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COMPARISON OF CARDIOVASCULAR MANIFESTATIONS AND CLINICAL CHARACTERISTICS BETWEEN KAWASAKI DISEASE AND MIS-C

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Abstract:

Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C) share overlapping inflammatory features, yet they differ substantially in epidemiology, cardiac involvement, and clinical severity. This review compares their cardiovascular and clinical characteristics to clarify key distinctions. KD predominantly affects children under five years of age and shows coronary artery abnormalities in fewer cases. By contrast, MIS-C occurs in older children and adolescents, is more common in Black and Hispanic populations, and demonstrates more severe cardiac involvement, with exhibiting coronary dilation and majority presenting with shock or depressed ventricular function. Cardiac MRI in MIS-C frequently reveals diffuse myocardial edema without fibrosis, and left ventricular strain is significantly reduced compared with KD. MIS-C also presents with broader multisystem involvement, including gastrointestinal, neurological, and MAS-like inflammatory features. These differences highlight that, despite superficial overlap, KD and MIS-C represent distinct clinical entities requiring tailored diagnostic and therapeutic approaches. [1,5]

Keywords: Multisystem Inflammatory Syndrome in Children, MIS-C, SARS-CoV-2, COVID-19, Pediatric Inflammation, Coronary Artery Abnormalities, Myocardial Dysfunction, Cardiovascular Complications, Shock, Pediatric Cardiology, Epidemiology, Inflammatory Syndrome, Cardiac MRI, Ventricular Function, Multisystem Involvement

INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) is a systemic inflammatory condition that occurs after SARS-CoV-2 infection. Because MIS-C shares several clinical features with Kawasaki disease (KD), early reports proposed that MIS-C might represent a COVID-19–related form of KD. Recent evidence, however, indicates that although the two syndromes overlap in some manifestations, they show distinct epidemiologic and clinical patterns that suggest different underlying mechanisms.

One major difference is the age distribution. KD typically occurs in infants and young children, with a median age of about 1.5 years, whereas MIS-C is more commonly reported in school-aged children and adolescents. The racial and ethnic patterns also diverge. KD mainly affects children of East Asian ancestry, while MIS-C is disproportionately seen in African American, Hispanic, and Afro-Caribbean populations, and appears to be relatively rare in East Asian children. [1,6]

Clinically, MIS-C presents with broader and more severe multisystem involvement compared with KD. Children with MIS-C frequently show significant gastrointestinal symptoms, myocardial dysfunction, and shock, often requiring vasoactive support. In contrast, shock occurs in only a small minority of KD cases. These findings highlight that MIS-C, while superficially similar to KD, likely represents a distinct inflammatory process with its own characteristic phenotype.

Although both MIS-C and KD can lead to cardiovascular complications in children, the two conditions differ markedly in age of onset, inflammatory patterns, organ involvement, and the type of cardiac injury observed. These differences make rapid and accurate differentiation essential in clinical practice, especially in the post-pandemic era when febrile

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children with systemic symptoms must be evaluated for both syndromes.

In this review, we summarize recent findings from the past five years comparing the pathophysiology, clinical presentations, cardiac manifestations, diagnostic features, and treatment approaches of MIS-C and KD. By outlining these key distinctions, we aim to support clinical decision-making in children with systemic inflammatory disease and provide updated evidence relevant to pediatric cardiovascular care.

I. OVERVIEW OF DISEASES

Kawasaki disease (KD) is a rare pediatric illness characterized by sudden fever, typically affecting children under five years old. The diagnosis is based on clinical criteria, with a fever lasting five days or more and at least four of the following symptoms: bilateral conjunctival hyperemia, changes in the lips and oral cavity, cervical lymphadenopathy, redness and swelling of the hands and feet, desquamation around nails in the subacute phase, and a polymorphous rash. If a child has a fever lasting five days but only two or three of these symptoms, it is classified as incomplete or atypical KD.

Despite some similarities, Kawasaki disease and MIS-C differ in several key aspects. Both conditions share common features like fever, rash, conjunctivitis, and cervical lymphadenopathy. However, MIS-C tends to cause more gastrointestinal issues, shock, and coagulopathy, which are less common in KD. Additionally, MIS-C often leads to significant cardiac complications, including myocardial inflammation, coronary artery aneurysms, and dysfunction of the left ventricle.

Epidemiologically, MIS-C is more prevalent in children of Hispanic, African, or Latino descent, while KD is more common in Northeast Asia. KD predominantly affects children under five, whereas MIS-C is more commonly seen in older children. The etiology of these diseases is unclear and multifactorial; however, infections (mainly viral) play a crucial role in both cases

Kawasaki patients were treated mainly with IVIG and did not require intensive care or additional therapies such as corticosteroids, enoxaparin, anakinra, mechanical ventilation, or plasma exchange. In contrast, MIS-C patients often needed intensive care and were more likely to receive treatments like corticosteroids, enoxaparin, and plasma exchange, with some even requiring advanced support such as ECMO. Although both groups used IVIG and had similar use of anakinra and mechanical ventilation, MIS-C patients generally needed more intensive and varied treatment, stayed in the hospital longer, while Kawasaki patients experienced fever for a longer period.

These differences in clinical presentation, pathology, and epidemiology suggest that KD and MIS-C are distinct conditions. The challenge of distinguishing between the two has become particularly evident during the SARS-CoV-2 pandemic, with some patients presenting symptoms that overlap with both diseases. While many studies have compared KD with MIS-C, fewer have explored the specific differences, which is the focus of this study.

II. PATHOPHYSIOLOGICAL COMPARISON

The recently proposed model of Kawasaki Disease (KD) arteriopathy describes three temporally overlapping pathological processes involving medium-sized arteries, particularly the coronary arteries.

The first process, necrotizing arteritis, develops within the initial two weeks after fever onset and is driven by a neutrophil-predominant inflammatory response. This destructive process extends through the arterial wall and into the adventitia, leading to early aneurysm formation. Importantly, it is self-limited and resolves without ongoing tissue destruction. The second process, subacute and chronic vasculitis, also begins within the first two weeks but may persist for months or years in a minority of patients. This stage is characterized by lymphocytes, plasma cells, eosinophils, and fewer macrophages infiltrating the arterial wall. It progresses asynchronously and frequently overlaps with the other processes, sustaining vascular inflammation over time. The third process, luminal myofibroblastic proliferation (LMP), arises from the transformation of medial smooth muscle cells into myofibroblasts. LMP can continue for months to years and results in progressive luminal narrowing. Unlike simple scar formation, it represents an active proliferative response associated with ongoing subacute or chronic inflammation. LMP is a major contributor to long-term coronary stenosis in patients with significant coronary artery abnormalities. [4]

Together, these processes explain the evolution from acute vascular injury to chronic arterial remodeling observed in KD.

Multisystem Inflammatory Syndrome in Children (MIS-C) is a post-infectious hyperinflammatory condition that typically develops weeks after SARS-CoV-2 exposure. Unlike KD, its pathophysiology is dominated by dysregulated systemic immune activation rather than a specific arteriopathy.

Adaptive immune abnormalities are prominent. T-cell lymphopenia involving CD4+, CD8+, γδ, and regulatory T cells is common, while activation

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of CX3CR1+ CD8+ T cells has been linked to vascular and cardiac dysfunction. Some patients display expansion of double-negative T cells, suggesting atypical T-cell responses. B-cell activation is also notable, with increased plasmablasts and autoantibodies targeting endothelial and immune cells, potentially contributing to vascular injury.

Innate immune activation further amplifies inflammation. Activated neutrophils and monocytes exhibit heightened inflammatory gene expression and form neutrophil extracellular traps (NETs), which can promote thrombosis and endothelial damage. Elevated pro-inflammatory cytokines—including IL-6, IL-10, IL-17A, TNF, IFN-γ, and a wide range of chemokines—reflect broad activation of both myeloid and lymphoid pathways and are a hallmark distinction from acute COVID-19 in children. Emerging evidence suggests that gut barrier dysfunction may contribute to MIS-C pathogenesis. Persistent intestinal SARS-CoV-2 and dysbiosis can increase zonulin release, enabling microbial or viral antigens to enter the circulation and trigger systemic hyperinflammation. Genetic susceptibility, including variants affecting immune regulation (e.g., SOCS1, XIAP, CYBB, certain HLA class I alleles), may further heighten vulnerability to excessive immune activation. [3, 6]

Collectively, MIS-C represents a multisystem hyperinflammatory state driven by coordinated dysregulation of innate and adaptive immunity, with secondary effects on the cardiovascular system.

III. CARDIAC INVOLVEMENT

Cardiac complications are central to both Kawasaki disease (KD) and Multisystem Inflammatory Syndrome in Children (MIS-C), but they differ in prevalence, severity, and pathophysiology.

Cardiac manifestations are common and frequently severe. Left ventricular systolic dysfunction is the predominant finding, with depressed ejection fraction reported in 31–100% of patients undergoing imaging. In critically ill cohorts, 72% of children presented with mild-to-moderate dysfunction (LVEF 30–50%) and 28% with severe dysfunction (LVEF <30%). Most patients recover rapidly, with 70–95% regaining normal function within one week or before discharge. Myocarditis and pericarditis are frequent, affecting 44–53% and 25–32% of patients, respectively, with adolescents demonstrating higher rates of myocarditis (up to 81%). Coronary artery abnormalities, including dilation and aneurysms, are reported in 47–93% of patients, while giant aneurysms remain rare. Cardiac MRI and echocardiography typically reveal diffuse myocardial edema without fibrosis, and global left ventricular strain is lower than in KD. Standardized treatments with IVIG and corticosteroids have reduced both severity and incidence of cardiac complications.

Cardiovascular involvement determines both short- and long-term outcomes. Coronary arteries are primarily affected, though inflammation can also involve the pericardium, myocardium, and endocardium. Three pathological processes underlie coronary artery damage: necrotizing arteritis within the first two weeks, subacute/chronic vasculitis, and luminal myofibroblastic proliferation (LMP), which can cause progressive stenosis. Clinically, tachycardia and a hyperdynamic precordium are common, with mild mitral regurgitation observed in 25% of patients and small pericardial effusions frequent. Myocarditis appears early but usually causes mild, rapidly reversible left ventricular dysfunction. Coronary artery involvement ranges from transient dilation to aneurysms; large or giant aneurysms carry risks of thrombosis, stenosis, myocardial ischemia, and rare rupture. IVIG therapy has markedly improved outcomes, reducing coronary complications and mortality.

Compared with KD, cardiac involvement in MIS-C is more frequent and often more severe. While untreated KD carries a 25% risk of coronary artery abnormalities, contemporary treatment reduces this to <10%, whereas MIS-C reports range from 14–48% despite emerging standardized protocols. Shock and severe myocardial dysfunction are more common in MIS-C, and diffuse myocardial edema without fibrosis is a typical imaging finding. Both diseases share systemic inflammation and potential coronary complications, but MIS-C more frequently requires intensive care and shows broader multisystem involvement.

Laboratory abnormalities in MIS-C consistently reflect systemic inflammation, myocardial injury, and coagulation activation. Inflammatory markers, including CRP, ferritin, procalcitonin, and IL-6, are markedly elevated in the majority of patients. Evidence of cardiac involvement is supported by substantial elevations in troponin and NT-proBNP. Coagulation abnormalities are also common, with elevated D-dimer and fibrinogen levels, alongside frequent findings of lymphocytopenia, neutrophilia, hypoalbuminemia, anemia, and thrombocytopenia. [7]

In KD, laboratory findings similarly indicate systemic inflammation, though typically with less pronounced myocardial injury or coagulopathy compared with MIS-C. Elevated CRP, ESR, and leukocytosis are common, whereas troponin elevations are generally mild during the acute phase. Coagulation

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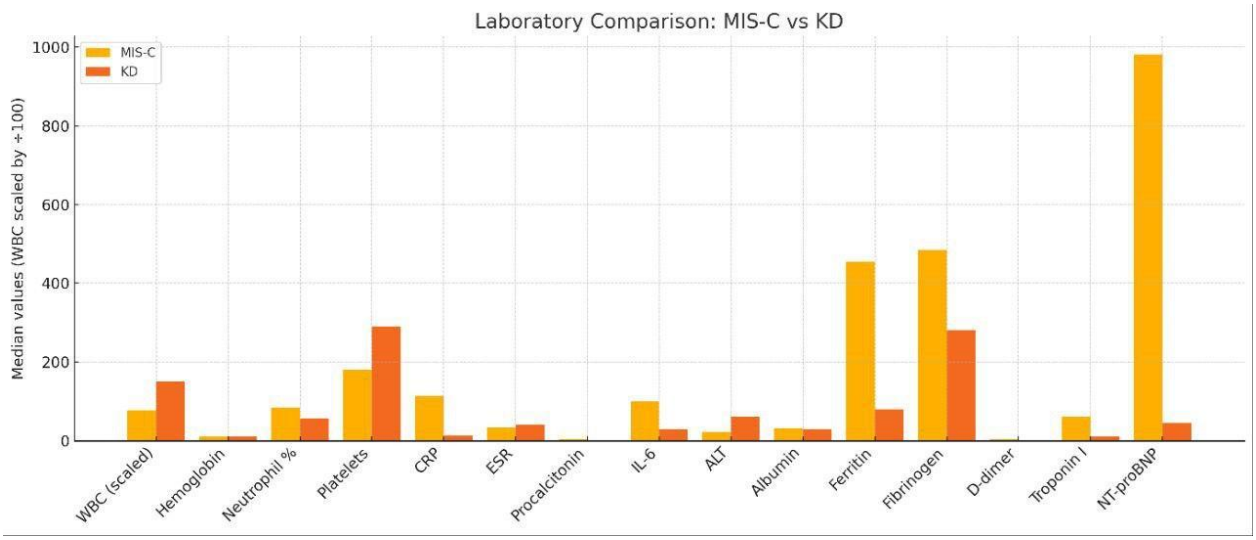
abnormalities are less prominent, and significant thrombocytopenia usually occurs only in the subacute or chronic stages. [5, 6]

Overall, MIS-C is distinguished by more profound systemic inflammation, myocardial injury, and coagulation activation than KD. Laboratory abnormalities in MIS-C are often more extensive due to the multisystem involvement and are valuable for identifying patients at risk of myocardial dysfunction and shock. By contrast, KD laboratory profiles primarily reflect inflammation associated with coronary artery involvement, with severe coagulation abnormalities being uncommon.

IV. CLINICAL FEATURES & LABORATORY FINDINGS

Recent findings highlight distinct clinical features associated with Kawasaki disease (KD) and Multisystem Inflammatory Syndrome in Children (MIS-C).

In patients with Kawasaki disease, symptoms such as rash, changes in mouth mucosa, cervical lymphadenopathy, bilateral conjunctival injection, and hand and foot erythema and edema were notably more common. Conversely, MIS-C patients exhibited a higher incidence of acute gastrointestinal signs, acute respiratory manifestations, and hypotension. [4,5]



To improve visual comparison, the markedly elevated WBC value was adjusted so it would not dominate the scale of the graph. Median values for all markers were also normalized to a comparable range, allowing clearer interpretation of relative differences between the two disease groups.

Laboratory findings further differentiate the two conditions. MIS-C patients showed increased percentages of neutrophils and elevated levels of various inflammatory markers, including CRP, procalcitonin, ferritin, fibrinogen, D-dimer, IL-6, troponin I, and BNP. In contrast, patients with Kawasaki disease had elevated ALT values, increased white blood cell counts, higher platelet counts, and a longer duration of fever. [2,7]

Notably, there were no significant differences in hemoglobin, ESR, or albumin levels between the two groups. This information underscores the importance of recognizing these differing clinical and laboratory findings for accurate diagnosis and treatment. [7]

V. DIAGNOSTIC APPROACH

Kawasaki disease (KD) is diagnosed based on clinical criteria. Patients who meet the case definition through the main clinical signs are classified as complete (or typical) KD. Those who do not show enough main clinical signs may be diagnosed with incomplete (or atypical) KD. In the absence of a specific diagnostic test, additional clinical, laboratory, and echocardiographic findings can support the diagnosis of incomplete KD when the patient's presentation suggests KD but does not fully meet the standard case definition. [1,5]

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AHA KD DIAGNOSTIC CRITERIA
Classic KD is diagnosed in the presence of fever for at least 5 d (the day of fever onset is taken to be the first day of fever) together with at least 4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 d of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 d of fever in rare cases :
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
A careful history may reveal that ≥1 principal clinical features were present during the illness but resolved by the time of presentation.
Patients who lack full clinical features of classic KD are often evaluated for incomplete KD. If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases.
Laboratory tests typically reveal normal or elevated white blood cell count with neutrophil predominance and elevated acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate during the acute phase. Low serum sodium and albumin levels, elevated serum liver enzymes, and sterile pyuria can be present. In the second week after fever onset, thrombocytosis is common.

Chart showing diagnostic criteria for Kawasaki disease (KD), adapted from American Heart Association (AHA) guidelines.

MIS-C CRITERIA
A person under 21 years who exhibits a temperature of 38.0 °C or higher for at least 24 h, or a report of a 24 h or longer subjective fever and signs of inflammation, including but not restricted to elevated levels of ESR, CRP, procalcitonin, ferritin, fibrinogen, lactic acid dehydrogenase, D-dimer or interleukin-6, as well as decreased lymphocytes, low albumin, and increased neutrophils, with clinically severe disease necessitating hospitalization, and multisystem involvement with two or more of dermatologic, renal, gastrointestinal, respiratory, hematologic, cardiac or neurological organs; AND
• No viable alternative diagnoses; AND
• Exposure to COVID-19 within the four weeks preceding symptom onset or a positive result for recent or active SARS-CoV-2 infection, as confirmed by antigen testing, serology, or RT-PCR.
Extra remarks
If a person meets the MIS-C case definition, they still need to be reported, regardless of whether they, in whole or in part, satisfy the criteria for Kawasaki disease.
All cases of juvenile death associated with SARS-CoV-2 infection must be assessed for MIS-C.

This chart showing diagnostic criteria for MIS-C, established by the Centers for Disease Control and Prevention (CDC)

Clinical features of the disease rarely manifest simultaneously, making early diagnosis challenging. Likewise, in patients presenting after 1–2 weeks of fever, certain signs may have already resolved; a thorough review of prior symptoms is therefore essential for accurate diagnosis. [1]

VI. TREATMENT MODALITIES

MIS-C often presents with shock and cardiovascular involvement, for which high-dose glucocorticoids are recommended and have been used successfully. Current ACR guidelines advise IVIG as first-line therapy in hospitalized patients, adding glucocorticoids for shock, organ-threatening disease, or refractory cases. In one study of 181 children, IVIG combined with methylprednisolone had a lower failure rate than IVIG alone (OR 0.25; 95% CI 0.09–0.70), although a larger multinational study of 615 children found no difference in acute outcomes between IVIG alone, IVIG with steroids, or steroids alone. [6]

For refractory MIS-C, anakinra (IL-1 receptor antagonist) has been used, extrapolating from its success in IVIG-resistant Kawasaki disease. Zonulin-dependent intestinal barrier dysfunction may contribute to hyperinflammation, and the zonulin antagonist larazotide showed benefit in a patient unresponsive to standard anti-inflammatory therapy.

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Given the high risk of hypercoagulability (D-dimer elevated in 92% of patients), anticoagulation with aspirin and/or enoxaparin has been reported, following strategies used in Kawasaki disease. [6,7,8]

The mainstay of treatment for acute Kawasaki disease (KD) is intravenous immunoglobulin (IVIG), which has been shown to significantly reduce the risk of coronary artery abnormalities. The recommended regimen is 2 g/kg as a single infusion over 10–12 hours, typically administered together with aspirin. IVIG exerts generalized anti-inflammatory effects, including modulation of cytokine production, neutralization of pathogenic agents, augmentation of regulatory T-cell activity, suppression of antibody synthesis, and provision of anti-idiotypic antibodies. Higher peak serum IgG levels are associated with improved outcomes and lower incidence of coronary artery changes.

Acetylsalicylic acid (ASA) is used in combination with IVIG for its anti-inflammatory and antiplatelet properties. During the acute phase, high-dose ASA is administered at 80–100 mg/kg/day in the United States and 30–50 mg/kg/day in Japan and Western Europe, divided every 6 hours. Following the acute phase, low-dose ASA (3–5 mg/kg/day) is continued until there is no evidence of coronary artery abnormalities, typically 6–8 weeks after disease onset. While ASA does not appear to reduce the frequency of coronary artery complications on its own, it remains an important adjunct to IVIG therapy during the acute management of KD. [6]

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