Original Research

CLINICAL PROFILE AND BIOMARKER ANALYSIS IN KAWASAKI DISEASE: A PROSPECTIVE COHORT STUDY FROM NORTH INDIA

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ABSTRACT

Objective: To study the clinical profile, biomarker patterns, and cardiovascular outcomes of children admitted with Kawasaki Disease (KD) at a tertiary care center in Shimla. **Study Design:** Prospective observational cohort study. **Participants:** 29 children aged 2 months to 18 years admitted to the pediatric ward with a diagnosis of Complete or Incomplete KD. **Methods:** Clinical history, physical examination, and laboratory parameters were recorded. Coronary artery status was assessed by 2D-Echocardiography at discharge and at 3-months follow-up. **Results:** The mean age of the cohort was 46.4 months with a male-to-female ratio of 1.23:1. Only 41.4% of patients met the criteria for Classic KD, while the majority (58.6%) presented with Non-Classic (Incomplete or Atypical) forms. Oral mucosal changes (93.1%) and cervical lymphadenopathy (65.5%) were the most consistent clinical features, whereas polymorphous rash (51.7%) and conjunctivitis (41.4%) were less frequent. Male gender was significantly associated with the Incomplete phenotype (87.5%). Coronary artery dilatation was observed in 82.8% of patients at discharge; however, 93.1% of these normalized by the first follow-up, indicating transient ectasia. IVIG resistance was observed in only 3.6% of treated patients. Biomarker analysis revealed elevated mean Procalcitonin (3.28 ng/mL) and D-Dimer levels (1075 ng/mL). **Conclusion:** Non-classic presentations of KD are predominant in this setting, often lacking classic mucocutaneous signs like rash. Despite a high incidence of acute coronary involvement (82.8%), the long-term prognosis is favorable with timely therapy, as most lesions represent transient ectasia.

Keywords: Coronary Artery Ectasia, D-Dimer, Incomplete Kawasaki Disease, Kawasaki Disease, Procalcitonin.

INTRODUCTION

Kawasaki Disease (KD) is an acute, self-limited systemic vasculitis of unknown etiology that predominantly affects medium-sized arteries, with a striking predilection for the coronary arteries [1, 2]. Although historically prevalent in Northeast Asia, KD is now recognized as the leading cause of acquired heart disease in children in developed nations, having surpassed rheumatic fever in incidence [1]. Without timely intervention, approximately 25% of affected children develop coronary artery aneurysms (CAAs), which may lead to myocardial infarction or sudden death [2].

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While the administration of Intravenous Immunoglobulin (IVIG) within the first 10 days of illness reduces this risk to 3–5%, a subset of patients remains refractory to initial therapy, constituting a high-risk group for cardiac sequelae [2, 3].

Diagnosis currently relies on non-specific clinical criteria established by the American Heart Association (AHA) [1, 4]. However, a significant clinical challenge is posed by "Incomplete KD," where patients present with prolonged fever but fewer than four principal clinical features. This presentation is increasingly common and is associated with a paradoxically higher risk of coronary abnormalities due to delays in diagnosis and treatment [5]. The diagnostic difficulty is compounded in tropical settings like India, where clinical features of KD overlap significantly with common infectious diseases such as scrub typhus, dengue, and measles [6, 7].

In the Indian context, the "Indian phenotype" of KD presents unique challenges distinct from Western or Japanese cohorts [8]. Furthermore, established risk

stratification tools for predicting IVIG resistance, such as the Japanese Kobayashi score, have consistently demonstrated poor predictive value in Indian populations [9, 10]. Consequently, there is an urgent need to validate region-specific clinical profiles and investigate novel biomarkers, such as Procalcitonin and NT-proBNP, that can aid in early diagnosis and prognostication [11, 12]. This prospective study aims to characterize the clinical profile, including atypical and incomplete presentations, and analyze the utility of inflammatory biomarkers in children admitted with Kawasaki Disease at a tertiary care center in North India.

METHODS

Study Design and Setting: This prospective observational cohort study was conducted over a period of 12 months in the Department of Pediatrics at Indira Gandhi Medical College (IGMC), Shimla, a tertiary care center in North India. The study protocol was approved by the Institutional Ethics Committee (IEC). Written informed consent was obtained from the parents or legal guardians of all enrolled children prior to participation. The study enrolled children aged 2 months to 18 years admitted to the pediatric ward with a diagnosis of Kawasaki Disease (KD).

Inclusion Criteria: Children meeting the clinical criteria for Complete KD or the algorithmic criteria for Incomplete/Atypical KD as defined by the American Heart Association (AHA) 2017 guidelines [1].

Exclusion Criteria: Children with other confirmed rheumatological disorders, active malignancies, or proven non-KD infections were excluded. Patients who left against medical advice (LAMA) or died before enrolment were also excluded.

Clinical and Laboratory Evaluation: Detailed demographic and clinical data were recorded using a pre-designed proforma, focusing on the duration of fever and the presence of principal clinical features (conjunctivitis, oral mucosal changes, polymorphous rash, extremity changes, and cervical lymphadenopathy). Peripheral venous blood (5–7 mL) was collected for hematological and biochemical analysis. Investigations included Hemoglobin, Total Leukocyte Count (TLC), Platelet count, C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), serum albumin, and hepatic transaminases (AST/ALT). Biomarkers including Procalcitonin (PCT), D-Dimer, and Serum Ferritin, were assessed to evaluate disease severity and macrophage activation status. Throat swabs were obtained to rule out streptococcal pharyngitis.

Echocardiography and Outcome Assessment: All patients underwent 2D-Echocardiography at discharge and at a 3-month follow-up visit to assess coronary artery status [13]. Coronary artery abnormalities were classified using body surface area-adjusted Z-scores according to AHA guidelines:

- **Dilatation:** Z-score 2.0 to < 2.5
- **Small Aneurysm:** Z-score ≥ 2.5 to < 5.0
- **Medium Aneurysm:** Z-score ≥ 5.0 to < 10.0 (and absolute dimension < 8 mm)
- **Giant Aneurysm:** Z-score ≥ 10.0 (or absolute dimension ≥ 8 mm).

"IVIG Resistance" was defined as persistent or recrudescent fever ≥ 36 hours after the completion of the initial IVIG infusion [14].

Statistical Analysis: Data was entered into Microsoft Excel and analyzed using SPSS software, Version 29. Qualitative variables were expressed as frequencies and percentages. Quantitative variables were assessed for normality; normally distributed data were presented as Mean ± Standard Deviation (SD), while non-normally distributed data were presented as Median with Interquartile Range (IQR). Associations between qualitative variables (e.g., clinical phenotype and gender) were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A p-value of < 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 29 children with a diagnosis of Kawasaki Disease (KD) were enrolled during the study period. The mean (SD) age of the cohort was 46.4 (28.0) months, with a median of 38 months. The majority of patients (72.4%) were aged between 1 and 5 years. There was a male preponderance, with 16 (55.2%) boys and 13 (44.8%) girls (ratio 1.23:1). A significant proportion of the study population (62.1%) resided in rural areas. The mean BMI of the cohort was 14.6 kg/m², with the lowest BMI observed in patients with the Incomplete KD phenotype.

All patients (100%) presented with fever, with a mean duration of 7.34 (3.78) days at the time of admission. Among the principal clinical features, oral mucosal changes were the most consistent finding, observed in 93.1% of patients, followed by periungual desquamation (72.4%) and cervical lymphadenopathy (65.5%). Notably, classic features such as polymorphous rash (51.7%) and non-purulent conjunctivitis (41.4%) were observed in approximately half of the cohort. Systemic involvement was frequent; gastrointestinal symptoms including diarrhea (24.1%) and vomiting (20.7%) were the most common non-cardiac presentations (**Table 1**).

Diagnostic Classification: Based on the American Heart Association (AHA) criteria, only 12 patients (41.4%) met the definition for Classic KD. The majority (58.6%) presented with non-classic forms, comprising Atypical (31.0%) and Incomplete (27.6%) phenotypes. Analysis of demographic associations revealed a significant male predominance in the Incomplete subgroup, where

87.5% of cases were male. Patients with Incomplete KD also had a longer mean duration of hospital stay (10.0 days) compared to those with Classic KD (8.17 days) or Atypical KD (6.44 days).

Laboratory and Biomarker Analysis: Baseline laboratory parameters indicated a state of systemic inflammation with anemia (mean hemoglobin 11.2 g/dL) and leukocytosis (mean TLC 12,631 /µL). Acute phase reactants were universally elevated; the mean CRP was 77.04 mg/L and mean ESR was 49.93 mm/hr. Biomarker analysis revealed significantly elevated serum Procalcitonin levels (mean 3.28 ng/mL; range 0.12–23.60 ng/mL) and D-Dimer levels (mean 1075 ng/mL).

Hyperferritinemia (>500 ng/mL) was observed in severe cases, with a maximum recorded value of 2000 ng/mL. Throat swab cultures were sterile for Group A Streptococcus in all patients, supporting the non-infectious etiology of the pharyngeal erythema (**Table 2**).

Treatment and Outcomes: Intravenous Immunoglobulin (IVIG) was administered to 27 (93.1%) patients. The response to therapy was favorable, with 96.4% of treated patients showing defervescence within 36 hours. IVIG resistance was observed in only one patient (3.6%).

Echocardiographic assessment at discharge revealed coronary artery dilatation (Z-score ≥2.0) in 24 (82.8%) patients. The involvement was mild-to-moderate, with a maximum Z-score of +3.7; no giant aneurysms were detected. At the 3-month follow-up, coronary dimensions had normalized in 27 (93.1%) patients. Persistent coronary artery abnormalities were restricted to 2 (6.9%) patients, indicating that the majority of lesions represented transient coronary ectasia rather than permanent sequelae.

DISCUSSION

This prospective study highlights the changing epidemiological and clinical landscape of Kawasaki Disease (KD) in a North Indian tertiary care setting [13]. Our findings reinforce the growing consensus that "Classic" KD is becoming the minority presentation, necessitating a shift from pattern recognition of mucocutaneous signs to a risk-stratification approach involving biomarkers and early echocardiography.

The demographic profile of our cohort, with a quarter of patients aged above 5 years, aligns with recent literature from India suggesting a "right-shift" in age distribution compared to Japanese cohorts [15]. While the male preponderance (1.23:1) is consistent with global data, our study identified male gender as a significant risk factor for "Incomplete" KD (ratio 7:1) [17]. This creates a "double jeopardy" for male children, who are biologically predisposed to higher coronary risk yet less likely to manifest classic diagnostic signs.

A salient finding of this study is the predominance of non-classic phenotypes (58.6%), comprising Incomplete and Atypical forms. Consequently, classic features like polymorphous rash (51.7%) and conjunctivitis (41.4%) were notably absent in nearly half the cohort. This contrasts with Western literature where these signs are reported in >90% of cases [16, 17]. Conversely, cervical lymphadenopathy was observed in 65.5% of our patients, significantly higher than global estimates (~15-50%), [14] likely reflecting the overlap with bacterial lymphadenitis mimics in our setting or the older age profile of Indian patients. The significantly longer hospital stay observed in Incomplete KD (mean 10 days) versus Classic KD (mean 8 days) underscores the "diagnostic lag" inherent to these presentations, where clinicians often await the maturation of clinical criteria or exclude tropical infections like scrub typhus before initiating therapy [18].

Biomarker analysis revealed a hyper-inflammatory profile distinct from simple viral fevers. Contrary to traditional teaching that Procalcitonin (PCT) is low in KD, our cohort exhibited elevated mean PCT levels (3.28 ng/mL). This supports recent evidence that high PCT in KD reflects severe cytokine storm (TNF- α surge) and correlates with coronary risk, rather than bacterial sepsis [7]. Furthermore, the presence of "subclinical Macrophage Activation Syndrome (MAS)" features, including hyperferritinemia (>500 ng/mL), thrombocytopenia, and elevated D-Dimer in a subset of patients identifies a high-risk phenotype requiring vigilance for thrombotic complications [9].

The cardiovascular outcomes in this study highlight the phenomenon of "Transient Coronary Ectasia." While a striking 82.8% of patients had coronary dilatation (Z-score ≥ 2.0) at discharge, 93.1% of these normalized by the 3-month follow-up [4, 7]. This suggests that the majority of acute phase lesions represent reversible vasodilation and mural edema rather than permanent necrotizing arteritis. However, the presence of persistent abnormalities in 6.9% of patients confirms the potential for long-term morbidity.

Therapeutically, the cohort demonstrated a favorable response to IVIG, with a resistance rate of only 3.6%. This is notably lower than the 10-20% resistance rates reported in Japan and the West [14, 16]. This discrepancy suggests that Japanese risk stratification tools (e.g., Kobayashi score) may not be applicable to the Indian population, who appear to mount a robust inflammatory response that remains sensitive to immunomodulation.

The study is limited by its small sample size (n=29) and single-center design, which precludes robust multivariate analysis of risk factors. The lack of a febrile control group limits the calculation of specificity for biomarkers like Procalcitonin. Additionally, missing data for NT-proBNP prevented the evaluation of this cardiac biomarker in our setting.

CONCLUSIONS

Kawasaki Disease in this North Indian cohort predominantly presents as "Incomplete" or "Atypical" forms, frequently lacking rash or conjunctivitis. Male gender and lower BMI are associated with incomplete presentations. Despite high initial rates of coronary ectasia, the long-term prognosis is excellent with timely IVIG therapy. Clinicians should maintain a low threshold for echocardiography in children with unexplained prolonged fever and elevated inflammatory markers, even in the absence of classic clinical criteria.

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Table 1: Clinical Profile and Systemic Manifestations (N=29)

Clinical Feature	Frequency (n)	Percentage (%)
Principal Diagnostic Criteria		
Fever (>5 days)	29	100
Oral Mucosal Changes	27	93.1

Strawberry Tongue	24	82.8
Periungual Desquamation	21	72.4
Cervical Lymphadenopathy (>1.5 cm)	19	65.5
Polymorphous Rash	15	51.7
Non-purulent Conjunctivitis	12	41.4
Systemic & Other Features		
Diarrhea	7	24.1
Vomiting	6	20.7
Pulmonary Involvement	2	7.1
Joint Pain (Arthralgia)	2	6.9
Beau Lines (Nail changes)	2	6.9
Shock / Meningitis	0	0

Table 2: Laboratory Parameters and Biomarker Profile

Parameter	Mean ± SD	Median	Range (Min – Max)
Hematology			
Hemoglobin (g/dL)	11.26 ± 1.42	11.4	6.60 – 12.90
Total Leukocyte Count (/µL)	12,631 ± 6,782	9,630	5,800 – 31,000
Platelet Count (Admission) (/µL)	274,275 ± 139,287	2,50,000	79,000 – 639,000
Inflammatory Biomarkers			
C-Reactive Protein (mg/L)	77.04 ± 60.54	70	9.26 – 299.00
ESR (mm/hr)	49.93 ± 31.28	45	5.0 – 110.0
Procalcitonin (ng/mL)	3.28 ± 5.23	1.2	0.12 – 23.60
Serum Ferritin (ng/mL)	283 ± 420	139	56 – 2000
D-Dimer (ng/mL)	1075 ± 1579	456	0.15 – 5853
Biochemistry			
Serum Albumin (g/dL)	3.65 ± 0.46	3.7	2.65 – 4.40
AST (U/L)	51.02 ± 56.40	36	14.00 – 311.00
ALT (U/L)	45.31 ± 48.15	-	-

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