ORIGINAL ARTICLE

Clinical and Laboratory Profile of Macrophage Activation Syndrome in Kawasaki Disease: A Single Centre Cross-Sectional Study

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Received: Nov 28, 2023; Initial review: Jan 01, 2024; Accepted: May 18, 2024

PII: S097475591600651

ABSTRACT

Objective: To study the prevalence of Macrophage Activation Syndrome (MAS) in children with Kawasaki disease (KD) and to devise a classification tree for predicting MAS in early KD based on easily available clinical and laboratory information using artificial intelligence (AI) technology.

Methods: A prospective cross-sectional observational study was conducted (March 2020 – October 2021) during which hospitalized children aged 1-18 years with KD were consecutively enrolled. Those with positive RTPCR test or IgM/IgG serology for COVID-19 were excluded. The clinical and laboratory profiles of children with and without MAS were studied. A multivariable logistic regression (LR) model was developed utilizing backward elimination method to determine the relationship between select candidate predictor variables and MAS in patients with KD. A classification tree was created based on these using artificial intelligence algorithms.

Results: Sixty-two children were diagnosed with KD during the study period, of these, 42 children with KD were included; 14 (33.3 %) were diagnosed with MAS. The median (IQR) duration of fever (days) was significantly more in MAS than those without MAS [7 (5, 15) vs 5 (5, 9), $P < 0.05$]. Serum albumin (g/dL) was significantly lower in those with MAS [2.3 (2.2, 2.7) vs 2.8 (2.3, 3.1), $P = 0.03$]. The classification tree constructed by the AI-based algorithm predicted that in children with KD who had myocardial dysfunction, serum albumin ≤ 2.8 g/dL and fever > 6 days duration at admission had increased likelihood of developing MAS. In children without myocardial dysfunction, alanine transaminase (ALT) levels > 70 U/L and fever > 5 days were equally predictive of MAS.

Conclusion: Nearly one-third of the children with KD had MAS. Clinicians should consider screening all children with KD for MAS at admission. A classification tree based on the presence of myocardial dysfunction, duration of fever > 6 days, ALT levels and hypoalbuminemia can identify MAS in the course of KD.

Keywords: *Albumin, immunomodulation, myocardial dysfunction, classification tree*

INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis with an increased predilection for coronary artery involvement that is seen predominantly in young children [1]. Physicians have to rely on clinical signs and symptoms like fever, rash, mucocutaneous changes and lymphadenopathy for establishing a diagnosis, as there are no confirmatory laboratory tests. Due to a varied presentation and a considerable overlap in clinical features of atypical KD and other tropical infections like measles, chikungunya or dengue, diagnosis of KD can be challenging [2,3]. Timely recognition is essential as delayed diagnosis and treatment may not only result in life-threatening systemic complications like shock, myocarditis, acute kidney injury (AKI), multi-organ dysfunction syndrome (MODS) and macrophage activation syndrome (MAS), but also lifelong cardiac sequelae [3].

Macrophage activation syndrome is a secondary hemophagocytic lymphohistiocytosis (HLH) syndrome usually described in the context of systemic onset juvenile idiopathic arthritis (SOJIA), systemic

lupus erythematosus (SLE) and also (unknown to many clinicians) KD. Concurrent KD and MAS is associated with higher rates of coronary artery abnormalities [4,5] and mortality (13%) than isolated KD [6]. Recognition of coexisting MAS in KD is pertinent as timely administration of high dose pulse corticosteroid therapy, infliximab and/or cyclosporine has better prognosis [6,7].

The prevalence of MAS in KD was reportedly 1-2 % [5-7] before the COVID-19 pandemic. However, since the COVID-19 pandemic, Verdoni et al and Riphagen et al reported a 30-fold increase in the incidence of KD, and a higher prevalence of concurrent MAS (up to 50%), respectively [9,10]. This trend was also observed in our institute which prompted us to start screening all patients with KD for MAS at admission. As per the International Consensus Criteria, the diagnosis of MAS requires testing for additional laboratory parameters like serum ferritin, fibrinogen and triglyceride levels [11]. However, these may not be easily available in low resource settings leading to a delayed or missed diagnosis of MAS. Given this background, the aim of this prospective study was to determine the proportion of children with KD identified with concurrent MAS at presentation. We also attempted to create an artificial intelligence (AI) based clinical decision algorithm that would help identify MAS in KD using preliminary clinical and laboratory parameters that are available even in resource-limited centers.

METHODS

This cross-sectional observational study was conducted in a tertiary care hospital in North India from March 2020 to October 2021 after obtaining approval from the Institutional Ethics Committee. All consecutive children aged 1 month to 18 years, presenting to our hospital with fever ≥ 5 days and clinical features of KD as per American Heart Association (AHA) 2017 criteria were enrolled [1]. We also included children who satisfied criteria for incomplete or atypical KD [1]. We excluded children with positive serology or real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) to rule out possible confounding cases of multisystem inflammatory syndrome in children (MIS-C) [12]. Written informed consent or assent was obtained from caregivers. We calculated a sample size of 42 participants based on assumed prevalence of MAS in KD as 50% [9], margin of error 15%, confidence level 95%, and alpha error of 0.05.

The following study specific details of all participants were recorded in a standardized proforma: clinical manifestations; investigation results of ferritin, fibrinogen, triglycerides, quantitative D-dimer, and N terminal pro-B-type natriuretic peptide (NT-pro BNP) and two-dimensional echocardiography (performed by a pediatric cardiologist), and management. Standard definitions were used for known complications. Myocardial dysfunction was defined as shock in the presence of indicators of myocardial injury: elevated biochemical markers i.e., CPK-MB > 45 IU/L, NT-pro BNP > 500 pg/mL, or positive Troponin-T (commercial colorimetric kit), or; echocardiographic evidence of myocardial dysfunction. Acute kidney injury was determined as per the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 definition [12]. MAS was defined according to Ravelli's International Consensus Criteria [13] i.e., ferritin > 685 mg/L with two of the following abnormal laboratory parameters: platelet count ≤ 1.81 x 10^9/L; serum aspartate transaminase (AST) > 48 U/L; triglyceride > 156 mg/dL, and; fibrinogen ≤ 360 mg/dL. Significant dilatation

of the right coronary artery, left main coronary artery and/or left anterior descending artery on echocardiography was defined according to z-scores [1].

Therapeutic details included the first-line immune-modulator used, its dose and time taken for response (resolution of fever), and need for second line drugs with indication. All patients received intravenous immunoglobulin (IVIG, 2 g/kg over 12 - 18 hours), aspirin (50 mg/kg/day for 48 hours, followed by 5 mg/kg/day) and prednisolone (2 mg/kg/day for 2 weeks with slow tapering). The children with MAS also received pulse IV methylprednisolone (30 mg/kg/day for 5 days) followed by tapering with prednisolone. Second-line drugs (cyclosporin, atorvastatin or infliximab) were provided when indicated as per institutional protocol [7].

Statistical analysis: Descriptive statistics was used for qualitative data. Clinical and laboratory parameters were compared using Chi square or Fisher exact test in KD with and without MAS, depending on the normality of data. Logistic regression (LR) analysis was used for predicting odds of MAS in KD using generalised linear model (GLM) function for binomial family with logit link in R software version 4.1.0. Initially simple LR analysis was performed to derive unadjusted odds of known predictors, which were selected after an exhaustive literature review including the 2017 AHA guidelines [1]. These included age, duration of fever, presence of infections, central nervous system (CNS) dysfunction, shock, AKI, myocardial dysfunction, hemoglobin, C- reactive peptide, serum albumin and presence of elevated ALT (>70 U/L). Age was the only quantitative predictor which followed a linear relation with log-odds of MAS in KD. Hence, the remaining quantitative predictors were categorised as hemoglobin ≤ 7 g/dL, C reactive protein ≥ 100 mg/L, and serum albumin ≤ 2.5 g/dL for further evaluation in LR. The duration of fever was categorised into ≥ 7 days, ≥ 10 days and ≥ 14 days [5-7]. Predictors having coefficients of unadjusted odds with *P* value < 0.25 were selected for multivariable LR to determine the adjusted odds using backward elimination method (to preserve precision). The first predictive model was made with all predictor variables with *P* value < 0.25. The variable with the maximum *P* value was dropped, and the next model was made with the remaining variables. This process continued until all the variables were statistically significant and a model was built with the best area under receiver operating characteristic curve (AUROC). Goodness of fit of each model was compared with the previous one by ANOVA test and likelihood ratio test.

Since our sample size for regression was sub-optimal for secondary analysis, we performed classification modelling using the C.50 package based on AI algorithms. This built a classification tree that identified features in patients that were specific for MAS in KD using the seven variables selected for multivariable LR. Eighty percent of the data was divided into a training set and the remaining 20% into a testing set. The almost equal proportions of patients with MAS in both sets ensured proper randomization. The model was trained on to the training set and a final classification tree was plotted using machine-learning algorithms. The performance of this model was evaluated on the testing set, with construction of a confusion matrix to derive sensitivity, specificity, precision, accuracy and error rates.

RESULTS

Of the 62 patients who were diagnosed with KD, 20 were excluded due to IgM and/or IgG positivity for SARS CoV-2 **(Fig. 1).** The study population comprised of 42 patients; 29 (69%) children with incomplete

KD and 13 (31%) with complete KD. MAS was identified in 14 (33%) cases. The clinical and laboratory profiles of all patients are summarized in **Table I,** with an embedded comparison of children with and without MAS**.** The proportion of incomplete KD was 11 (64.7%) and 18 (72%) in both, respectively. Nine children (6 MAS and 3 non-MAS) had IVIG resistance (recurrence of fever after 36 hours completion of IVIG) [1] that required a single infliximab infusion (5 mg/kg). No mortality was observed during the study duration.

The five predictive models are depicted in **Table II.** Model 5 had an AUROC of 0.8, best Akaike information criterion (AIC) value of 52.48, and did not display loss of information by ANOVA and likelihood ratio test. The regression equation was as follows: 'ln (Odds of having MAS) = - 2.03 + 2.67 *a + 1.33 *b + 1.38 *c': wherein, 'a' is 1 if fever ≥ 14 days, and 0 if fever < 14 days; 'b' is 1 if serum albumin ≤ 2.5 g/dL, and 0 if serum albumin > 2.5 g/dL, and; c is 1 if ALT > 70 U/L, and 0 if ALT < 70 U/L. The generated classification tree with seven terminal nodes is shown in **Fig. 2.** Terminal node 6 (*n* = 2) and 12 (*n* = 7) included 9 out of the total 14 patients with MAS which made the use of the 'if- then sequential classification rules' to predict MAS in KD applicable. Sensitivity, specificity, positive predictive value, accuracy and misclassification were 75%, 100%, 100%, 88.89% and 11.11%, respectively.

DISCUSSION

A published systematic review in the pre-COVID-19 pandemic period on MAS in KD reports only 67 patients derived from multiple sources worldwide, out of which three-fourth were diagnosed later in the course of disease [6]. To the best of our knowledge based on an exhaustive review of literature, this study reports the largest number of children with KD and MAS from a single centre. This is probably due to the fact that we screened all children with KD for MAS. In addition, our study was conducted during the pandemic and the change in immunological dysregulation secondary to COVID-19 could theoretically have led to more severe phenotypes of KD including concurrent MAS [9,10]. The incidence of MAS in pre-pandemic KD may not be a true representation as universal screening for MAS was not practiced [3-7] and children were investigated only after a clinical suspicion arose based on the progression and severity of illness in the presence of hepatosplenomegaly, cytopenia and coagulopathy.

Our study population of children with KD comprised of similar proportions below 5 years as observed in existing literature, though the median age of presentation was much lower (24, IQR 9, 72 months). The male-to-female ratio of 2:1 was similar to previous Indian studies [14,15]. In literature, most reported patients of KD with MAS are older than 5 years of age [3,4-7], but we observed a median age of 4 years (range 2-72 months). An increase in prevalence and age-related downward shift was also observed during the pandemic in Subacute sclerosing panencephalitis (SSPE), a known immune-mediated illness, that was hypothesized to be triggered by some unidentified factor that resulted in immune dysregulation [16]. Whether this applies to cytokine-mediated MAS needs to be explored further.

We found a significant association of hypoalbuminemia in children with MAS that may be due to two reasons. Firstly, increased albumin leakage is known to occur in the acute phase of illness. Secondly, albumin is a negative acute phase reactant in systemic inflammatory reaction that results from the unbridled cytokine storm observed in MAS [5-7]. Earlier studies have reported thrombocytopenia and hyperferritinemia

as biomarkers suggesting underlying MAS [3-7,13]. In the present study ferritin levels were significantly higher in KD with MAS, but platelet counts were not significantly lower. We also did not find any association of hypertriglyceridemia, hypofibrinogenemia and hyponatremia in either of the subgroups of KD; with and without MAS. This may be explained by the fact that these findings usually occur later in the course of disease, whereas our patients were identified relatively earlier. Thus, these clinical biomarkers may not have been unveiled. Coronary artery aneurysms (CAA) can be present in 25% cases of untreated KD, which decreases to 4% with IVIG therapy [1]. Existing literature shows that MAS may be an underlying risk factor for CAA with the prevalence reportedly higher (10–50%) in patients with KD and MAS [1,7,17-18]. We observed a similar increase in the subgroup of KD with MAS, albeit this was not statistically significant. None of our cases had any residual CAA during a 12-month follow-up, presumably due to the early aggressive therapy.

The large number of cases of KD in our study made it feasible for us to construct a clinical prediction model for early assessment of MAS in KD. The LR modelling was performed to determine the relation (if any) between the select predictor variables derived from existing literature and the probability of MAS in KD**.** The AI-based algorithm provides a simple 'yes/no' and 'if –then' flowchart to predict MAS in KD using baseline clinical and laboratory parameters. Significantly, our classification tree modelling can identify MAS patients 'very early' in the natural history of illness, is simple to use, and will help clinicians identify MAS that will facilitate timely addition of high dose corticosteroids to the standard therapeutic regimen. Our algorithm shows that the presence of all three parameters (myocardial dysfunction, hypoalbuminemia, and fever > 6 days) have a 100% likelihood of having MAS. Similarly, it also demonstrates equal likelihood of MAS when the fever is more than 5 days, the ALT is raised (> 70 U/L) and there is no myocardial dysfunction **(Fig. 1)**. This algorithm is in alignment with the pre-pandemic evidence, which indicates that in patients with KD aged more than 5 years, fever persisting for more than 10 days and incomplete KD is highly predictive of underlying MAS [4-6]. These findings along with the evidence corroborates our model and makes it biologically plausible. It is important to realize that this model is valid even now when the pandemic is over, since the most common reason for underdiagnosis of KD is lack of clinical suspicion. Thus, the use of this model at admission will help in increasing detection.

Despite the fact that we had a large number of children with MAS in KD from a single center, the sample size was still not adequate for multivariable LR modelling. This limitation was offset by the method by which the AI algorithm-based classification tree was modelled by dividing the data based on the seven parameters selected in the final model of LR. Though this model is biologically plausible, and backed by supportive scientific evidence, and sensitivity, specificity, positive predictive value and accuracy appear to be acceptable, these results will need to be tested and validated on larger data sets. Further research using a multicentric design with adequate sample size and patients identified in the early clinical course would be the next logical step forward.

We observed encouraging benefits by changing our policy to universal early screening for MAS in children with KD. These included early recognition, timely therapy of MAS in addition to treatment of KD, and good outcomes with no mortality. Based on this, we propose that clinicians consider screening for MAS

in KD at initial presentation The use of the proposed classification tree with easily available clinical information (duration of fever, myocardial dysfunction, ALT and serum albumin) may be helpful in predicting MAS early in the course of disease.

Contributors: AM, SG: Study design, acquisition, analysis and interpretation of data, drafting the manuscript; VK, KDR: Data acquisition, tabulating results and review of literature; AM: Conceived the idea, critical revision of manuscript at all its stages, final approval of manuscript; SG: Statistical analysis along with the logistic regression and formulation of the final model; MA: Laboratory analysis. SB, DM: Contributed to analysis and interpretation of data. All authors critically reviewed and approved the final manuscript.

Ethics Clearance: LHMC/IEC/2020/97 dated Nov 6, 2020; LHMC/IEC/2021/03/98 dated Sep 14, 2021.

Funding: None; *Competing interests*: None stated.

WHAT THIS STUDY ADDS

- All children with Kawasaki Disease (KD) should be screened for macrophage activation syndrome (MAS)
- Early identification of MAS translates into timely treatment with high dose pulse methylprednisolone in addition to standard treatment of KD that is associated with better outcomes.
- An artificial intelligence-based algorithm using easily available clinical information (duration of fever, markers of myocardial injury, ALT and serum albumin) may predict MAS early in the course of illness.

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Table I Clinical and laboratory profile of children with Kawasaki Disease with and without Macrophage Activation Syndrome (MAS)

Parameters	*Children with KD* (*n* =42)	*MAS* (*n* = 14)	*Non-MAS* (*n* = 28)	*P value*
Clinical Characteristics				
Age (months)[a]	24 (9, 72)	48 (2, 72)	24 (12, 72)	0.7
Male	28 (66.7)	11 (64.7)	17 (68)	1
Duration of fever (days)[a]	6 (5, 10)	07 (5, 15)	05 (5, 9)	0.04
Rash	25 (59.5)	10 (58.8)	15 (60)	1
Mucositis	20 (47.6)	08 (47)	12 (48)	1
Lymphadenopathy	9 (21.4)	03 (17.6)	06 (24)	0.72
Eye redness	22 (52.3)	11 (64.7)	11 (44)	0.32
Desquamation of the skin	8 (19.0)	5 (29.4)	03 (12)	0.23
IVIg resistance	9 (21.4)	6 (40)	3 (10)	0.025
Acute kidney injury	9 (21.4)	06 (35.3)	03 (12)	0.12
Liver dysfunction	16 (38.1)	09 (52.9)	07 (28)	0.19
Shock	22 (52.4)	11 (64.7)	11 (44)	0.32
Myocardial dysfunction	17 (40.4)	10 (58.8)	07 (28)	0.09
Coronary Artery Aneurysm	7 (16.6)	03 (21.4)	04 (14.2)	0.40
CNS dysfunction	4 (9.5)	03 (17.6)	01 (4)	0.29
Laboratory parameters[a]				
Hemoglobin (g/dL)	9.5 (7.9, 10.2)	9.7 (7.9, 10.4)	9.5 (7.9, 10.2)	0.48
TLC (x 10^9/L)*	11.5 (8.3, 20.1)	11.2 (7.7, 25)	13.4 (8.6, 18.3)	0.59
Platelet count (x10^9/L)	180 (107, 267)	140 (100, 590)	230 (127, 260)	0.75
CRP (mg/L)	130 (57.5, 211.5)	114 (56, 205)	130 (60, 213)	0.64
D-dimer (ng/mL)	1170 (701.5, 2100)	1980.5 (768.5, 2150)	1068.5 (555.75, 1915.75)	0.75
Fibrinogen (mg/dL)	345 (193, 403)	378 (248, 446)	390 (346, 466)	0.32
Albumin (g/dL)	2.8 (2.4, 3.1)	2.3 (2.2, 2.7)	2.8 (2.3, 3.1)	0.03
Triglyceride (mg/dL)	220 (174.5, 308.5)	136 (123, 212)	134 (116, 177)	0.69

CNS Central nervous system, CRP C-reactive protein, TLC Total leukocyte count
Values expressed as n (%), [a]median (IQR)
**No case of cytopenia was seen*

Table II: Predictors of Macrophage Activation Syndrome in Kawasaki Disease

Predictor[a]	*Unadjusted Odds Ratio (95% CI)*	*Model 1*	*Model 2*	*Model 3*	*Model 4*	*Model 5*
Fever ≥ 14 days	10 (1.4, 203.3)	12.2 (0.8, 374.2)	12.3 (1.0, 347.1)	12 (1.2, 328.1)	14.4 (1.4, 390.4)	14.4 (1.6, 351.1)
S Albumin ≤ 2.5 g/dL	3.6 (1.0, 14.4)	3.4 (0.6, 19.2)	3.3 (0.7, 17.7)	3.4 (0.8, 17.6)	3.58 (0.8, 18.5)	3.8 (0.9, 18.8)
Myocardial dysfunction	3.6 (1.0, 14.2)	2.2 (0.2, 24.3)	2.2 (0.4, 11.5)	2.2 (0.5, 10.3)	2.2 (0.5, 10.3)	
Acute kidney injury	4 (0.8, 21.9)	1.7 (0.3, 12.79)	1.7 (0.2, 12.6)	1.8 (0.3, 12.6)		
CNS dysfunction	5.1 (0.5, 109.6)	0.8 (0.04, 31)	0.8 (0.04, 30.0)			
Shock	2.3 (0.6, 8.7)	0.9 (0.08, 9.6)				
ALT ≥ 70 U/L	2.8 (0.8, 10.9)	2.7 (0.4, 18.5)	2.8 (0.5, 17.6)	2.7 (0.5, 16.2)	3.4 (0.8, 17.7)	3.9 (0.9, 20.0)
Baseline odds (Exponentiated odds)		0.1 (0.01, 0.4)	0.1 (0.02, 0.4)	0.1 (0.02, 0.4)	0.1 (0.02, 0.4)	0.1 (0.03, 0.5)
(AUROC)	-	0.79	0.79	0.79	0.79	0.78
(AIC)	-	58.976	56.976	54.983	53.369	52.478

AIC Akaike information criterion, ALT Alanine transaminase, AUROC Area under receiver operating characteristic curve, CNS Central nervous system

[a]*The seven variables selected on simple LR by virtue of unadjusted odds ratios with* $P < 0.25$

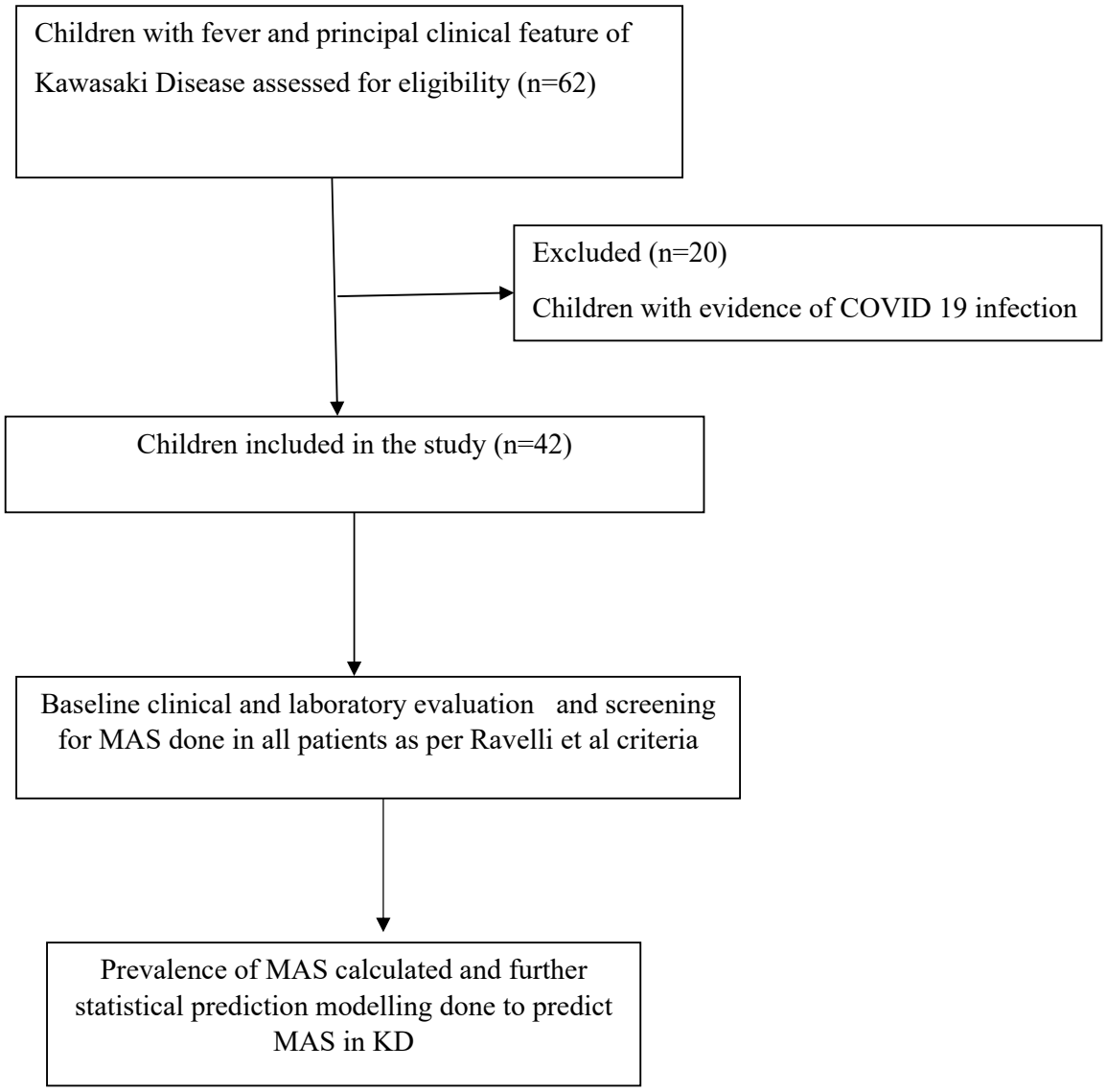

Fig. 1 Study flow chart depicting enrolment and follow-up of participants

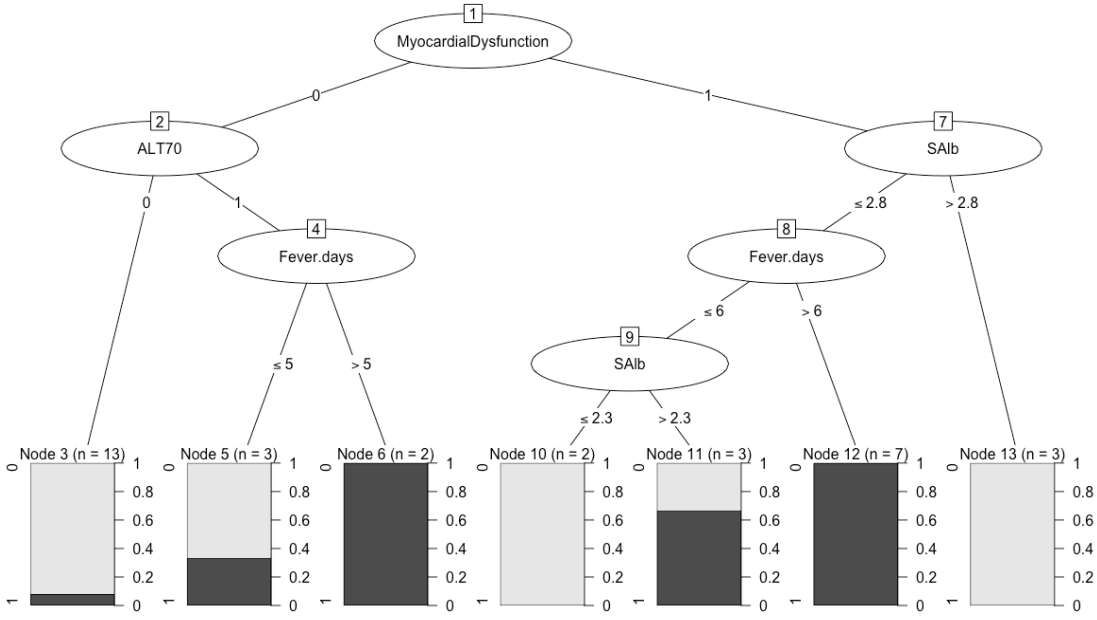

Fig. 2. Classification tree predicting macrophage activation syndrome in Kawasaki disease in children

Note: Terminal nodes 3, 5, 6, 10, 11, 12 and 13 depict the proportions of patients with and without MAS. Terminal nodes 6 and 12 included only patients with MAS.

**ALT > 70 (0 No, 1 Yes)*