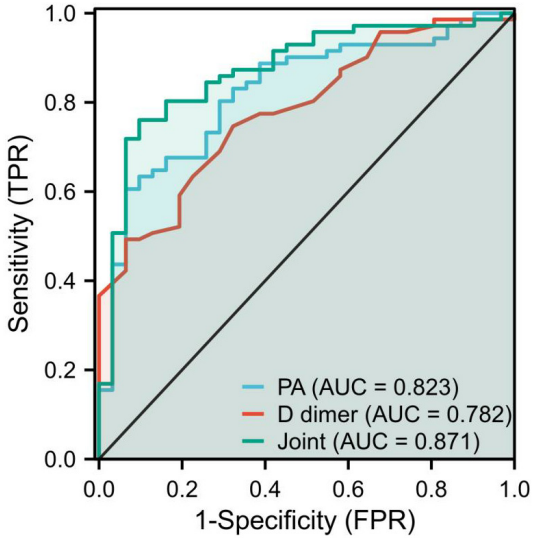


**Figure 5.** Predictive efficacy of serum plasminogen activator and D-dimer for coronary artery lesion in children with Kawasaki disease.

findings suggest that KD, as a systemic vasculitis, intensifies the inflammatory response, potentially exacerbating the condition. Serum PA, an inflammation marker, typically decreases during inflammation, indicating more severe inflammatory responses in KD patients with lower serum PA levels. Additionally, inflammatory responses can impact children's appetite and the efficiency of digestion and absorption, leading to inadequate nutritional intake and further decreasing serum PA levels.

Furthermore, KD can provoke endothelial inflammation and thrombus formation [25], processes that enhance D-dimer production due to the degradation of thrombi [26]. The elevated levels of D-dimer in the bloodstream

**Table 2.** ROC curve-related parameters of serum PA and D-dimer levels for predicting CAL in children with KD

| | PA | D dimer | Joint |
|---|---|---|---|
| Specificity | 93.55% | 93.55% | 90.32% |
| Sensitivity | 60.56% | 49.30% | 76.06% |
| Accuracy | 70.59% | 62.27% | 80.39% |
| AUC | 0.823 | 0.782 | 0.871 |

PA, plasminogen activator; CAL, coronary artery lesion; KD, Kawasaki disease.

**Table 3.** Pairwise comparison of ROC curves[a]

| | |
|---|---|
| D dimer-PA | |
| Difference between areas | 0.0409 |
| 95% Confidence Interval | -0.0649 to 0.147 |
| Significance level | P = 0.4487 |
| D dimer-Joint | |
| Difference between areas | 0.0891 |
| 95% Confidence Interval | 0.0166 to 0.162 |
| Significance level | P = 0.0160 |
| PA-Joint | |
| Difference between areas | 0.0482 |
| 95% Confidence Interval | 0.00269 to 0.0936 |
| Significance level | P = 0.0379 |

[a]DeLong et al. [10], 1988. PA, plasminogen activator.

reflect ongoing vascular wall damage and tissue injury in KD. Additionally, the observed negative association between PA and D-dimer levels in KD children could stem from the inflammatory inhibition of PA synthesis and activity, coupled with increased coagulation activity.

In this study, the combined measurement of serum PA and D-dimer levels demonstrated a relatively high predictive value for CAL in KD patients, achieving an AUC of 0.871. This value surpasses the AUCs for serum PA alone (0.823) and D-dimer alone (0.782). The findings suggest that the joint predictive efficacy of serum PA and D-dimer levels is superior to using either marker independently, indicating their utility in forecasting the occurrence of CAL in KD patients. This offers new avenues for developing preventive and therapeutic strategies for CAL in KD cases. Consistent with this, Yin et al. [27] reported that combined testing of D-dimer, prothrombin time, and red blood cell distribution width is beneficial for predicting CAL in children with acute KD, supporting the conclusions of the current study.

The study's limitations include its single-center design and small sample size, which restricted the exploration of the relationship between serum PA and D-dimer levels and the therapeutic efficacy or long-term prognosis of KD children. Future research with a larger cohort is necessary to monitor changes in serum PA and D-dimer levels more closely during diagnosis and treatment, and to analyze their specific roles in the pathogenesis of KD. This would provide a solid foundation for understanding the underlying mechanisms of the disease. Additionally, as this was a retrospective analysis, it faced limitations related to incomplete and potentially biased data collection. The criteria used to assess severity were also not sufficiently objective. Future studies should therefore consider a prospective design that includes clinical follow-up data to enhance the reliability and depth of the findings.

In conclusion, in children with KD, serum PA levels are negatively associated with disease severity, while D-dimer levels show a positive association. Moreover, the combination of these biomarkers has proven to be effective in predicting CAL, underscoring their significant role in assessing the disease and guiding treatment strategies.

## Disclosure of conflict of interest

None.

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