# Eosinophil as the major factor of the nomogram model to differentiate Kawasaki disease from other febrile illnesses

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**Research article**

**Keywords:** Kawasaki disease, nomogram model, white blood cell, Alanine transaminase, eosinophil, albumin, C-reactive protein

**Posted Date:** December 17th, 2019

**DOI:** https://doi.org/10.21203/rs.2.19021/v1

# Abstract

Background: Kawasaki disease (KD) is a systemic vasculitis in children less than 5 years old. At present, no single laboratory data can distinguish KD from other febrile diseases. To establish a differential diagnosis laboratory data model between KD and other febrile diseases, which can avoid coronary artery complications.

Methods: A total of 800 children (249 KD and 551 non-KD febrile illness) were enrolled. Laboratory findings were analyzed by of univariable multivariable logistic regression and nomogram.

Results: 562 children were randomly selected as the model group and 238 as the validation group. The predictive nomogram included eosinophil percentage 100 points, C-reactive protein (93 points), alanine transaminase (84 points), albumin (79 points), and white blood cell 64 points, which generated an area under the curve of 0.873 for model group, and 0.905 for validation. Eosinophil showed highest OR: 5.015 (95% CI: 3.068-8.197) during multiple logistic regression. The sensitivity and specificity were 84.1% and 86% in the validation group. The calibration curves of the validation group for the probability of KD showed nearly agreement to the actual probability.

Conclusion: Eosinophil is the major factors in this nomogram model and had a high precision to predict KD. This is the first report from literature review showed the important role of eosinophil in KD.


# Background

Kawasaki disease (KD) is a form of systemic vasculitis that primarily occurs in children under 5 years of age. Small and medium-sized arteries are mainly involved, with coronary arteries being the most important. Recent epidemiological investigations have indicated that the incidence of this disease is increasing every year (1). Furthermore, it has become the main cause of acquired cardiovascular diseases in children, thus attracting even more attention. The etiology and mechanism of KD remain unknown. In general, KD is diagnosed based on clinical manifestations and laboratory findings, which may increase the rate of missing diagnosis (2). Studies have reported that about 20%-25% of KD children without treatment develop coronary aneurysms (CAA), while intravenous immunoglobulin (IVIG) (2 g/ (kg/day)) can reduce the incidence of CAA to 3%-5% (3).Coronary artery lesions formation (including transient dilatation) was found in about 30% KD patients(4). Therefore, the establishment of an effective early diagnosis method and scheme is of great clinical significance for the clinical diagnosis and treatment of KD.

From the literature review, most predictive score systems are for IVIG resistance (white blood cell, albumin, C reactive protein, sodium, neutrophil, lymphocyte, eosinophilia, total bilirubin, platelet, red blood cell distribution width, etc.) (5) or coronary artery lesion (T help 2 cytokiens, albumin, Tenascin-C, monocytes, eosinophils, etc.) (6). Few studies involve a predictive score for differentiating KD from other febrile illnesses (7). In this study, we aimed to establish a score system using only clinical laboratory data

to differentiate KD patients from those with fever. Using laboratory data but not using clinical symptoms or signs will decrease the subjective effect on the results.

Nomogram is the visualization of the complex mathematical formulas resulting from such traditional statistical methods as multivariable logistic regression or Cox proportional hazards analysis. It has been used to calculate the continuous probability of an event of interest entirely based on the individual's disease characteristics, without averaging or combining within a category (8). Nomogram is now widely used in the prognosis of cancer and other specialized diseases to help clinicians make important treatment decisions (9). Compared with previous prediction models, nomogram is more accurate and has better performance characteristics (10). Furthermore, the nomogram does not require the interpretation of imaging or other precise measures to predict the functional outcome. Therefore, for busy clinicians, the nomogram is a simpler and easier method for predicting functional outcome in routine practice.

In this study, we wanted to set up a clinical predictive score system to distinguish KD from non-KD fever controls, which may have an impact on artificial intelligence in the future.

# Methods

Study Participants

Children who had a fever for more than three days (38°C ear temperature), were less than 10 years old without any IVIG or steroid therapy in the past one month in Shenzhen Baoan District Maternal and Child Health Hospital in China from August 2016 to July 2019 were enrolled in this study. We excluded anyone with a history of autoimmune diseases or congenital cardiovascular diseases. Participants were divided into the KD group and non-KD febrile illness group. Clinical diagnostic criteria of KD is based on the 2017 American Heart Association (AHA) revised diagnostic criteria of KD (11) .

Data Collection

General information such as gender, age, and body weight of the enrolled children were recorded, as were laboratory examination results, including white blood cell count (WBC), neutrophil percentage (N%), Lymphocyte percentage (L%) hemoglobin, platelet count (PLT), eosinophil percentage (E%) mononuclear cell percentage (M%), C reactive protein (CRP), procalcitonin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, and erythrocyte sedimentation rate (ESR) for further analysis.

Statistical Analysis

We used SPSS13.0 statistical software for analysis. The nomogram was drawn based on the R software (Math Soft, Cambridge, Massachusetts). Mean ± standard deviation (x ±s) was used for measurement data, and n and percentage were used for enumeration data. The normal distribution data were compared using independent sample t-test or single factor analysis of variance. We adopted rank sum test to compare non-normal distribution data. Chi-square test was performed, and $P<0.05$ was considered statistically significant. Multivariate logistic regression was used to analyze factors that influenced KD.

Continuous data are converted into classified data according to the data cutoff value corresponding to the largest area under the receiver operating characteristic curve (ROC) for each purpose. The nomogram is drawn according to the result of the logistic regression equation. Hosmer and Lemeshow were used to determine whether the logistic prediction equation was suitable. We assessed performance of the nomogram using discrimination and calibration. We calculated area under the Receiver Operating Characteristics (AUC-ROC) curve to assess discrimination of the model (12).The calibration of the models can be assessed by calibration plots, which can predict probabilities against the actual observed risk (13).

**Ethics approval and consent to participate:** All subjects gave their informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of Baoan Maternal and Child Health Hospital, Shenzhen, China approved the study (IRB No. LLSCHY2019-07-01-01).

**Patient consent**: Informed consent from participants' parents/legally authorized representatives was not obtained due to the retrospective nature of the study.

# Results

In total, 800 cases were enrolled in this study, with an average age of 25.5 ± 19.2 months, including 485 cases (60.6%) of males, 315 cases (49.4%) of females, 249 cases (31.1%) of KD patients, and 551 cases (68.9%) of non-KD febrile illness cases in the control group.

Selected Model Factors

We observed no statistical difference in gender, age, or body weight under univariate analysis ($p>0.05$). WBC, neutrophil percentage, lymphocyte percentage, eosinophil percentage, monocyte percentage, hemoglobin, platelet, CRP, procalcitonin, ALT, AST, albumin, and ESR all demonstrated a significant difference ($P<0.05$), as shown in Table 1.

Predictive Nomogram for the Probability of KD

The 800 children were randomly divided into the modeling group (70%) and the validation group (30%)according to previous report (14). Of those, 562 cases were in the modeling group, including 178 cases of KD (31.6%) children and 384 cases of non-KD febrile illness, and 238 cases were in the validation group, including 71 cases of KD (29.8%) children and 167 cases of non-KD febrile illness. The appropriate cutoff value was selected using the ROC curve. Multiple logistic regression analysis was performed on the modeling group. As shown in Table 2, the statistical results showed that WBC, E%, albumin, ALT, and CRP were independent risk factors for differentiating KD from febrile illness. In this study, febrile illness included bronchopneumonia or pneumonia (80.5%), bronchitis (8.6%), upper respiratory infection (2.7), sepsis (2%), and enteritis (1%).

The nomogram was made according to the logistic regression results of the modeling group, as shown in Figure 1. In the prediction model, E% is the largest predictor of KD (100 points), followed by CRP (93 points), ALT (84 points), ALB (79 points), and WBC (64 points). The total score is 420, and the KD occurrence probability of the corresponding score is shown in Table 3. The total score can be easily calculated by adding each single score. Through the total score analysis and reflection of the lower total point scale, we were able to estimate the probability of KD from other febrile illnesses.

Performance of the Nomogram

Based on the receiver operating characteristic analysis, the nomogram showed good discrimination, with an area under the ROC of 0.873 (95% confidence interval, CI: 0.839-0.907) in the modeling group and 0.905 (95% CI: 0.862-0.948) in the validation group. The sensitivity and specificity were 75% and 89.1%, respectively, in the model group and 84.1% and 86% in the validation group. A calibration curve of the nomogram is presented in Figure 2, which shows that the KD probabilities predicted by the nomogram agreed with the actual probabilities. Calibration curves for KD outcome demonstrated no apparent departure from fit, with good correspondences between predicted outcome and actual outcome.

# Discussion

As a febrile disease that primarily occurs in children < 5 years old, the pathological mechanism of KD is an immune-mediated systemic vascular inflammatory change. Although self-limited, it has a high incidence of coronary artery damage, generally caused by coronary artery dilatation, stenosis, and even atretic rupture (15). Currently, KD diagnosis is mainly made by doctors according to clinical manifestations, laboratory results, and echocardiography. No specific laboratory tests are available for distinguishing KD from febrile illness. Current diagnostic methods are subjective, but timely diagnosis and treatment for KD is vital for preventing long-term sequela of CAL. Although changes in laboratory indicators are not specific, some indicators are still of great value in differentiating KD. In this study, we used univariate, multivariate logistic regression, ROC curve, and nomogram to establish a novel prediction score system with WBC, CRP, albumin, ALT, and eosinophil, among which eosinophil has the highest weight point for differentiating KD from febrile illness.

In many reports, for KD children during the acute stage, the peripheral blood WBC count significantly increases, as do the plasma levels of CRP, but these changes cannot effectively distinguish KD from other illness with fever of more than 3 days. Some studies have reported that total WBC counts were significantly higher in KD children than that of non-KD febrile illness (maybe most from viral infection) (16). The total WBC of KD is higher than in viral fever children but lower than in bacterial fever children (17). The WBC counts were higher in KD with delayed diagnosis and associated with left ventricular systolic function (16).

Many studies have reported that CRP is significantly increased in KD patients with coronary artery complications (CALs) compared with KD patients without CALs (18). Although the specificity of these two conventional inflammatory indicators (WBC, CRP) is not high enough, they are widely used in clinical

practice and have more practical guiding significance for clinical diagnosis in the AHA guidelines for KD (19).

In our report, E% is the highest weighted score for risk factor of KD, making it an important predictor in the novel nomogram prediction model. Elevated eosinophil in KD, which was also found in our previous studies, showed that eosinophilia was associated with IVIG-responsiveness and could prevent CAL formation (6, 20). Some data showed that the eosinophils percentage and absolute eosinophil count were elevated in acute KD and that the percentage of eosinophils continued to rise, peaking in the convalescent phase (21). Some studies have pointed out that the incidence of eosinophilia in the peripheral blood of patients with incomplete KD is significantly higher than that of the KD group. For diagnosing incomplete KD, unexplained eosinophilia may be helpful in suggesting the diagnosis (22). The mechanism of increased eosinophils in KD remains unclear, but eosinophils accumulation in micro vessels and the increase of eosinophils in peripheral blood may be involved in the pathogenesis of KD (23). Altogether, eosinophil may play a protective role or have an anti-inflammatory effect through the T-helper 2 cytokine (IL-4) in KD (6, 24).

In our study, albumin reduction is one of the predictors of the KD diagnostic model, but the mechanism of albumin reduction in KD children is still unclear. Dominguez et al. reported that the plasma levels of albumin were significantly lower in KD children than in febrile controls (25). Decreased albumin levels may be related to increased vascular permeability caused by the acute vascular inflammatory response of KD. Increased vascular permeability can cause the extravasation of endovascular substances, which may possibly be mediated by hormones, nerve innervation, or cytokines (especially il-2, interferon-alpha, and il-6) (26). The degree of decrease in albumin levels can reflect the severity of vascular inflammatory response. A study by Kuo et al. indicated that the lower the albumin level in KD children, the greater the risk of CALs (27).

In this study, increased ALT is also one of the independent predictors differentiating between KD and non-KD febrile illness. Most patients with elevated transaminase had only a mild elevation, less than twice the normal upper limit. ALT elevation is not an important cause of morbidity or mortality in KD patients, but it is a common finding during acute KD. Liver involvement ranges from the mild asymptomatic elevation of liver enzymes to severe cholestatic hepatitis and/or cholecystoid effusion (28). A US study identified ALT > 60 IU/L as a risk factor for IVIG non-responsive KD (29). Studies have indicated that KD patients with abnormally elevated liver enzymes tend to have an increased proportion of CALs (30).

From the literature review, this model is the first prediction model that uses a nomogram to distinguish KD from non-KD febrile illness. Compared with other clinical prediction tools or scoring systems, the nomogram has higher precision and optimal identification characteristics. The nomogram uses continuous scales to calculate the continuous probability of a particular outcome (10). Therefore, the nomogram provides superior personalized risk estimates that can contribute to modern medical decision-making.

This study has certain limitations. First, this is a single retrospective study but not of an entire country or multiple centers and thus may have selection bias. Second, the sample size is relatively small, but the variables of the qualified patients enrolled are complete and correct.

# Conclusion

In conclusion, our study demonstrated a novel prediction score system by using WBC, CRP, E%, albumin, and ALT to identify KD from other febrile illness. This study is the first to use a nomogram to develop a prediction model for KD, as well as to demonstrate the importance of eosinophil.

# Declarations

**Ethics approval and consent to participate:** All subjects gave their informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of Baoan Maternal and Child Health Hospital, Shenzhen, China approved the study (IRB No. LLSCHY2019-07-01-01).

**Consent for publication:** Not applicable

**Availability of the data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author upon a reasonable request.

**Competing interests:** We declared that we have no conflicts of interest in this work.

**Funding:** This study was supported by the Shenzhen Basic Research Grant (JCYJ 20170413165432016) and Sanming Project of Medicine in Shenzhen (SZSM201606088).

**Authors' contributions:** XPL, YSH and HCK conceptualized and designed the study, conceptualized the analyses for this article, drafted the manuscript, and revised each version of the manuscript. HBX conceptualized and designed the study, participated in the design of the questionnaire, conceptualized the analyses for this article, supervised all data analyses, and reviewed and revised each version of the manuscript. YS participated in the design of the questionnaire, conducted the analyses, and created the tables. XLL, WDH, ZQL, CYL and XL helped conceptualize this article, contributed to the interpretation of the study findings, and reviewed and revised the manuscript. All authors participated in team discussions of data analyses, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

**Acknowledgments:** We are particularly grateful for the patients who participated in this study.

# Abbreviations

Kawasaki disease, KD;

coronary aneurysms, CAA;

intravenous immunoglobulin, IVIG;

white blood cell count, WBC;

neutrophil percentage, N%;

Lymphocyte percentage, L%;

platelet count, PLT;

eosinophil percentage, E%;

mononuclear cell percentage, M%;

C reactive protein, CRP;

alanine aminotransferase, ALT;

aspartate aminotransferase, AST;

albumin, and erythrocyte sedimentation rate, ESR.

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# Tables

Table 1. Demographic data of the Kawasaki disease and non-KD febrile illness groups

| Group | KD | Non-KD febrile illness | P-value |
|---|---|---|---|
| Male gender (%) | 61.4% | 60.3% | 0.75 |
| Age (month) | 25.9±19.4 | 25.3±19.1 | 0.68 |
| Bodyweight (Kg) | 11.9±3.8 | 13.8±3.8 | 0.44 |
| WBC (x10^9/L) | 14.3±5.8 | 10.4±5.3 | 0.001 |
| Hemoglobin (g/L) | 107.8±10.5 | 113.3±12.3 | 0.001 |
| Platelet (x10^9/L) | 366.8±138.6 | 316.3±131.1 | 0.001 |
| N% | 60.3±17.2 | 45.8±27.5 | 0.001 |
| L% | 29.5±15.7 | 43.9±17 | 0.001 |
| M% | 7.8±3.5 | 10.2±5.7 | 0.001 |
| E% | 2.5±2.6 | 0.9±1.7 | 0.001 |
| CRP (mg/L) | 177.6±58.9 | 26.9±33.6 | 0.001 |
| ALB（g/L） | 37±5.3 | 40.8±4.1 | 0.001 |
| ALT (U/L) | 57.5±100.9 | 22.9±29.9 | 0.001 |
| AST (U/L) | 65.9±111 | 50.9±49.3 | 0.001 |
| PCT (ng/L） | 1.7±3.4 | 0.86±4.9 | 0.023 |

KD, Kawasaki disease; WBC, white blood cell count; N%, neutrophil percentage; L%, Lymphocyte percentage; PLT, platelet count; E%, Eosinophilic granulocyte percentage; M%, Mononuclear cell percentage; CRP, C reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; ESR, erythrocyte sedimentation rate

Table 2. Multivariate Logistic regression analysis of Kawasaki disease and non-KD febrile illness

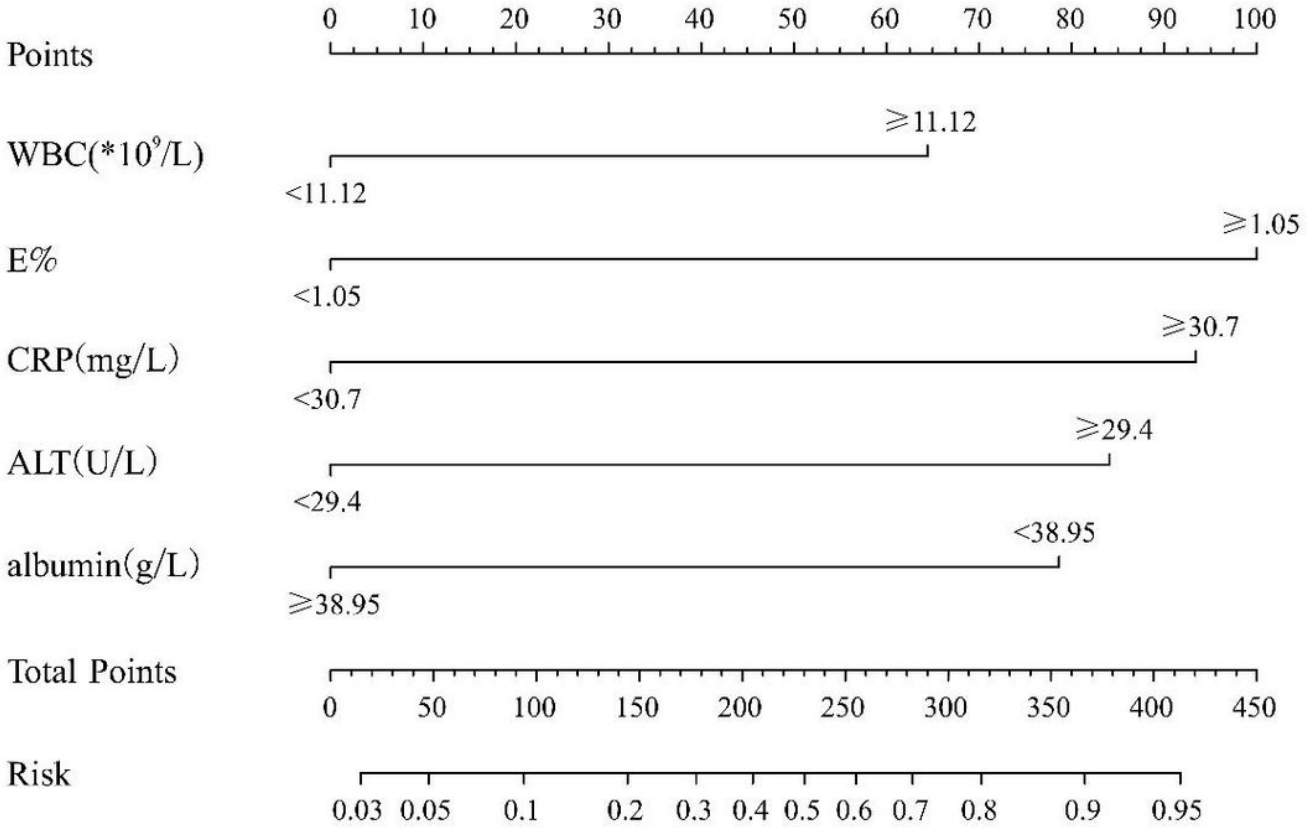
| | Sig. | OR | 95% C.I. for OR | |
|---|---|---|---|---|
| | | | Lower | Upper |
| WBC（≥11.12*10^9/L，＜11.12*10^9/L） | <0.001 | 2.826 | 1.723 | 4.637 |
| E% (≥1.05%,＜1.05%) | <0.001 | 5.015 | 3.068 | 8.197 |
| CRP (≥30.7mg/L,＜30.7mg/L) | <0.001 | 4.510 | 2.727 | 7.456 |
| ALT (≥29.41U/L,＜29.40U/L) | <0.001 | 3.881 | 2.193 | 6.869 |
| ALB (≥38.95g/L,＜38.95g/L) | <0.001 | 3.554 | 2.183 | 5.784 |
| Constant | <0.001 | 0.024 | | |

OR, Odds ratio; CI, confidence interval, WBC, white blood cell count; E%, Eosinophil percentage; CRP, C reactive protein; ALT, alanine aminotransferase; ALB, albumin

Table 3. The incidence risk of Kawasaki disease corresponding to the total score

| Total points | Kawasaki disease risk prediction (%) |
|---|---|
| 15 | 0.03 |
| 48 | 0.05 |
| 94 | 0.10 |
| 144 | 0.20 |
| 178 | 0.30 |
| 205 | 0.40 |
| 230 | 0.50 |
| 255 | 0.60 |
| 283 | 0.70 |
| 316 | 0.80 |
| 366 | 0.90 |
| 413 | 0.95 |

## Figures




## Figure 1

The Nomogram prediction score of Kawasaki disease in the differential diagnosis of non-Kawasaki disease febrile illness. WBC, white blood cell count; E%, Eosinophilic granulocyte percentage; CRP, C reactive protein; ALT , alanine aminotransferase

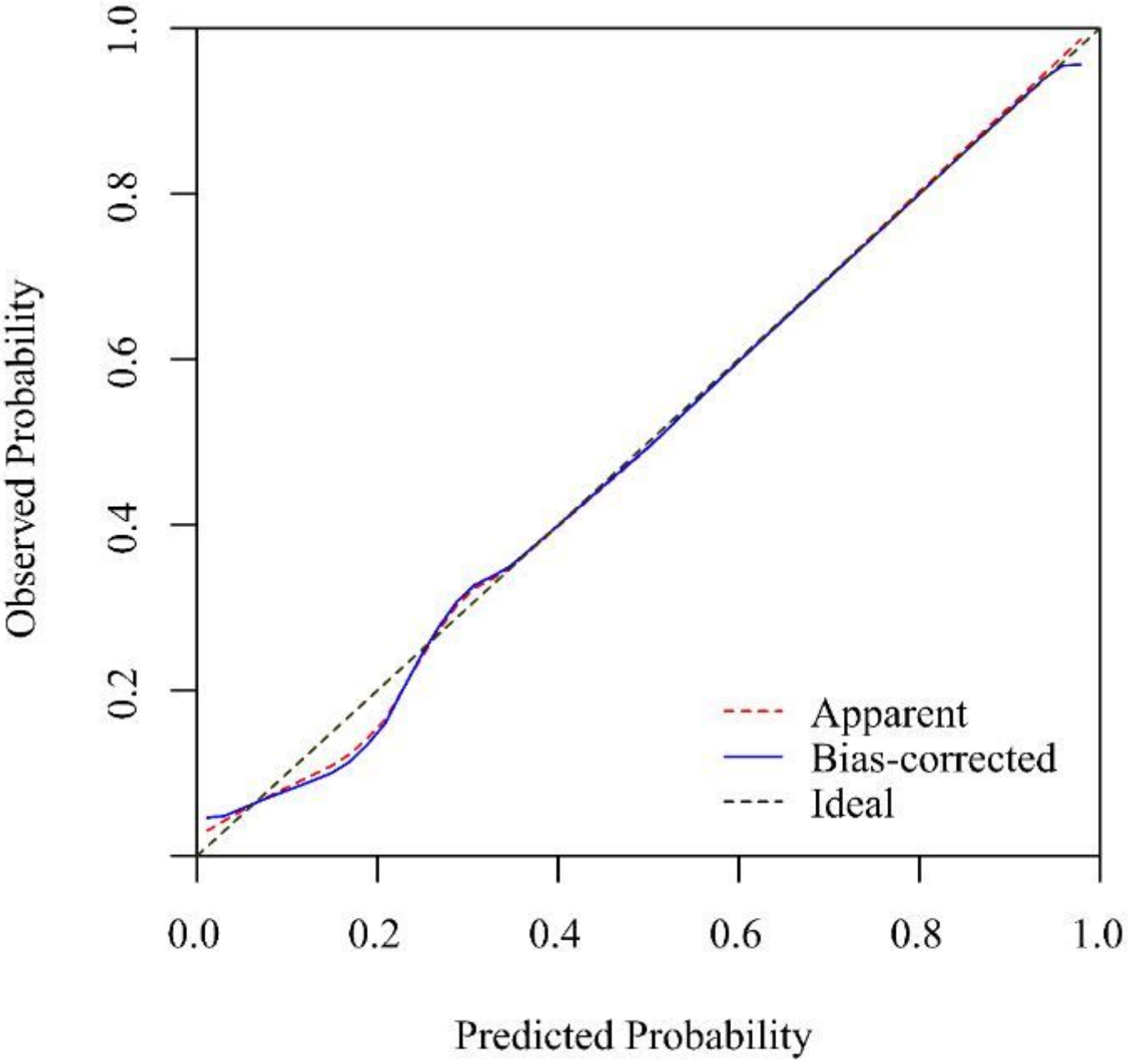



**Figure 2**

The calibration curves for the nomogram. The x-axis represents the nomogram-predicted probability, and the y-axis represents the actual probability of KD. Perfect prediction would correspond to the 45° black dashed line. The red dotted line represents the entire cohort (n = 238), and the blue solid line is bias-corrected by bootstrapping (B=1000 repetitions), indicating the observed nomogram performance.