Is There a Role for Laboratory Parameters in Predicting Coronary Artery Involvement in Kawasaki Disease?

Spielen Laborparameter bei der Vorhersage einer Beteiligung der Koronararterien beim Kawasaki-Syndrom eine Rolle?

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ABSTRACT

Background Kawasaki disease (KD) may cause cardiac and coronary complications. Since definite markers to accurately predict coronary involvement is not present, we aimed to analyze the role of hematological indices [neutrophil-to lymphocyte ratio (NLR), platelet-to lymphocyte ratio (PLR), lymphocyte-to monocyte ratio (LMR), and mean platelet volume (MPV)-to lymphocyte ratio (MPVLR)], prognostic nutritional index (PNI) and systemic immune-inflammation index (SII) in predicting coronary involvement of KD.

Patients The medical records of 134 KD patients admitted between January 2008 and December 2019 were investigated. Also, 268 age-matched healthy controls (HCs) were included in the study.

Methods KD patients were divided into two groups: KD with coronary artery lesions (KD-CALs) and KD without CALs. Logistic regression analysis was performed to determine parameters that may predict coronary involvement in children with KD.

Results Among KD patients, 39 (29.1 %) had CALs. When compared with HCs, the median levels of WBC, neutrophils, monocytes, eosinophils, platelets, MPV and, the values of NLR, PLR, MPVLR, SII were significantly higher; whereas lymphocyte count, PNI, platelet distribution width (PDW), LMR were markedly lower in the KD group ($p<0.001$ for all, except for $p = 0.010$ for eosinophil count). The CALs group's SII, PLR, and PNI values were significantly lower than those without ($p = 0.030$, $p = 0.032$, and $p <0.001$; respectively). Multivariable regression analysis revealed that PNI, SII, and gender (male) were associated with CALs in KD.

Conclusion Our analysis revealed that male sex, lower PNI, and lower SII levels were independently associated with CALs in children with KD.

ZUSAMMENFASSUNG

Hintergrund Die Kawasaki-Krankheit (KD) kann kardiale und koronare Komplikationen verursachen. Da definitive Marker zur genauen Vorhersage einer koronaren Beteiligung nicht vorhanden sind, wollten wir die Rolle hämatologischer Indizes [Neutrophilen-zu-Lymphozyten-Ratio (NLR), Thrombozyten-zu-Lymphozyten-Ratio (TLR), Lymphozyten-zu-Monozyten-Ratio (LMR) und mittleres Thrombozytenvolumen (MPV)-zu-

Lymphozyten-Ratio (MPVLR)], prognostischer Ernährungsindex (PNI) und systemischer Immunentzündungsindex (SII) bei der Vorhersage einer koronaren Beteiligung von KD analysieren.

Patienten Die Krankenakten von 134 KD-Patienten, die zwischen Januar 2008 und Dezember 2019 aufgenommen wurden, wurden untersucht. Außerdem wurden 268 altersangepasste gesunde Kontrollen in die Studie aufgenommen.

Methoden KD-Patienten wurden in zwei Gruppen eingeteilt: KD mit Koronararterien-Läsionen (CALs) und KD ohne CALs. Es wurde eine logistische Regressionsanalyse durchgeführt, um Parameter zu bestimmen, die eine koronare Beteiligung bei Kindern mit KD vorhersagen können.

Ergebnisse Unter den KD-Patienten hatten 39 (29,1 %) Koronararterien-Läsionen. Verglichen mit gesunde Kontrollen, waren die Medianwerte von Leukozyten, Neutrophilen, Monozyten, Eosinophilen, Blutplättchen, MPV und die Werte von NLR, TLR, MPVLR, SII signifikant höher, während Lymphozytenzahl, PNI, Blutplättchenverteilungsbreite (PDW), LMR deutlich niedriger als in der KD-Gruppe ($p = 0{,}001$ für alle, außer $p = 0{,}010$ für die Eosinophilenzahl) waren. Die SII-, PLR- und PNI-Werte der CALs-Gruppe waren signifikant niedriger als die ohne ($p = 0{,}030$, $p = 0{,}032$ bzw. $p < 0{,}001$). Eine multivariable Regressionsanalyse ergab, dass PNI, SII und Geschlecht (männlich) mit CALs bei KD assoziiert waren.

Schlussfolgerung Unsere Analyse ergab, dass männliches Geschlecht, niedrigere PNI- und niedrigere SII-Werte unabhängig voneinander mit CALs bei Kindern mit KD assoziiert waren.

Introduction

Kawasaki disease (KD) is a multisystemic vasculitis typically seen in children under five years. It is the leading cause of acquired heart disease in children, especially in developing countries [14]. Some clinical and epidemiological data support an infectious cause, but the etiology and pathogenesis remain unclear [4]. It is diagnosed when four of the five typical clinical findings (bilateral non-exudative conjunctivitis, polymorphous rash, oral mucosal changes, erythematous induration of the extremities, and cervical lymphadenopathy) are present and other clinically similar diseases are excluded. If not treated, it may cause coronary artery aneurysms and myocardial ischemia, infarction, and sudden death. The presence of parameters to predict coronary involvement may be important since morbidity and mortality mainly occur because of cardiac or coronary complications [14].

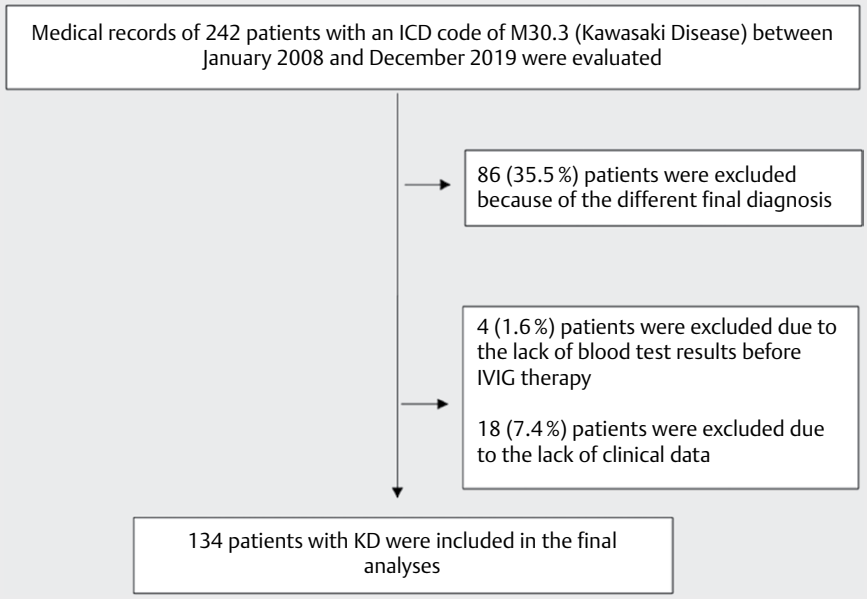
There is not any definite marker that may accurately predict coronary involvement. However, some published articles suggest the importance of hematological indices, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and mean platelet volume (MPV)-to-lymphocyte ratio (MPVLR) for predicting coronary involvement in KD [3, 4, 9, 12]. Another parameter studied is the prognostic nutritional index (PNI), calculated by a formula including serum albumin level and lymphocyte count [16]. Systemic immune-inflammation index (SII), positively correlated with neutrophil, platelet counts and negatively correlated with lymphocyte counts, was studied recently in patients with cancer, coronary artery stenosis, and infective endocarditis [1, 8, 15]. Although some studies suggest marginal to moderate relationships between these parameters and KD characteristics, data is limited on this subject. Furthermore, we aimed to evaluate the role of these parameters in the prediction of coronary involvement in patients with KD.

Materials and Methods

This retrospective case-control study was conducted by evaluating the medical records of patients with KD aged between 1–18 years who had been hospitalized between January 2008 and December 2019. The diagnosis of KD was made according to the American Heart Association (AHA) guideline [14]. Complete Kawasaki disease (cKD) was diagnosed when the children had a fever persisting at least five days, and ≥ 4 principal clinical findings were present (rash, conjunctivitis, cervical lymphadenopathy, erythema and edema of the hands and feet, oral mucosa changes). Patients with four or fewer principal clinical findings were diagnosed with incomplete Kawasaki disease (iKD) when supportive laboratory, clinical and echocardiographic findings were present. All patients with KD were treated with intravenous immunoglobulin (IVIG) (2 g/kg as a single intravenous infusion) plus oral aspirin (60 mg/kg/day) within the first 10 days of illness from the beginning of fever. The aspirin dose was tapered to 5 mg/kg/day as the fever was absent for 48–72 hours and administered for 6–8 weeks. In patients with coronary artery lesions (CALs), aspirin was continued until there was no evidence of CALs. IVIG resistance was defined as a persistent fever lasting > 36 h after IVIG completion or recurrent fever associated with KD symptoms after an afebrile period [14]. The second IVIG (2 g/kg given as a single intravenous infusion) was administered if the patient had IVIG resistance. No patients received additional treatment such as infliximab, plasma exchange, and cytotoxic agents.

The exclusion criteria were as follows: (1) patients who received IVIG therapy in another hospital; (2) lack of clinical and laboratory data records during hospitalization; and (3) patients with other diagnoses that are known to mimic KD. A schematic description of the inclusion/exclusion of patients is shown in ▶ **Fig. 1**. Two hundred sixty-eight age and sex-matched healthy controls (HCs) who had hemogram and albumin results for any reason were selected to show and compare normal values of indexes.

Patients underwent standardized transthoracic echocardiograms by Philips iE33 xMATRIX [Bothell, WA 98021-8431 USA]. Coronary artery lesion was defined as Z scores that were normalized according to body surface area as follows: (i) no involvement (z score < 2.0); (ii) dilation (z score ≥ 2.0 to < 2.5) or if initially < 2, an increase of ≥ 1 in z score during follow-up; (iii) aneurysm (z score ≥ 2.5; z ≥ 10 for giant aneurysm) [14]. Echocardiography was performed at admission and the 2nd and 4th weeks, 3rd and 6th months after disease onset. KD patients were divided into two groups: KD with CALs and KD without CALs.



▶ **Fig. 1** Schematic description of inclusion/exclusion of patients. 75x53 mm (300 x 300 DPI)

Patient demographics, findings on examination, laboratory parameters at admission such as white blood cell count (WBC), hemoglobin, mean corpuscular volume (MCV), mean platelet volume (MPV), platelet distribution width (PDW), red blood cell distribution width (RDW), platelet, neutrophil, lymphocyte, monocyte and eosinophil counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin levels were recorded. The same hemogram parameters and albumin levels (except for acute phase reactants) were also recorded for the HCs group. In KD patients, we compared the laboratory results obtained at admission before IVIG administration.

The NLR, PLR, MPVLR were calculated by dividing the neutrophil count, platelet count, and MPV values by lymphocyte count; LMR was calculated by dividing the lymphocyte count by monocyte count. Prognostic nutritional index was calculated with a formula that includes serum albumin level and lymphocyte count [PNI = 10 x albumin (mg/dl) + 0.005 x lymphocyte count (/mm^3)] [7]. The systemic immune-inflammation index was calculated with a formula including the neutrophil counts, lymphocyte, and platelet levels (SII = platelets × neutrophils/lymphocytes) [8].

Statistical methodology

The SPSS software for Windows was used for all analyses. Normality of distribution was assessed with Q-Q plots and the Shapiro Wilk test for quantitative variables. Comparisons between groups for quantitative parameters were performed with the Student's *t*-test or Mann-Whitney *U* test depending on normality of distribution. Categorical variable analyses were conducted via Chi-square tests. Multivariable regression with the backward conditional method was performed to determine independently effective factors on the presence of coronary involvement. The parameters with a p-value lower than or equal to 0.100 in univariate comparisons were added to the model. The receiver operating curve (ROC) analysis was used to analyze the capability of various parameters in identifying coronary involvement according to the area under curve (AUC) values. The Youden *J* Index was calculated for the determination of cut-off values. Any *p* value lower or equal to 0.05 was accepted to demonstrate statistical significance.

Results

A total of 134 KD patients [89 (66.4 %) males, median age 37 months (range, 12–107 months)] and 268 HCs [164 males (%61.1), median age 37 months (range, 12–120 months)] were enrolled. Among the KD patients, 74 (55.2 %) were diagnosed as iKD and 60 (44.7 %) as cKD. Duration of fever at admission was median 7 days (min-max, 3–15 days). All patients were treated with IVIG. Six (4.4 %) patients were IVIG resistant, and the second IVIG infusion was commenced, and none were treated with steroids or other immunosuppressant agents.

When compared with HCs, the median levels of WBC, neutrophils, monocytes, eosinophils, platelets, MPV and, the values of NLR, PLR, MPVLR, SII were significantly higher; whereas lymphocyte count, PNI, PDW, LMR were markedly lower in the KD group (▶ **Table 1**).

Coronary artery lesions were detected in 39 (29.1 %) patients, 30 (22.3 %) of them were iKD, and 9 (%6.7) were cKD. Three (2.2 %) patients had coronary aneurysms, and none of them had a giant coronary aneurysm. Comparisons were performed between patients with and without CALs. The SII, PLR, and PNI values were significantly lower in the CALs group (▶ **Table 2**). Two (5.1 %) of the patients with coronary involvement did not attend follow-up visits two years after the KD diagnosis, and coronary dilatation persisted in these two years. In other 37 patients, all demonstrated a return to normal coronary limits, and the time elapsed until regression of coronary dilatation was median 4 months (range, 2–48 months).

▶ **Table 1** Comparison of laboratory parameters between the Kawasaki disease (KD) group and healthy controls.

	KD group (n = 134)	Healthy controls (n = 268)	p-value
WBC ($x10^3$/μl)	12.26 (3–29.7)	8.14 (5–15.4)	<**0.001**
Neutrophil ($x10^3$/μl)	7.42 (1.21–21.86)	3.07 (1.33–8.63)	<**0.001**
Lymphocyte ($x10^3$/μl)	3.05 (1.01–13.20)	3.80 (0.81–9.8)	<**0.001**
Monocyte ($x10^3$/μl)	0.89 (0.21–3.11)	0.40 (0.12–1.16)	<**0.001**
Eosinophil ($x10^3$/μl)	0.24 (0.1–3.3)	0.20 (0.01–1.3)	**0.010**
Platelet count ($x10^3$/μl)	450.5 (111–1226)	350 (201–684)	<**0.001**
MPV (fl)	7.9 (6.1–10.6)	7.6 (6.2–10.1)	<**0.001**
PDW (%)	38.05 (10–61.8)	43.4 (12.8–64.3)	<**0.001**
NLR	2.56 (0.22–12.5)	0.79 (0.18–6.11)	<**0.001**
PLR	146.2 (20.6–425.6)	89.1 (35.7–285.1)	<**0.001**
MPVLR	2.6 (0.59–9.34)	2 (0.77–9.38)	<**0.001**
LMR	3.55 (0.85–13.47)	9.6 (1.76–25.79)	<**0.001**
PNI	35 (20.03–47.02)	43.04 (36.02–51.01)	<**0.001**
SII	1107 (113–7912.7)	280 (65.7–1715.8)	<**0.001**

All values are given as median (min-max). KD: Kawasaki disease, LMR: lymphocyte-to-monocyte ratio, MPV: mean platelet volume, MPVLR: mean platelet volume-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PDW: platelet distribution width, PLR: platelet-to-lymphocyte ratio, PNI: Prognostic nutritional index, SII: Systemic immune-inflammation index, WBC: white blood cell count.

▶ **Table 2** Comparison of laboratory parameters between Kawasaki disease patients with and without coronary artery lesions (CALs)

	KD patients with CALs (n = 39)	KD patients without CALs (n = 95)	p-value
WBC ($x10^3$/μl)	12.30 (3–26.6)	12.21 (4.7–29.7)	0.754
Neutrophil ($x10^3$/μl)	6.17 (1.2–21.10)	7.66 (1.33–21.86)	0.097
Lymphocyte ($x10^3$/μl)	3.52 (1.01–13.2)	2.89 (1.01–7.43)	0.221
Monocyte ($x10^3$/μl)	0.91 (0.29–2.33)	0.84 (0.21–3.11)	0.161
Eosinophil ($x10^3$/μl)	0.21 (0.01–1.20)	0.29 (0.03–3.30)	0.473
Platelet count ($x10^3$/μl)	422 (157–910)	464 (111–1226)	0.227
MPV (fL)	7.80 (6.50–9.2)	7.90 (6.10–10.60)	0.680
PDW (%)	37.9 (13–56.1)	38.4 (10–61.80)	0.946
NLR	1.81 (0.22–10.17)	2.66 (0.40–12.50)	0.097
PLR	127 (30–344.3)	159.6 (20.6–425.6)	**0.032**
MPVLR	2.22 (0.59–9.34)	2.63 (1.01–7.91)	0.418
LMR	3.64 (0.87–12.57)	3.50 (0.85–13.47)	0.739
PNI	29.01 (21.01–38.02)	36.02 (20.03–47.02)	<**0.001**
SII	742.6 (126.6–4446.5)	1140.8 (113–7912.7)	**0.030**

All values are given as median (min-max). CAL: Coronary artery lesions, KD: Kawasaki disease, LMR: lymphocyte-to-monocyte ratio, MPV: mean platelet volume, MPVLR: mean platelet volume-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PDW: platelet distribution width, PLR: platelet-to-lymphocyte ratio, PNI: Prognostic nutritional index, SII: Systemic immune-inflammation index, WBC: white blood cell count

▶ **Table 3** Factors independently associated with coronary artery lesions of KD, multivariable regression analysis.

	β	Standard Error	p-value	Exp(β)	95.0% Confidence Interval for Exp(β)	
PNI	−0.305	0.059	**<0.001**	0.737	0.657	0.828
SII	−0.001	0.000	**0.031**	0.999	0.999	1.000
Male sex	1.731	0.588	**0.003**	5.644	1.782	17.877

Dependent Variable: Coronary artery lesions; Nagelkerke $R^2 = 0.476$. KD: Kawasaki disease, PNI: prognostic nutritional index, SII: systemic immune-inflammation index

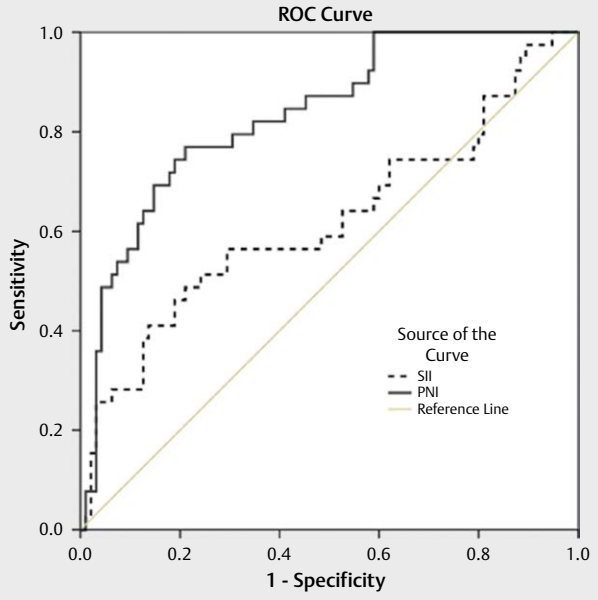
Multivariable regression analysis was performed with coronary involvement as the dependent variable, and the backward conditional method revealed that PNI, SII, and gender (boys) were associated with CALs in KD (▶ **Table 3**). Next, ROC curve analysis was performed to identify the diagnostic ability of PNI and SII in determining coronary involvement among patients with KD (▶ **Fig. 2**). Values of AUC, cut-off points determined by the Youden J Index, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for each parameter are depicted in ▶ **Table 4**.

Discussion

The importance of some hematological parameters has been studied in a variety of diseases such as cancer [5], pulmonary embolism [20], ischemic heart diseases, and coronary artery disease [6]. The role of these parameters in predicting coronary artery involvement in patients with KD is not clear. Some articles claim that these parameters could help predict CALs, while others claim the opposite. Most publications exploring these parameters in KD studies have attempted to predict IVIG resistance [10, 17, 21]. The current study revealed that male sex, lower PNI, and lower SII levels were independently associated with CALs in children with KD.

The Harada score, commonly used in patients with KD to predict IVIG resistance and coronary aneurysm, identified male sex as a factor associated with coronary artery aneurysms [18]. In our study, the male sex increased the risk of coronary involvement by 5.6 fold. This has been supported by studies showing that the male sex increased the risk of CALs [2]. Our results were also compatible with previously reported effects of sex; therefore, physicians should conduct a detailed follow-up of boys since they appear to be more likely to develop coronary complications.

The prognostic nutritional index is a nutritious and immunologic parameter of which higher levels were thought to be related to better outcomes due to better nutrition and immune capacity. That was used to predict mortality in cancer patients [22], the outcome of children who underwent cardiac surgery [19], and mortality in patients with myocardial ischemia [11]. A study that compared PNI levels of KD patients with and without coronary aneurism found that PNI was a predictor for coronary aneurism. They detected a cut off point of PNI with the level of 55.24, with a sensitivity of 50 % and a specificity of 67.8 % [16]. In our study, similar to the previous one, PNI was lower in patients with CALs. Our results showed that PNI might be used as a predictor with a cut-off level of < 31.5 in KD patients with CALs. We did not group the patients with coronary aneurism, and we included all patients with any coronary involvement. Our lower threshold may be due to characteristic, age-related and genetic variations of patients included. We believe that using PNI level, which may be calculated only with albumin and lymphocyte levels, can be used to predict coronary involvement in KD patients.



▶ **Fig. 2** ROC curves for the diagnosis of coronary involvement with PNI and SII values. PNI indicates prognostic nutritional index, and SII indicates systemic immune-inflammation index. 74x53 mm (300 x 300 DPI)

SII is a new marker which has been studied recently in predicting coronary artery stenosis in adult patients [8] and mortality in infective endocarditis [1]. Since KD is a systemic inflammatory disorder and blood cell counts change in the acute phase, we investigated whether this parameter was used to predict CALs in children with KD. In our study, SII levels were significantly higher in patients with KD than HCs. Also, we found lower levels of SII in KD patients with CALs than those without. Our results showed that SII may be used to predict coronary involvement in children with KD with a cut-off level of < 668.6. A recent study investigated SII and its predictive ability in IVIG resistance and cardiovascular complications of KD patients. The authors found significantly higher levels of SII in KD patients with myocarditis, and valve regurgitation; however, they did not explicitly evaluate the role of SII in coronary artery lesions. They suggested that SII may only serve as a complementary laboratory marker [13]. We believe that further studies may be helpful to better understand its role in KD.

The importance of all these indices includes that they can be calculated easily with a routine blood check alone which is always obtained when KD is suspected, without any additional tests or cost. Also, because these indices are the result of calculations, we think they may be more reliable than individual blood parameters. Previous studies focused on these parameters in predicting IVIG resistance; since the percentage of our patients who had IVIG resistance was lower, we could not investigate these parameters in predicting IVIG resistance. To our knowledge, this study is among a very few studies which evaluated all these indices together in coronary involvement of patients with KD. The strength of this study includes a relatively high number of KD patients and age-matched control group and the evaluation of both hematological indices, PNI, and SII levels. Limitations of this study include a single-center setting, retrospective design, and all restrictions associated with this design. The dynamic variability of these parame-

▶ **Table 4** Diagnostic accuracy analysis of parameters that were identified to be predictive for coronary artery lesions in KD patients

	AUC (95 % CI)	Cut-off point	Sensitivity	Specificity	Accuracy	PPV	NPV
PNI	0.834 (0.761–0.908)	< 31.5	74.4 %	81.1 %	79.1 %	61.7 %	88.5 %
SII	0.620 (0.506–0.734)	< 668.6	48.7 %	78.9 %	70.1 %	48.7 %	78.9 %

AUC: Area under the curve, NPV: Negative predictive value, PLR: platelet-to-lymphocyte ratio, PNI: prognostic nutritional index, PPV: Positive predictive value, SII: Systemic immune-inflammation index

ters during the disease course should also be considered; however, a single measurement does not reflect their dynamics. Also, other possible confronting factors affecting the level of hematological indices- such as standardization and instrument-related variations, may be another limitation.

Conclusion

Various parameters have been studied to predict cardiac and/or coronary involvement of KD. Our analysis revealed that male sex, lower PNI, and lower SII levels were associated with coronary involvement in children with KD. The present results are interpreted concerning the published literature, we believe that nutritional and immunological status, as measured by PNI, could prove to be a supportive factor in the assessment of CALs risk in patients with KD. It may be feasible to suggest that patients with KD who have a PNI level of < 31.5 should be more carefully assessed about cardiac involvement. Early therapy initiation may help prevent cardiac complications in these patients. Further studies should aim to categorize patients' clinical and demographic characteristics better when attempting to elucidate the role of these parameters in KD and its complications.

Contributor's Statement

Contribution to study concept and design. All authors Literature review. All authors Acquisition of data. All authors Analysis and interpretation of data. R.Yalçınkaya, A. Fettah, F.N. Öz Drafting or revising the manuscript. R. Yalçınkaya, F.N. Öz, G. Tanır

Conflict of Interest

The authors declare that they have no conflict of interest.

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