

Impact of serial changes of D-dimer in patients with Kawasaki disease: Correlation between the peak D-dimer level and coronary arterial lesions

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Abstract

Purpose

D-dimer levels are thought to reflect coronary artery lesion activity in patients with Kawasaki disease (KD). This study aimed to clarify the relationship between peak D-dimer levels and coronary artery abnormalities by analyzing serial changes in D-dimer levels in patients with KD.

Methods

D-dimer levels were measured in pediatric 62 patients with KD and in 36 febrile subjects serving as controls. All patients with KD received intravenous immunoglobulin (IVIG). In the KD group, D-dimer and other laboratory parameters were assessed serially at the following time points: pre-IVIG (on admission) and post-IVIG (after the first IVIG, at discharge, 1 month, and 4 months). The peak D-dimer level during the clinical course was determined, and maximum Z scores of the right and left main coronary arteries were evaluated by echocardiography.

Results

Pre-IVIG D-dimer levels were significantly higher in patients with KD than in the control group ($p < 0.001$). In patients with KD, D-dimer levels did not normalize rapidly after IVIG treatment. The Z score of the right coronary artery (RCA), the highly involved site, was significantly correlated with the peak D-dimer level. A peak D-dimer cutoff value of > 2.6 mg/dL predicted coronary artery lesions, with a sensitivity of 70.0% and a specificity of 69.2%.

Conclusions

Failure of D-dimer levels to decrease after IVIG treatment may indicate ongoing coronary artery involvement. In such cases, repeat echocardiography and consideration of additional treatment are warranted.

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis syndrome that occurs in infants and children and is now the most common cause of acquired pediatric heart disease, such as coronary artery lesions (CAL) in developed countries.^{1), 9)} The goal of treatment in KD is to suppress the onset of CAL by resolving inflammation rapidly. Treatment guidelines for KD recommend that intravenous immunoglobulin (IVIG) should be instituted as early as possible, within the first 10 days of illness onset of fever, that is, as soon as the diagnosis can be established.⁹⁾ Coronary arteritis in KD was reported to

begin around days 6 to 8 after the onset of inflammatory cell infiltration into the intima and adventitia of coronary arteries. Around day 10, inflammation progresses to involve the entire thickness of the arterial wall and simultaneously extends circumferentially within the coronary arteries^{1), 7), 9)}. Despite prompt initial IVIG treatment, coronary arteritis may still develop in patients with KD, reflecting treatment resistance. Therefore, serial assessment of inflammatory activity after IVIG therapy is essential, as coronary artery inflammation may persist or progress beyond day 10.

D-dimer is a well-known biomarker of fibrin formation and degradation, and elevated levels may indicate not only acute thrombosis, but also a variety of inflammatory illnesses³⁾. D-dimer was reported to reflect local vascular inflammation, including that of the coronary arteries³⁾. Because KD is a form of systemic vasculitis involving small to medium-sized arteries such as the coronary artery⁹⁾, several studies demonstrated an association between D-dimer and various aspects of KD, which might indicate treatment failure/resistance, and complications^{4), 10), 5), 11)}. However, the D-dimer level study in KD in previous studies was limited to only before IVIG treatment. No studies have examined post-IVIG serial D-dimer levels, and the relationship between the peak D-dimer level and CAL in KD. This study aimed to investigate the serial changes in D-dimer levels in patients with KD, and to compare inflammatory marker levels with those in a control group. As the next step, the relationships between CAL in KD and both the pre-IVIG and peak levels of inflammatory markers, including D-dimer, albumin, white blood cell (WBC) count, platelet (PLT) count, and C-reactive protein (CRP), were evaluated using univariate and multivariate logistic regression analyses. In the present study, CAL were assessed using the newly established Z score for coronary arteries in the Japanese population.²⁾

Methods

Study Populations

In this retrospective study, children with KD under 14 years old, who were admitted to Uji Tokusyukai hospital from February 2020 to December 2024, were included as the KD group. Diagnostic criteria and treatment of KD were performed according to the JCS/JSCS 2020 guideline¹⁾. In KD, IVIG treatment was performed under hospitalization (median hospital stay was 9 days). As a control group, we enrolled 36 febrile children with the same age range. The control group excluded children with rheumatic immune system disease, congenital heart disease, and inherited metabolic disorders, as well as those who received drug therapy (such as IVIG and aspirin).

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Uji Tokusyukai Hospital (TGE, Approval No.02404-007). Informed consent was obtained from all participants or their legal guardians. The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Coronary artery evaluation: Echocardiography was performed by experienced sonographers to detect CAL before and after IVIG treatment. The ultrasound instrument Philips Affiniti or EPIQ (Philips Healthcare, Bothell, WA, USA) with a frequency of 1–5 MHz probe was used in this study. Coronary arteries were measured at four sites: (1) proximal right coronary artery (RCA), (2) left main coronary trunk (LMT), (3) proximal left anterior descending coronary artery (LAD), and (4) proximal left circumflex coronary artery (LCX). Z scores of each site of the coronary artery were calculated according to a Japanese multicenter, prospective, observational study²⁾, and of > 2.0 was defined as CAL.

Data collection

Information on the children's demographic characteristics, echocardiography, and blood examination results was collected retrospectively. Serial levels of inflammatory markers in KD patients were obtained in pre-IVIG (on admission) and post-IVIG (after initial IVIG and at discharge as a subacute phase) as well as at one month as a convalescent phase, and four months as a remission phase. Blood biomarker data, including D-dimer, CRP, WBC, PLT, and albumin, were collected. The maximum levels of D-dimer, CRP, WBC, and PLT and the minimum level of albumin were used as the peak value. In the control group, blood biomarkers were collected once at febrile point. In the KD group, the maximum Z score of each coronary artery site during the clinical course was used for statistical analysis.

Statistical analysis

Variables are expressed as mean $\pm$ standard deviation (SD). All laboratory parameters in the control and the KD group on admission (before IVIG) were compared using the unpaired student's t-test. Serial D-dimer levels in each period and those in the control were compared using the multiple comparison test (One way ANOVA). The Pearson correlation coefficient was used to estimate the correlation between the Z score of each coronary artery site and the levels of each laboratory parameter before IVIG treatment or the peak levels. To determine independent predictors of CAL of each coronary artery site, multiple linear regression analysis with stepwise selection was performed. All laboratory parameters which correlated significantly with CAL by univariate analysis were selected as candidate predictors. To evaluate the performance of the peak D-dimer level in predicting CAL in KD patients, the area under the curve (AUC) using receiver operating characteristic $\pm$ (ROC) analysis was performed. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

Results

A total of 62 patients with Kawasaki disease and 36 control subjects during the observation period were enrolled in this study.

Baseline characteristics of subjects

The baseline characteristics of the 62 patients with KD and the 36 control subjects are shown in **Table 1**. There were no significant differences in age or sex between the two groups. Fever duration ($p < 0.001$) and the levels of WBC ($p < 0.01$), CRP ($p < 0.001$), and D-dimer ($p < 0.001$) were significantly higher in the KD group than in the control group. In contrast, the albumin level was significantly lower in the KD group ($p < 0.001$). The average maximum Z scores at each coronary artery site in the KD group were all below 2.0. Serial changes in laboratory parameters before and after IVIG treatment in the KD group are summarized in **Table 2**. The levels of WBC, CRP, PLT, and albumin changed significantly after IVIG treatment, whereas the D-dimer level did not show a significant change. At 4 months post-IVIG, four of the 62 patients had CAL. At the follow-up of a median 4 months (range: 3-4 months), all patients with KD are alive.

Serial change of levels of D-dimer in the KD group

D-dimer levels at pre-IVIG (on admission) and post-IVIG (after initial IVIG and at discharge) as well as at 1 month and 4 months, in the KD and those in control group are shown in **Figure 1**. D-dimer levels in the KD group, both pre-and post-IVIG treatment, were significantly higher than those in the control group (pre-IVIG vs. control, $p < 0.001$; post-IVIG vs. control, $p < 0.001$). Peak D-dimer levels were in these timepoints. However, no significant difference was observed between pre- and post-IVIG D-dimer levels. The median day of the maximum D-dimer level was day 7 (range, day 3–12). D-dimer levels at 1 month and 4 months after IVIG treatment were significantly lower than those pre-IVIG levels (1 month, $p < 0.001$; 4 months, $p < 0.001$), indicating recovery process. The median day at discharge was day 12 (range, day 8–26). Furthermore, the D-dimer level at 4 months after IVIG treatment was significantly lower than that at discharge ($p < 0.05$).

Correlations between the Z score of coronary artery site and each laboratory parameter before IVIG treatment

Correlations between the maximum Z score of each coronary artery site and each laboratory parameter (mean $\pm$ SD) at pre-IVIG treatment are shown in **supplementary material**. All maximum Z scores of each coronary artery site were not correlated with each laboratory parameter at pre-IVIG treatment.

Correlations between the Z score of each coronary artery site and each peak laboratory parameter during the clinical course

In the past, the incidence of various sites of CAL in KD was reported in descending order as RCA (46%), LMT (24%), LCX (20%), and LAD (7.4%), respectively¹². Correlations between the maximum Z score of each coronary artery site and the peak laboratory parameters before IVIG treatment are shown in **Table 3**. The Z score of the RCA was significantly correlated with peak D-dimer levels ($r = 0.44$, $p < 0.001$) and peak WBC counts ($r = 0.30$, $p < 0.05$). The Z score of the LAD was significantly correlated with the peak albumin level ($r = -0.30$, $p < 0.05$). In contrast, the Z scores of the LMT and LCX were not significantly correlated with the peak levels of any laboratory parameters.

A stepwise multivariate linear regression analysis of variables influencing the Z score of each coronary artery site

The results of the multivariate analysis are presented in **Table 4**. Stepwise multiple linear regression analysis was performed to identify independent variables associated with the Z scores at each coronary artery site. The dependent variables included the peak levels of D-dimer, WBC, and albumin, as these parameters showed significant correlations with the Z scores at each coronary artery site in univariate analyses. The peak D-dimer level was identified as a significant independent predictor of the Z score of the right coronary artery (RCA) ($p < 0.001$). In addition, the peak albumin level was a significant independent predictor of the Z score of the left anterior descending artery (LAD) ($p < 0.05$).

ROC analysis

The ROC curves using the peak D-dimer level to predict CAL in the KD group were analyzed (**Figure 2**). The ROC curve analysis indicated the best cutoff value for the D-dimer level of > 2.6 mg/dL, with an AUC of 71.1%, a sensitivity of 70.0%, and a specificity of 69.2%.

Discussion

The present study clarified several important findings. First, pre-IVIG D-dimer levels in the KD group were significantly higher than those in the control group and did not normalize after initial IVIG treatment. Second, the Z score of the RCA was significantly correlated with the peak D-dimer level, which was identified as the only independent factor associated with the RCA Z score in multivariate linear regression analysis. Third, the optimal cutoff value of peak D-dimer for predicting CAL was > 2.6 mg/dL, yielding a sensitivity of 70.0% and a specificity of 69.2%.

D-dimer has been reported to be elevated in several vascular diseases, including coronary artery disease and deep venous thrombosis ⁶⁾. KD is an inflammation-mediated vasculitis that activates the vascular endothelium and leads to endothelial injury, which can be reflected by elevated D-dimer levels. D-dimer is a fibrin degradation product generated from cross-linked fibrin formed by thrombin-activated coagulation factors and subsequently hydrolyzed by fibrinolytic enzymes ³⁾. Therefore, increased D-dimer levels are associated with a hypercoagulable state, macrophage activation, and aggravated tissue damage.

Previously, Imamura et al. and Zou Y. et al. showed that the D-dimer levels in KD patients were significantly higher than those in the control group ^{4), 11)}. Masuzawa et al. reported that the D-dimer level in the CAL group in KD patients was significantly higher than that in the non-CAL group, with a positive correlation of increased D-dimer and CAL in univariate and multivariate analysis ⁵⁾. Zhou Y et al. demonstrated that a significantly correlated relationship between D-dimer level and coronary artery diameter ¹¹⁾. The significant correlation found in the present study between the peak D-dimer level and the Z-score of RCA is consistent with previous reports; however, serial changes in D-dimer levels (pre-

and post-IVIG) in KD patients, as well as the relationship between the maximum D-dimer level and CAL, have been barely investigated.

We also demonstrated that IVIG treatment significantly improved WBC and CRP levels, whereas D-dimer and albumin levels did not improve after initial IVIG treatment (Table 2). Previous studies have reported that D-dimer and albumin reflect local vascular remodeling leading to aneurysm formation in several inflammatory diseases, including systemic and pulmonary hypertension and coronary artery disease ⁸⁾. The differing responses to IVIG treatment between WBC/CRP, which represent systemic inflammation, and D-dimer/albumin, which reflect local vascular inflammation, suggest the presence of a time lag in the resolution of vascular inflammation.

Masuzawa et al. also reported a strong correlation ($R = 0.610$) between albumin and D-dimer levels in patients with KD ⁵⁾. The delayed response of D-dimer and albumin following IVIG treatment may reflect the temporal progression of histopathological changes in the coronary arteries of KD patients. During days 8–10 of illness, inflammatory cells infiltrate from the intima and adventitia into the media, resulting in pan-arteritis involving the entire arterial wall ^{7), 9)}. This pathological course of coronary artery involvement in KD corresponds with our findings, as the median day of peak D-dimer levels was day 7.

Accordingly, even when initial IVIG treatment rapidly reduces systemic inflammatory markers such as WBC and CRP, serial monitoring of D-dimer and albumin levels remains essential. Our findings are consistent with those of Maggio MC et al., who reported significantly higher post-IVIG D-dimer levels in non-responders compared with responders ¹⁴⁾. If D-dimer levels fail to improve after IVIG treatment in KD patients, particularly when levels exceed 2.6 mg/dL during the clinical course (Fig. 2), we recommend repeat echocardiographic evaluation of the coronary arteries, together with consideration of additional second-line therapies.

In the present study, the peak minimum albumin level was significantly correlated with the Z score of the LAD in both univariate and multivariate analyses. Previously, Terai et al. reported that serum albumin levels after IVIG treatment were significantly lower in non-responders than in responders ¹⁰⁾. Therefore, serial monitoring of albumin levels after IVIG treatment may be clinically useful in patients with KD, as hypoalbuminemia is thought to reflect ongoing local vascular inflammation resulting from increased vascular permeability and enhanced albumin leakage.

In this regard, Belayneh et al. reported an asymptomatic giant right coronary artery aneurysm in a patient with KD and reviewed previously published case reports ¹³⁾. They speculated that giant CALs tend to preferentially involve the proximal RCA. Similarly, Suzuki et al. demonstrated that the incidence of coronary artery dilatation and aneurysm formation was higher in the RCA than in the LMT, LAD, or LCX (dilatation: RCA 55%, LMT 20%, LAD 10%, LCX 14%; aneurysm: RCA 46%, LMT 24%, LAD 7.4%, LCX 22%) ¹²⁾. Although the etiology underlying the laterality of CAL in patients with KD has not been fully elucidated, D-dimer may be involved in coronary arterial inflammation, particularly in the RCA. Nevertheless, further accumulation of cases is required to clarify this association.

Study Limitations

This study has several limitations. **First**, it was a small, retrospective, single-center study, which may introduce inherent biases. Moreover, as all participants were from a Japanese population, the findings may not be directly generalizable to other ethnic or geographic populations. **Second**, the Z scores of the coronary artery segments evaluated in this study were relatively low, and no moderate-to-giant coronary artery aneurysms were observed among patients with KD. Given that the incidence of moderate-to-giant coronary artery aneurysms in KD is approximately 2% or less, further accumulation of cases is required to examine the coronary artery aneurysms. **Third**, we speculated the association between the peak D-dimer level and CAL, however, we did not investigate that the speed of recovery of D-dimer. To investigate the speed of recovery of D-dimer is helpful for the timing of additional therapy for inflammation after initial IVIG.

Abbreviations

CAL: coronary artery lesions

CRP: C-reactive protein

IVIG: intravenous immunoglobulin

KD: Kawasaki disease

LAD: left ascending coronary artery

LMT: left main coronary trunk

LCX: left circumflex coronary artery

PLT: platelet

RCA: right coronary artery

WBC: white blood cell

Declarations

Conflict of Interest Disclosures

(includes financial disclosures): The authors declare no conflict of interest. There is no funding source to disclose for this report.

Declaration of Generative AI usage

This text was written by a human without the use of AI.

Disclosures

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Author Contribution

Contributors Statement Kenichi Okumura conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. Kyosuke Izumi, Takuma Sugawara, Kento Itoi, Kunpei Sekine, Takuzou Wada, Motokazu Nishikado, Yuuko Amimoto, Hitoshi Awaguni, Ikumi Arai, Mayumi Nagasawa, and Jun Shinozuka collected data and reviewed and revised the manuscript. Kenji Hamaoka conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

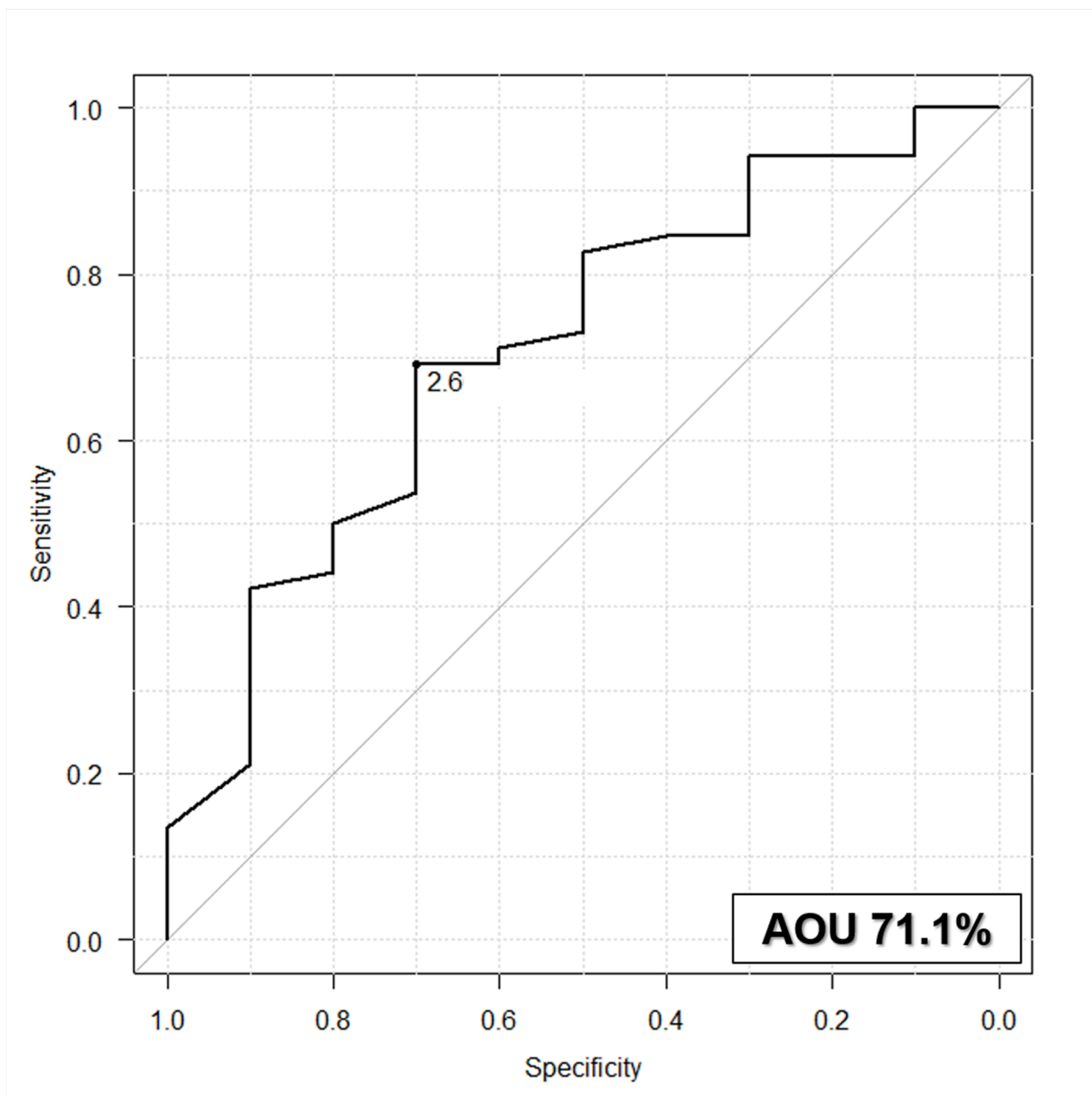


Figure 2

The receiver operating characteristic curves of using the peak D-dimer level to predict coronary artery lesion in Kawasaki disease patients.

Supplementary Files

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