RESEARCH PAPER

Neutrophil-Lymphocyte Ratio for Predicting Coronary Artery Lesions in Children With Kawasaki Disease

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Received: April 26, 2022;
Initial review: June 06, 2022;
Accepted: November 30, 2022.

Background: Coronary artery lesions (CAL) are a specific feature of Kawasaki disease (KD), and develop during the second week of illness. This study was conducted to determine whether Neutrophil: Lymphocyte Ratio (NLR), assessed between the fourth and sixth day of fever onset in children with KD, can predict coronary artery lesion (CAL) development. **Methods:** In this review of hospital records, data of patients with KD admitted at our center between January, 2016 and January, 2020 was retrieved. The patients were divided into two groups based on the presence of CAL, and clinical characteristics of patients were compared between the two groups. **Results:** Out of the 79 patients enrolled, CAL was found in 40 (50.6%) patients and intravenous immunoglobulin (IVIg) resistance was seen in 13 (16.5%) patients. Multivariate logistic regression revealed NLR as an independent predictor of CAL [OR (95% CI) 2.0 (1.2,3.1); $P < 0.001$], and erythrocyte sedimentation rate (ESR) [OR (95% CI) 1.03 (1.001,1.1) $P=0.04$], as an independent predictor of IVIg resistance. NLR ≥2.08 was 82% sensitive and 80% specific in predicting CAL. ESR ≥88 mm/h was 85% sensitive and 64% specific in predicting IVIg resistance. **Conclusions:** NLR is an independent predictor of CAL in KD. NLR ≥2.08 done between the fourth and sixth day of fever onset may identify children with KD at risk of CAL.

Keywords: *Aneurysm, Erythrocyte sedimentation rate, Intravenous immunoglobulin resistance, Prognosis.*

PII: S097475591600477

Kawasaki disease (KD) is a systemic vasculitis resulting in inflammation of medium-sized vessels, predominantly the coronary arteries [1], with an incidence of 4.54 cases per 1,00,000 children below 15 years [2]. The most dreaded complication of Kawasaki disease is coronary artery aneurysm, which occurs in around 15-25% of patients [3].

Prognostic scores/biomarkers predicting the development of CAL will be of significant clinical utility to initiate early, aggressive treatment and follow up strategy, especially in resource-limited settings. The existing scoring systems- Kobayashi, Egami and Sano scores were designed to predict IVIg resistance rather than CAL [4]. The Harada score, which was designed to predict CAL, identified CAL with 90% sensitivity in US population, and with 83% sensitivity and 47% specificity in Turkish population [5]. Other novel biomarkers like NT-proBNP, thrombospondin-1, IL-12, IL-17, tenascin C have not been reliably validated in predicting CAL [6].

This study was conducted to study the role of Neutrophil-lymphocyte ratio (NLR) and other markers in predicting the development of coronary artery abnormalities and intravenous immunoglobulin resistance in children with KD.

METHODS

We extracted hospital data of all admitted children diagnosed as KD between January, 2016 and January, 2020 at tertiary referral hospital. Those with incomplete laboratory or echocardiographic details were excluded. As per hospital protocol, all patients suspected to have KD underwent 2D-echocardio-graphy at admission or before administering intravenous immunoglobulin (IVIg) and at least 24 hours after IVIg administration. The coronary artery *z*-scores were calculated using the Cardio Z application, Version 3.0, as per reference values by Dallaire, et al. [7]. All patients were treated according to the American Heart Association (AHA) guidelines [8]. A repeat dose of IVIg (2 g/kg) was administered no earlier than 36 hours after the first dose completion for patients with IVIg resistance.

The standard definitions included Classical KD,

incomplete KD, atypical KD, CAL and IVIg resistance were defined according to AHA, 2017 guidelines [8]. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count in the first complete blood count (CBC) sample between the fourth and sixth days of onset of fever. Platelet-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the absolute lymphocyte count in the first CBC sample between the Day 4-6 of onset of fever. Time to occurrence of CAL was the total number of days since the onset of fever till the day the echocardiography demonstrated CAL for the first time.

The patients were divided into two groups based on the presence or absence of CAL, and the clinical characteristics of the patients were compared across the two groups.

Statistical analysis: Normality was assessed using the Kolmogorov-Smirnov test. Continuous data were expressed as median (IQR), and nominal data were expressed as proportions. The predictive factors for CAL and IVIg resistance were compared and analyzed using the Chi-square test for nominal variables and the Mann-Whitney *U* test for continuous variables. $P<0.05$ was considered statistically significant. Those variables with $P<0.05$ were analyzed for their predictive capacity using multivariate logistic regression for categorical variables, and linear regression for continuous variables. The receiver operating characteristic (ROC) curve was plotted for the variables found significant in multivariate analysis, and cut off value with the maximum Youden index was estimated. Survival analysis was undertaken with time to occurrence of CAL as the time to event. Kaplan-Meier survival analysis was plotted for the time to occurrence of CAL and the risk factors and compared using the Log-Rank test. The Cox-proportional hazard model was used to determine the significant predictors of time to occurrence of CAL. Data were evaluated using SPSS version 25.0.

RESULTS

Of the 103 records of eligible children identified, data of 79 patients was eligible for inclusion; 49 of them being diagnosed with incomplete disease, and 11 with atypical disease. CAL was found in 40 (50.6%) patients. Thirty-two (40.5%) patients had CAA, and 8 (10.1%) had CAD. IVIg resistance was seen in 13 (16.5%) patients.

Table I Baseline Clinical and Demographic Characteristics of Children With Kawasaki Disease Enrolled in the Study (*N*=79)

	Without CAL (n=39)	*CAL (n=40)*	*IVIg responsive (n=66)*	*IVIg resistant (n=13)*
Male[a]	27 (69.2)	29 (72.5)	48 (72.7)	8 (61.5)
Conjunctivitis[a]	27 (69.2)	22 (55)	43 (65.2)	6 (46.2)
Rash[a]	25 (64.1)	25 (62.5)	40 (60.6)	10 (76.9)
IVIg resistance[a]	2 (5.1)	11 (27.5)[b]	-	-
CAL[a]	-	-	33 (50)	11 (84.6)[b]
Age (years)	3 (1.17, 8.5)	2 (0.75, 5)	3 (0.9, 7.2)	2 (0.5, 4)
Hemoglobin (g/dL)	9.9 (8.6, 10.9)	9.4 (8.4, 10.4)	9.7 (8.4, 10.5)	9.6 (7.8, 10.3)
Total leukocyte count (x10^9 cells/L)	12.19 (9.2, 15.7)	17 (10.4, 23.2)[b]	13.5 (8.9, 19.1)	22.0 (16.1, 27.6)
Platelet count (x10^9 cells/L)	3.46 (1.5, 5.1)	4.0 (2.3, 5.4)	3.4 (1.4, 5.1)	4.6 (3.6, 7.0)
Neutrophil-lymphocyte ratio	1.6 (1.2, 2.7)	3.5 (2.1, 4.5)	2.44 (1.76, 4.11)	3.06 (1.92, 4.83)
Platllet-Lymphocyte ratio	85.5 (51.7, 90.6)	110.8 (71.5, 104.8)[b]	86.9 (54.7, 160.3)	110.8 (73.5, 135.9)
Aspartate aminotransferase (U/dL)	38 (24.5, 49)	30 (22.5, 40.5)	33 (22, 51)	28.5 (23, 41.5)
Alanine aminotransferase (U/dL)	28 (16.5, 73)	27 (17, 33.5)	26.5 (18, 49.7)	21 (13, 28.8)
Albumin (g/dL)	3.2 (2.9, 3.5)	3.2 (2.9, 3.6)	3.2 (2.7, 3.6)	3.2 (2.9, 3.4)
C-reactive Protein (mg/dL)	6.1 (3.4, 12.5)	6.4 (4.1, 16.2)	6.2 (3.1, 17.3)	6.4 (3.6, 8.3)
Erythrocyte sedimentation rate (mm/h)	79 (58, 97.5)	92 (58.8, 113.5)	80 (58.8, 104.3)	110 (93.8, 128.8)[b]
Sodium (mEq/L)	133 (131, 134)	132 (131, 134.5)	132 (130, 134)	132 (132, 133)
Duration of fever at presentation (d)	5 (3, 5)	5 (3,6)	5 (4, 7.2)	7 (5, 9.5)
Time to detection of CAL (d)	-	7 (6, 10.2)	-	-
Time to IVIg administration (d)	7 (5.5, 9)	7 (6, 10.2)	6 (5, 10)	8 (7, 11)
Time to defervescence (d)	8 (6, 10)	8 (7, 12.5)	7 (6, 11)	13 (10.3, 22.8)[b]

Values are in median (IQR) or [a] no.(%). [b]P,0.05. CAL-coronary artery lesion, IVIg-intravenous immunoglobulin.

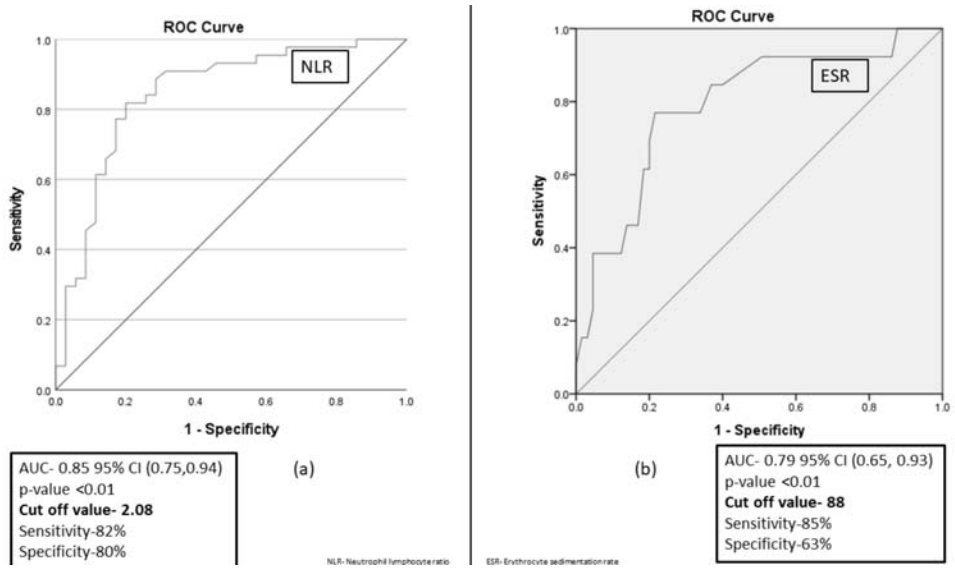

Fig. 1 Receiver-operating characteristic curve showing *a*) neutrophil-lymphocyte ratio (NLR) in predicting coronary artery lesions, and *b*) erythrocyte sedimentation rate (ESR) in predicting IVIg resistance.

Table I depicts the comparison of demographic and clinical characteristics between patients with and without CAL, and IVIg resistance, respectively. While children without CAL had significantly higher prevalence of conjunctivitis, children with CAL had higher total leukocyte count (TLC), NLR and PLR. Children with CAL were more likely to be IVIg resistant than those without. Further, children with IVIg resistance had higher TLC, ESR and were more likely to have had CAL than those without IVIg resistance.

On multivariate regression analysis (**Table II**), NLR was found to be an independent predictor for CAL [OR (95% CI) 2.0 (1.2,3.1); *P*<0.001]. Also, ESR was an independent predictor for IVIg resistance [OR (95% CI) 1.03 (1.0,1.1); *P*=0.04].

Table II Multivariate Analysis of the Risk Factors for Coronary Artery Lesion and IVIg Resistance

Risk factors	OR (95% CI)	*P value*
Coronary artery lesion		
Conjunctivitis	0.3 (0.1, 1.1)	0.06
IVIg resistance	2.6 (0.4, 17.4)	0.32
TLC	1.0 (1.0, 1.0)	0.15
NLR	2.0 (1.2, 3.1)	<0.001
PLR	1.0 (1.0, 1.0)	0.51
IVIg resistance		
CAL	1.80 (0.3, 12.8)	0.56
TLC	1.00 (1.0, 1.0)	0.51
Platelet count	1.10 (0.8, 1.6)	0.61
NLR	1.02 (0.9, 1.2)	0.81
ESR	1. 03 (1.0, 1.1)	0.04

IVIg-intravenous immunoglobulin; CAL-coronary artery lesion; TLC-total leukocyte count; NLR-neutrophil-lymphocyte ratio; PLR-platelet lymphocyte ratio.

ROC curves for NLR and ESR were constructed to determine the appropriate cutoff values that predicted CAL and IVIg resistance, respectively (**Fig. 1**). An NLR value of 2.08 and above was 82% sensitive and 80% specific in predicting CAL [AUC (95% CI) 0.85CI (0.75, 0.94); *P*<0.001)]. ESR of ≥88 was 85% sensitive and 64% specific in predicting IVIg resistance [AUC (95% CI) 0.79 (0.65, 0.93); *P*=0.002]. The time to development of coronary artery lesion in patients with NLR ≥2.08 was 7.7 days as compared to 25.6 days in those with NLR<2.08 [hazard ratio (95%CI) 1.08 (1.03,1.13); *P*<0.001] (**Fig. 2**).

DISCUSSION

In our study, the prevalence of CAL was 50.6%, which was higher than previous studies. This could partly be attributed to referral bias, retrospective nature of the study, exclusion of cases due to incomplete data, and partly to the fact that some of the incomplete KD masquerade viral exanthem and hence could be misdiagnosed unless a CAL is found. This relatively higher frequency of CAL needs to be confirmed in prospective studies.

In the early phase of KD, activated neutrophil-mediated endothelial injury is the likely pathogenesis of KD vasculitis. Therefore, NLR is higher in the initial phase, which gradually decreases with time. In our study, NLR and PLR, before administration of IVIg, were found to be significant predictors for CAL in univariate analysis. After

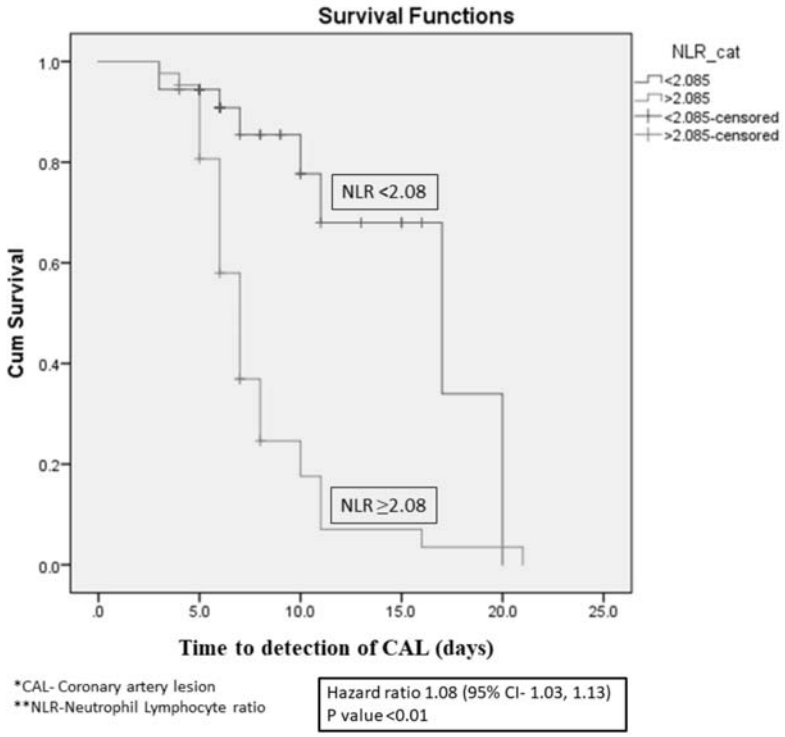

Fig. 2 Kaplan-Meier analysis curve showing time to detection of coronary artery lesions (CAL) in patients with neutrophil-lymphocyte ratio (NLR) of ≥2.08 and <2.08.

multivariate regression analysis, an NLR cut-off score of 2.08 reliably predicted CAL, with moderately good sensitivity and specificity. Seven out of 36 patients with NLR<2.08 had CAL, while 33 out of 43 patients with NLR>2.08 had CAL in our study. The usefulness of NLR in predicting CAL was demonstrated only in two studies previously [9,10], where one was less sensitive, and the other had poor specificity. Ha, et al. [9] concluded that an NLR cutoff of 5.49 during the febrile phase predicted IVIg resistance with 39% sensitivity and 86% specificity. A cut off of 4.86 predicted coronary aneurysms with 60% sensitivity and 72% specificity. In another study from Turkey, NLR>1.32 predicted CAL with 92.3% sensitivity but was only 38.8% specific [10]. A retrospective study from Japan introduced a scoring system constituting NLR and PLR and concluded that the combination of NLR ≥3.83 and PLR ≥1.5 predicted IVIg resistance with high sensitivity and specificity [11]. Further studies have shown the role of NLR and/or PLR in predicting IVIg resistance, but neither predicted the occurrence of CAL [12,13]. The meta-analysis [14] focusing on the role of NLR in predicting IVIg-resistant KD had an overall pooled sensitivity of 66% and specificity of 71%, with an area under the summary receiver operating curve (AUSROC) being 0.795. The subgroup analysis revealed that NLR detection after initial IVIg administration had larger AUSROC than pre-IVIg NLR [pooled sensitivity-58%; pooled specificity-77%; AUSROC-0.844]. In our study, NLR alone or in combination with PLR failed to predict IVIg resistance. An ESR cut-off of 88 predicted IVIg resistance with 85% sensitivity and 64% specificity, though the number of patients with IVIg resistance was low.

The median time to detect CAL in our study was seven days, and the median time to presentation to the hospital was five days. This gives a lead time of 2 days and NLR application on the day of admission could help predict CAL and administer IVIg upfront, reducing CAL incidence.

There are certain limitations in our study. Being a retrospective study, it was subject to bias. Patients who did not have documented blood investigations before the diagnosis of KD could not be enrolled. The NLR after administration of IVIg was not available and hence could not be computed. Moreover, only the presence of CAL was evaluated, while neither the morphological characteristics nor its severity was assessed owing to the study's retrospective nature.

To conclude, NLR could offer direction whenever a

WHAT THIS STUDY ADDS

- Neutrophil-lymphocyte Ratio ≥2.08, between the fourth and sixth days of onset of fever, can provide two days lead time in diagnosing coronary artery lesions in Kawasaki disease.

clinician faces a diagnostic dilemma of tropical infection in a child with clinical features compatible with incomplete KD. A high NLR value (≥2.08) between days 4 and 6 of fever onset, before administration of IVIg, reliably predicted CAL but did not predict IVIg resistance. An ESR value of ≥88mm/h predicted IVIg resistance. Further multicenter, prospective studies with a larger sample size are needed to validate the results.

Ethic clearance: IEC, JIPMER; No. IEC/2021/102, dated July 7, 2021.
Contributions: ACC: participated in study protocol preparations, recruited patients, participated in data analysis and drafted the first version of the manuscript; JGR: conceptualized the study design, supervised the data collection, interpreted the data and critically revised the manuscript; AA: assisted in recruitment of the patients, data analysis and drafting the manuscript. All authors contributed to protocol preparation, drafting of the manuscript, and approved the final version of the manuscript. JGR: shall act as the guarantor of the paper.
Funding: None; *Competing interests*: None stated.

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