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Original Article

Risk factors for coronary arterial involvement in Turkish children with Kawasaki disease: a multicenter retrospective study

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ABSTRACT

Background. Coronary arterial lesions (CALs) are the major component of Kawasaki disease (KD), associated with significant morbidity, which affect a substantial proportion of patients despite proper treatment. The aim of this study was to define the risk factors for CALs in Turkish children with KD.

Methods. Medical records of 399 KD patients from five pediatric rheumatology centers in Turkey were reviewed retrospectively. Demographic, clinical (including duration of fever before intravenous immunoglobulin [IVIG] and resistance to IVIG), laboratory and echocardiographic data were noted.

Results. The patients with CALs were younger, had a higher male ratio and a longer duration of fever before IVIG. They also had higher lymphocyte and lower hemoglobin values before the initial treatment. Multiple logistic regression analyses defined the following three criteria as independent risk factors for predicting CALs in Turkish children with KD: age ≤12 months, male gender and duration of fever before IVIG ≥9.5 days. High sensitivity rates of elevated risk of CALs up to 94.5% were calculated despite specificity values falling to 16.5%, depending on which of these three parameters are taken into account.

Conclusions. Based on the demographic and clinical features, we established an easily applicable risk-scoring system for predicting CALs in Turkish children with KD. This may be useful for choosing appropriate treatment and follow-up for KD to prevent coronary artery involvement. Further studies will show whether these risk factors can be used in other Caucasian populations as well.

Key words: coronary arterial involvement, intravenous immunoglobulin, Kawasaki disease, risk factors, Turkish children.

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Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a febrile vasculitis of the infancy period, that affects small and medium sized vessels including the coronary arteries.[1] Cardiovascular involvement may be irreversible and account for morbidity and mortality, while symptoms

such as prolonged fever, cervical adenitis, non-purulent conjunctivitis, oral mucosal changes and enanthems are self-limiting and reversible.[2-4] Nearly one quarter of children (15-25%) with KD suffer from coronary arterial lesions (CALs) if untreated.[5,6] Intravenous immunoglobulin (IVIG) is effective for the control of clinical signs and decrease in the rate of CALs, due to its immunomodulatory effects.[7] Unfortunately, CALs develop in nearly 10% of patients despite appropriate treatment.[1,8]

Previous studies in the literature defined several risk factors such as younger age, male gender, treatment delay, resistance to initial IVIG, high acute phase reactants and low albumin levels regarding increased risk of CALs.[9-14] Recent studies defined more specific parameters including brain natriuretic peptide (pro-BNP), immunoglobulin M, von-Willebrand factor and inflammatory cytokine levels along with sensitive measurement of coronary arteries, for defining increased risk.[14-18] However, clinicians need easily applicable and low-cost risk score systems to identify patients with increased risk of CALs as soon as possible.

On the other hand, different geographical regions of the world such as Europe, the Middle-East, Far-East and America should define their own self-risk-scoring systems, as current risk assessments are incapable of predicting CALs for all populations due to genetic and environmental differences.[5,6,13,19-27]

Recent studies about KD in Turkey reported more frequent CALs rates compared to Far-East populations.[4,6,14,24-27] Similar risk factors including IVIG resistance and treatment delay along with some laboratory parameters such as lower hematocrit with higher white blood cells (WBC) levels were defined for increased development of CALs.[26,27] However, these studies lack a risk scoring system for the development of CALs.

The objective of the present study was to define an easily applicable and cost-effective risk scoring system for the development of CALs in Turkish children with KD.

Material and Methods

Patients and Definition of KD

Medical records of 399 Kawasaki patients [233 boys (58.3%) and 166 girls (41.7%)] from five pediatric rheumatology centers in different regions of Turkey (Dokuz Eylul University from Izmir, Hacettepe University from Ankara, Cerrahpasa and Capa Faculty of Medicine of Istanbul University, and Umraniye Training and Research Hospital from Istanbul) who received IVIG treatment between 1990 and 2020 were reviewed in this study. The diagnosis of KD was made using previously defined clinical criteria including prolonged fever (>5 days), exanthema, mucosal changes of oral cavity, bilateral non-exudative conjunctival injections, changes in the peripheral extremities and acute non-suppurative cervical lymphadenopathy.[28] Patients, who met at least five of the six criteria were diagnosed as complete KD (cKD), while incomplete KD (iKD) was defined as having four or less.[29] Regarding demographical and clinical features, age, sex and duration of fever before initial IVIG treatment were also recorded.

Treatment Regimens and Terms of IVIG Resistance

High dose IVIG (2 g/kg) with high dose acetylsalicylic acid (80-100 mg/kg/day) were administered to all patients as the first line treatment. Resistance to IVIG treatment was defined as persistent fever 48 h after administration of the first dose.[23,30] Patients who were defined as IVIG resistant, received a second dose of IVIG, and high dose steroids (IV methylprednisolone 30 mg/kg dose), where appropriate, as second line treatment. Sixty-one patients (15.3%) were resistant to initial IVIG treatment in this study.

Laboratory Assessment

The following laboratory results were recorded from the laboratory records of all patients regarding both of the periods before and 48 hours after IVIG: (1) complete blood count parameters (white blood cells [WBC], absolute

neutrophil count [Neu], absolute lymphocyte count [Lym], hemoglobin levels [Hb], absolute platelet count [Plt], mean platelet volume-[MPV]) and (2) acute phase reactants (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]). (3) Biochemical parameters (serum albumin [Alb] and total bilirubin [T-bil], alanine and aspartate aminotransferase [ALT and AST], and electrolyte levels of sodium [Na], potassium [K] and calcium [Ca]).

Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratios (PLR) were calculated from the obtained data.

Echocardiographic Assessment and Definition of CALs

Pediatric cardiologists examined all patients, and echocardiographic assessment was performed at least twice; at the time of diagnosis and in the subacute phase (two weeks after initial IVIG treatment). CALs were defined by using echocardiographic measurement criteria, which were established by the Japanese Ministry of Health and Welfare Guidelines.[31] According to echocardiographic findings, patients with perivascular echogenicity, ectasia/dilatation and aneurysm formation were recorded as CALs positive in order of severity of lesions, respectively. Increased echogenicity of pericoronary tissue minus blood pool was defined as perivascular echogenicity. If the internal diameter was up to 1.5 times that of the adjacent segment, it was defined as coronary arterial ectasia. Furthermore, internal diameters over 4 mm or enlargements over 1.5 times the size of the adjacent segment (for ≥5 years old patients) were accepted as coronary arterial aneurism. Coronary artery involvement was determined in 126 patients (31.5%) prior to initial IVIG treatment.

The ethical approval was obtained from Dokuz Eylul University Ethics Committee (number: 2021/12-31).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 software. Kolmogorov-Smirnov test was performed to evaluate the normality of the variables. Normally distributed variables were presented as mean ± standard deviation, while heterogeneously distributed ones were as median and interquartile ranges (IQR 25-75). Chi-square test was used to examine differences between categorical variables. Normally distributed variables were compared by independent t-test, while non-normally distributed variables by Mann-Whitney U test. We used multiple logistic regression with stepwise backward elimination method for finding the independent variables that define risk factors. Variables having statistically significant differences among groups were evaluated by receiver operating characteristic (ROC) curves to determine the optimal cut-off values and area under curves (AUC). Subsequently, independent risk factors for CALs were determined, and the odds ratio (OR) and 95% confidence interval (CI) were calculated by the multiple logistic regression analysis. $p<0.05$ was considered as statistically significant.

Results

The medical records of 233 boys (58.3%) and 166 girls (41.7%) were included in this study. The median age at the time of diagnosis was 32 (17-54) months. Regarding the clinical type of KD, 252 patients (63.2%) were defined as cKD and 147 (36.8%) were iKD. The median duration of fever before the first IVIG treatment was 7 (5-10) days. In 126 patients (31.6%), CALs were determined in the first echocardiographic assessment, and resistance to initial IVIG treatment was observed in 61 patients (15.3%). There were no statistically significant differences between the IVIG responsive and resistant groups in terms of age, sex, frequency of CALs and the clinical type of KD.

Patients from the CALs positive and negative groups were compared regarding demographical and clinical findings. Patients from the CALs positive group had younger age, male predominance and a longer duration of fever before treatment when compared to the CALs negative group ($p<0.05$ for all parameters) (Table I).

In terms of laboratory parameters prior to the first IVIG treatment, the CALs positive group had lower hemoglobin ($p=0.006$) and higher lymphocyte ($p=0.048$) values than the CALs negative group. In further evaluation two days following IVIG treatment, we found higher WBC, Lym and lower Hb, MPV, bilirubin and potassium levels in the CALs positive group ($p<0.05$ for all parameters). Acute phase reactant levels such as ESH and CRP were higher in the CALs positive group both before and after treatment periods; however, differences were not statistically significant (Table II).

Multiple logistic regression analysis was performed with the possible risk factors which were determined in the univariate analysis. Variables such as gender, age, Hb, Lym and duration of fever before IVIG prior to the treatment period and WBC, Lym, Hb, MPV, bilirubin and potassium following the treatment period were evaluated. The variables including gender, age and duration of fever before IVIG were determined as independent risk factors of CALs in the multiple analysis with the backward elimination technique. The predictive value of the variables revealed male gender ($p<0.001$), age ($p=0.002$) and duration of fever prior to the first IVIG treatment ($p=0.036$) as independent predictors of CALs. When we applied a ROC analysis to numerical variables, the best cut-off values were calculated as duration of fever ≥9.5 days and age ≤12 months. Based on these cut-off values, binary logistic regression analysis was applied for each parameter, and odds ratios were calculated as 2.525 for male gender, 3.112 for age ≤12 months and 2.084 for duration of fever before initial IVIG ≥ 9.5 days (Table III). The final models' results were presented including odds ratios, 95% confidence intervals and p values in Table III and the results of the ROC curve analyses including optimal cut-off value, sensitivity, specificity, PPV, NPV and accuracy parameters for each variable and their binary and triple combinations were presented separately in Table IV.

Discussion

Coronary arterial involvement represents the major contributor to morbidity and mortality related to KD, and the main focus of researchers is to predict children at high risk for this complication. However, risk factors are not universal and may vary between populations due to genetic and environmental differences. Despite higher rates of CALs reported in some studies of Turkish children, there was, to the best of our knowledge, no defined risk scoring system.[25-28,32-34] In the current study, we defined an easily applicable risk scoring system prior to treatment for Turkish children, by using multicenter data, including only clinical features such as age, gender and duration of fever.

The current American Heart Association guidelines for KD recommend that younger infants should be evaluated as a risk group for cardiovascular involvement, and

Table I. Comparison of demographic and clinical data between CALs (+) and (-) groups.

Characteristics	CALs (+)	CALs (-)	p value
Gender (male/female)	2.40 (89/37)	1.11 (144/129)	<0.001
Age (months)*	27.5 (12-45)	36 (19.5-56.5)	0.002
Clinical type (complete/incomplete)	80/46	172/101	0.508
IVIG resistance, n (%)	22 (17%)	39 (14%)	0.249
Duration of fever before IVIG treatment (days)**	9.57 ± 6.11	7.89 ± 4.04	0.036

*median (IQR 25-75), ** mean ± SD. CALs: coronary arterial lesions, IVIG: intravenous immunoglobulin.

Table II. Comparison of laboratory parameters between coronary arterial lesions (+) and (-) groups.

Parameters	Before IVIG treatment			2 days after IVIG treatment		
	CALs (+)	CALs (-)	p value	CALs (+)	CALs (-)	p value
WBC (10^3/μL)	15.2 (11.8-17.6)	14.5 (14.4-18.3)	0.455	16.1 ± 7.3	10.4 ± 4.2	0.023
Neu (10^3/μL)	8.1 (6.6-11.9)	8.9 (6.5-13.2)	0.965	5.1 (4.6-5.8)	4.2 (1.8-6.7)	0.907
Lym (10^3/μL)	3.2 (2.3-5.5)	2.9 (1.8-4.5)	0.048	7.8 (3.3-9.1)	4 (2.9-5.8)	0.030
Platelet (10^3/μL)	386 (298-582)	395 (306-560)	0.258	442 (441-444)	492 (334-696)	0.156
Hb (g/dL)	10.3 ± 1.5	11 ± 1.3	0.006	8.45 ± 1.34	10.7 ± 0.92	0.029
NLR (Neu/Lym)	2.07 (1.2-3.97)	2.54 (1.4-4.9)	0.098	1.02 (0.37-1.26)	1.07 (0.31-1.98)	0.138
PLR (Plt/Lym)	120.5 (89-177.5)	139.2 (91-250)	0.313	84.6 (35.7-101)	118 (85-155)	0.091
MPV (fL)	7.3 (6.7-7.9)	7.1 (6.6-7.9)	0.938	7.05 ± 0.63	7.4 ± 0.56	0.010
ESH (mm/h)	68 (42-90.2)	63 (40-80)	0.786	124.5 (110-160)	59 (36-10.5)	0.532
CRP (mg/L)	82 (25-141)	68 (22.8-146.5)	0.550	48.4 (12.5-62)	15.6 (6.55-25)	0.888
ALT (U/L)	22.5 (13-52.2)	36 (16-80)	0.205	27.5 (8-32)	26 (20-37)	0.902
AST (U/L)	31.5 (21-46.5)	34 (25-57)	0.102	38 (19-46)	41 (22-54)	0.583
T. bilirubin (mg/dL)	0.28 (0.21-0.6)	0.41 (0.25-0.75)	0.004	0.27 (0.26-0.29)	0.39 (0.33-0.55)	0.03
Albumin (g/dL)	3.54 ± 0.56	3.6 ± 0.49	0.147	3 (2.8-3.4)	3.5 (3.2-3.6)	0.770
Sodium (mmol/L)	136 (135-137)	135 (133-137)	0.060	134.5 ± 2.1	138 ± 2.4	0.365
Potassium (mmol/L)	4.46 ± 0.66	4.32 ± 0.62	0.275	4.2 ± 0.84	4.7 ± 0.37	0.008
Caicium (mg/dL)	9 (8.6-9.5)	9.1 (8.8-9.6)	0.873	8.86 ± 0.47	9.4 ± 0.55	0.817

Data are presented as median (IQR 25-75) or mean ± standard deviation.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, CALs: coronary arterial lesions, CRP: C-reactive protein, ESH: erythrocyte sedimentation rate, Hb: hemoglobin, Lym: lymphocyte count, MPV: mean platelet volume, Neu: neutrophil count, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, T. bilirubin: total bilirubin, WBC: white blood cells.

Table III. Multiple logistic regression analysis of predicting factors for coronary arterial lesions.

Parameters	Cut-off value	β	SE	Wald	df	Sig	Exp B	%95 Confidence interval	
								Lower	Upper
Gender (male)		0.926	0.243	14.547	1	<0.001	2.525	1.569	4.065
Age	≤12 months	1.135	0.308	13.572	1	<0.001	3.112	1.701	5.693
Duration of fever before IVIG	≥ 9.5 days	0.735	0.241	9.270	1	0.002	2.084	1.299	3.343

IVIG: intravenous immunoglobulin.

echocardiographic assessment should be performed even if diagnostic criteria are not fulfilled.[1] McCrindle et al.[10] reported that younger age at presentation was the most risk-increasing factor in their CALs prediction scoring system. Also, in a study from China[34], age under 12 months was defined as an independent risk factor. In the current study, our results were consistent with the literature, and patients under one-year old were associated with an elevated risk, which had an OR of 3.11. Additionally, male gender had a higher prevalence (58.3%) and nearly two and a half times increased risk of CALs. In a study from the USA, Callinan et al.[35] reported that male patients with KD had a higher risk, accompanied by a younger age, Asian race and delayed treatment. Another multicenter study from Spain[36] also emphasized male gender as an increased risk for developing CALs in the course of KD. Similarly, Qiu et al.[14] defined female sex as an independent protective factor from CALs development.

Table IV. Results of receiver operating characteristic (ROC) analysis of predicting factors for coronary arterial lesions.

Variables and cut-off values	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy (%)
• Male gender	47.3	70.6%	0.408	0.777	54.4
• Age ≤12 months	87.3	26.4%	0.478	0.717	67.6
• Duration of fever before IVIG ≥9.5 days	74.4	37.2%	0.381	0.724	62.2
• Age ≤12 months • Male gender	94.5	16.7%	0.583	0.711	69.9
• Age ≤12 months • Duration of fever before IVIG ≥9.5 days	91.9	16.5%	0.476	0.712	68.7
• Male gender • Duration of fever before IVIG ≥9.5 days	71.0	47.1%	0.331	0.577	57.4
• Male gender • Age ≤12 months • Duration of fever before IVIG ≥9.5 days	70.6	29.3%	0.361	0.698	63.2

IVIG: intravenous immunoglobulin, NPV: negative predictive value, PPV: positive predictive value.

The main goal in KD treatment is to control the vascular inflammation in its earliest stages, since a time lag in the administration of IVIG could lead to an increased risk for CALs. The duration of the febrile period prior to therapy in this regard has been the focus of attention. Previously reported studies emphasized the related parameter and reported that the duration of the febrile period before treatment was positively correlated with the risk of coronary artery involvement and resistance to IVIG. This study also found that patients who received initial IVIG treatment later than 9.5 days had a doubled risk of CALs development. Our recent single-center study[27] reported the same critical cut-off value for the duration of fever before IVIG treatment, which was associated with both CALs and IVIG resistance. A similar result by Bal et al.[37] reported this cut-off value as 10 days. On the contrary, the well-known scoring systems from Japan such as Kobayashi et al.[38] and Egami et al.[39] reported a shorter duration of fever (≤4 days) had increased risk for IVIG resistance, leading to CALs development. They speculated that the patients treated in the early period had severe clinic and greater inflammation. We consider that delayed treatment causes a prolonged inflammation of vessel walls and increases risks for CALs.

A strong correlation between the risk of CALs development and IVIG resistance was reported in several studies by many researchers. Kobayashi et al.[38] defined a risk score system for predicting IVIG resistance by using elevated liver function tests, hyponatremia, thrombocytopenia, younger age and higher acute phase reactants. They also defined these risk factors for CALs development, because of the strong correlation between these two complications.[38] Similarly, in a study from the USA, Ghelani et al.[12] reported a higher incidence of CALs in IVIG resistant patients with an OR of 5.27. Our previous study as a single center also showed a positive correlation between these parameters; however, the current multicenter study did not find a statistically significant correlation between these two complications, unlike the literature. Thus, our risk scoring system mainly depends on the risk for CALs development, independent of IVIG resistance. It might be helpful for the early administration of additional treatments, such as steroids and/or biologics to prevent severe coronary arterial involvement.[40,41]

Although there is not a specific biomarker defined for KD and its complications, there has been a great focus on many laboratory markers

and their threshold values for predicting increased CALs development. Higher ESR and CRP values were associated with elevated risks for CALs indicating severe inflammation.[11-15,42,43] Hematological parameters such as lower hemoglobin and hematocrit levels, and elevated leukocyte and platelet counts were reported as positively correlated, as well.[15,34,43,44] In this study we found lower hemoglobin and higher lymphocyte counts, with elevated ESR and CRP levels prior to IVIG treatment in the CALs positive group; however, they were inadequate to be included in the risk scoring system.

In conclusion, based on clinical and demographical data, we presented a new scoring system to predict CALs in Turkish children: younger age (≤12 months), male gender and duration of fever before IVIG (≥ 9.5 days). We suggest that our score is easily applicable and has high sensitivity, although the specificity is low. Further prospective studies are needed to assess its performance in other ethnic groups and the correlation with possible biomarkers.

Ethical approval

The ethical approval was obtained from Dokuz Eylul University Ethics Committee (number 2021/12-31).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ST, BM, EÜ; data collection: ST, ÜAK, FÇ, FH, FD, TK, NÜ; analysis and interpretation of results: ST, BM, EÜ, SÖ, EK, YB, NAA, BS, ÖK; draft manuscript preparation: ST, UAK, FÇ, FH, FD, EK, TK, NÜ; revising the manuscript critically: BM, YB, EÜ, BS, NAA, ÖK, SÖ, EK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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