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Research Article

PIMS-TS Complicating SARS-CoV-2 Infection: A Report of 10 Pediatric Cases

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Abstract

SARS-CoV-2, or COVID-19, is a betacoronavirus identified by the WHO as the cause of the 2020 pandemic. Unlike most respiratory virus, children exhibit lower susceptibility to COVID-19 and generally develop milder disease courses, with reduced mortality rates. Recently, there have been reports of clustered cases characterized by shock states associated with elevated cardiac biomarkers and vasoplegia, necessitating treatment with inotropes, vasopressors, and fluid resuscitation. This clinical presentation has been linked to the emergence of Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS), also known as Kawasaki-like syndrome. This study is a retrospective analysis of 10 pediatric patients diagnosed with PIMS-TS secondary to COVID-19 infection, who were admitted to Mohammed VI International University Hospital in Casablanca, Morocco, from January 2021 to October 2023. The cohort's ages ranged from 2 to 13 years, with a mean age of 6 years, and demonstrated a male predominance (sex ratio 9M:1F). Clinical manifestations included prolonged fever, gastrointestinal disturbances, rash, conjunctivitis, and cheilitis. Laboratory findings revealed elevated levels of CRP, PCT, and ferritin, indicative of an atypical Kawasaki syndrome. These patients responded to intravenous immunoglobulin therapy, with adjunctive corticosteroids administered as needed. All patients experienced favorable outcomes, with resolution of systemic involvement and normalization of inflammatory markers, and no relapses or fatalities were recorded. The risk factors for PIMS-TS complicating COVID-19 infection remain unclear. However, there are noted parallels between PIMS-TS and Kawasaki syndrome diagnostic criteria, suggesting possible pathophysiological overlap. In conclusion, a novel multisystem inflammatory syndrome associated with COVID-19 infection, resembling Kawasaki syndrome, has been identified in pediatric patients. This emerging syndrome enhances our understanding of the complex pathophysiology associated with COVID-19 and underscores the need for continued research into its etiology and optimal management strategies.

Keywords

COVID-19, PIMS-TS, MIS-C, SRAS-COV-2, Kawasaki

1. Introduction

The SARS-CoV-2, or COVID-19, is a coronavirus strain that emerged in December 2019 in Wuhan, China, and was declared a pandemic by the WHO in March 2020 due to its high mortality rate, causing significant public health and economic impacts globally. [1, 2]

In the pediatric population, this beta-coronavirus triggers a

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"cytokine storm" or a multisystem inflammatory syndrome (PIMS-TS or MIS-C), resulting in a specific cardiogenic shock state reminiscent of Kawasaki syndrome. [2, 3]

This condition necessitates urgent medical attention as it can progress to severe complications such as myocarditis, posing a life-threatening risk to affected children.

Primary prevention strategies are paramount, while secondary prevention involves therapeutic interventions and vigilant symptom monitoring in pediatric patients.

Despite an increasing number of case series, scientific evidence to comprehensively understand the relationship between post-COVID-19 MIS-C and Kawasaki syndrome remains limited.

The objective of this retrospective study is to elucidate the connection between MIS-C complicating SARS-CoV-2 infection and Kawasaki syndrome, aiming to develop appropriate preventive and therapeutic approaches to address its complications.

2. SARS-CoV-2 Virus

2.1. Structure of the SARS-CoV-2 Spike Glycoprotein

The SARS-CoV-2, a β-coronavirus, exhibits a complex viral architecture characterized by spike proteins (S) organized in trimers on its surface. These proteins play a pivotal role in the infection process, divided into two functional subunits: S1 and S2. The S1 subunit specifically recognizes angiotensin-converting enzyme 2 (ACE2), expressed on the surface of various human organs. This interaction initiates viral entry into the host. Once bound to ACE2, the S2 subunit of the spike protein facilitates fusion of the virus with the host cell membrane, thereby releasing its viral genetic material into the host cell.

The sophisticated structure of the SARS-CoV-2 spike protein, characterized by its high affinity for ACE2 and the presence of a furin cleavage site, distinguishes it from other coronaviruses. This specific interaction with ACE2 is particularly significant in the respiratory tract, heart, kidneys, and other organs where ACE2 is expressed. This specificity enhances the virus's infectivity and pathogenicity in infected individuals.

By utilizing ACE2 as a key receptor, SARS-CoV-2 evades cellular defenses and exploits normal cellular processes for its entry and replication, thereby facilitating rapid spread of infection. Understanding the intricate structure and function of these mechanisms is crucial for guiding the development of targeted therapeutic and vaccine strategies against SARS-CoV-2. [4-6]

2.2. Molecular Architecture of the SARS-CoV-2

SARS-CoV-2 utilizes its spike protein (S protein) to infect host cells. This protein consists of two primary subunits, S1 and S2, with S1 containing the receptor-binding domain (RBD) crucial for specific interaction with angiotensin-converting enzyme 2 (ACE2) on human cell surfaces. Initially adopting a 'down' conformation with approximately 10 glycans, the RBD structure is susceptible to modification through glycosylation processes. Upon binding to ACE2, a significant conformational change occurs, termed 'RBD up,' enhancing its interaction with ACE2. [7, 8]

Binding of RBD to ACE2 can also activate proteolytic cleavage of the S protein by proteases like furin, between subunits S1 and S2. This cleavage exposes subunit S2, essential for fusion with the host cell membrane, thereby facilitating viral RNA entry into the host cell to initiate infection.

To ensure its infectious efficacy, SARS-CoV-2 must efficiently package its 30 kb RNA within a confined space of approximately 80 nm in virion diameter. Observations suggest that ribonucleoproteins (RNPs), consisting of viral RNA and viral proteins like nucleocapsid proteins (N-proteins), are densely packed within the viral lumen. This densely packed and sometimes locally ordered arrangement of RNPs minimizes RNA entanglement and potential damage, optimizing packaging efficiency and ensuring viral genomic stability.

Cryo-ET and SDS-PAGE/MS analysis indicates that these densities likely represent RNPs, aligned using spherical masks revealing bucket-like and reverse G-shaped architectures with specific dimensions. These structures are crucial for fusion with the host cell membrane and viral infection initiation, closely associated with the viral envelope, forming assemblies in 'hexagon' or 'pyramid' shapes depending on the virion's geometry. [4, 9]

In summary, this study underscores the pivotal role of RNPs in viral assembly, enhancing the virus's resilience against environmental and physical challenges. However, precise mechanisms governing RNP assembly and their interaction with other viral components remain to be fully elucidated. [5, 6]

2.3. Cryo-EM structure of the SRAS-COV-2 in the Prefusion Conformation

Operating at a resolution of 3.5 angstroms, cryo-electron microscopy delineates an "open" trimeric conformation of the receptor-binding domain (RBD), underscoring its accessibility for receptor binding and subsequent viral invasion. Notably, this crystallographic analysis highlights a robust affinity of approximately 15 nM between the Spike protein of SARS-CoV-2 and ACE2, surpassing that observed with related coronaviruses like SARS-CoV, thereby elucidating the heightened transmissibility observed with SARS-CoV-2 in human populations. [4, 10]

The detailed cryo-electron microscopy analysis of the Spike protein (S) from SARS-CoV-2 in its prefusion conformation reveals critical insights into its intricate architecture and functional mechanisms. As a class I trimeric fusion pro-

tein, Spike (S) undergoes substantial structural rearrangements in its metastable state to facilitate viral entry into host cells. Comprising two functional subunits, S1 and S2, the former harbors the receptor-binding domain (RBD) specific to angiotensin-converting enzyme 2 (ACE2), pivotal on the surface of host cells. [4, 10]

Upon encountering a human cell, the RBD of S1 binds ACE2 with high specificity, triggering a conformational shift within the Spike protein. Initially nestled in a "down" position against the protein, the RBD transitions to an "up" conformation, thereby exposing its binding epitope and optimizing interaction with ACE2. This structural alteration enhances the efficiency of viral entry into the host cell.

Once engaged with ACE2, the S2 subunit of the Spike protein facilitates membrane fusion between the viral envelope and the cellular membrane. This fusion event enables the release of viral genetic material into the host cell, initiating the viral replication cycle. [4, 10]

2.4. Structural Basis for the Recognition of SARS-CoV-2 by Full-Length Human ACE2

The recognition of SARS-CoV-2 by full-length human ACE2 involves intricate molecular interactions that govern viral entry and infectivity. SARS-CoV-2, a novel coronavirus that emerged in late 2019, utilizes its spike protein (S) to bind to the human ACE2 receptor on host cells, thereby facilitating viral entry and subsequent infection. Understanding the detailed molecular interactions between the viral S protein and ACE2 receptor is crucial for elucidating COVID-19 pathogenesis and developing effective therapeutic strategies.

The spike protein of SARS-CoV-2 consists of two functional subunits: S1, responsible for receptor binding, and S2, facilitating membrane fusion. Within the S1 subunit, the receptor-binding domain (RBD) specifically interacts with ACE2 on the host cell surface. High-resolution structural studies, including X-ray crystallography and cryo-electron microscopy, have provided key insights into this interaction. The RBD of the SARS-CoV-2 spike protein adopts a conformation that optimally binds to ACE2, similar to its predecessor SARS-CoV, despite distinct sequence variations.

Structural analyses have highlighted critical amino acid residues in both the spike protein RBD and ACE2 receptor that govern their affinity and specificity. Notably, amino acid residues such as lysine 31 and glutamine 42 on ACE2 form hydrogen bonds with residues on the RBD, enhancing binding affinity. This interaction induces a conformational change in the spike protein, facilitating membrane fusion and viral entry into the host cell. Insights from these structural studies not only deepen our understanding of viral entry mechanisms but also provide a foundation for developing targeted therapies, including neutralizing antibodies and small molecule inhibitors, aimed at disrupting the SARS-CoV-2-ACE2 interaction to effectively combat COVID-19. [4, 10]

2.5. The Mechanism of SARS-CoV-2 Entry

The SARS-CoV-2 virus, responsible for the global COVID-19 pandemic since 2020, belongs to the Betacoronavirus family and shares significant similarity with the SARS-CoV virus that caused the 2002-2004 SARS outbreak.

This enveloped, single-stranded RNA virus utilizes the angiotensin-converting enzyme 2 (ACE2) as its cellular receptor, a mechanism also exploited by other coronaviruses like HCoV-NL63 and MERS-CoV. The viral structure includes nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins, with the S protein being crucial for membrane fusion. The S protein, cleaved into S1 (for ACE2 binding) and S2 (for membrane fusion) subunits by proprotein convertases like furin, plays a vital role in the infection process. Viral infection induces the formation of perinuclear membrane-bound replication organelles likely derived from the endoplasmic reticulum, where viral replication and virion assembly occur. Upon assembly, virions are transported to the ER-Golgi intermediate compartment for final maturation and release. [4, 11]

The conformational changes induced by the S protein's interaction with ACE2 enable membrane fusion, facilitating the entry of viral genome into the host cell. The three-dimensional structure of the S protein, revealed through cryo-electron microscopy studies, provides crucial insights into its pre- and post-fusion conformations, particularly its receptor-binding domain (RBD), the primary site of interaction with ACE2 and a major target for neutralizing antibodies. The Spike protein (S) of SARS-CoV-2 plays a central role in viral infection by interacting with the ACE2 receptor on human cells. Comprising predominantly β-sheet structured C-terminal domains, the protein includes the critical receptor-binding domain (RBD).

This RBD facilitates virus attachment by linking the CTD1 and CTD2 domains of the Spike protein, essential for virus fusion with the cell membrane. In its prefusion form, the S2 subunit of the protein adopts a three-stranded coil conformation critical for structural stability. After fusion, this subunit reorganizes into a rigid six-helix bundle, promoting virus insertion into the host cell. ACE2, the receptor for SARS-CoV-2, is an enzyme primarily present in respiratory pathways but also in other tissues like the colon and kidneys. [4, 10]

The interaction between the Spike protein's RBD and ACE2 is crucial for viral entry into human cells, influencing the virus's ability to infect and spread within the body. ACE2 expression varies across tissues and can be modulated by factors such as age, sex, and medical conditions like hypertension and diabetes, potentially affecting COVID-19 severity in infected individuals. [4, 11]

2.6. The Immune Response to SARS-CoV-2 and Mechanisms of Immunopathological Changes in COVID-19

2.6.1. The Structure of the SARS-CoV-2

SARS-CoV-2, the virus responsible for the global COVID-19 pandemic that began in 2020, belongs to the Betacoronavirus family and shares significant similarity with SARS-CoV, the agent of the 2002-2004 SARS outbreak. This enveloped, single-stranded RNA virus uses angiotensin-converting enzyme 2 (ACE2) as its cellular receptor, a mechanism also employed by other coronaviruses such as HCoV-NL63 and MERS-CoV. [6, 12, 13]

The viral structure comprises nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins, with the spike protein being crucial for membrane fusion with the host cell. The spike protein is cleaved into S1 (responsible for ACE2 binding) and S2 (responsible for membrane fusion) subunits by proprotein convertases like furin, playing an essential role in the infection process. Infection by the virus induces the formation of perinuclear replication organelles derived likely from the endoplasmic reticulum, where viral replication and virion assembly occur. Once assembled, the virions are transported to the ER-Golgi intermediate compartment for final maturation and release. The conformational changes induced by the interaction of the spike protein with ACE2 allow membrane fusion, facilitating the entry of the viral genome into the host cell. The three-dimensional structure of the spike protein, determined by cryo-electron microscopy studies, reveals crucial details about its pre- and post-fusion conformation and its receptor-binding domain (RBD), the main site of interaction with ACE2 and a major target for neutralizing antibodies. [6, 12, 13]

2.6.2. Structure of the SARS-CoV-2 Spike Glycoprotein

The spike protein (S) of SARS-CoV-2 plays a central role in viral infection by interacting with the ACE2 receptor on human cells. Composed mainly of β-sheet structured C-terminal domains, the spike protein includes the crucial receptor-binding domain (RBD).

This RBD facilitates viral attachment by linking the CTD1 and CTD2 domains of the spike protein, essential for viral fusion with the cellular membrane. In its prefusion form, the S2 subunit of the spike protein adopts a three-stranded coil configuration crucial for structural stability. Post-fusion, this subunit rearranges into a rigid six-helix structure, promoting the insertion of the virus into the host cell. [6, 12, 13]

ACE2, the receptor for SARS-CoV-2, is an enzyme present primarily in the respiratory tract but also in other tissues like the colon and kidneys. The interaction between the RBD of the spike protein and ACE2 is crucial for viral entry into human cells, influencing the virus's ability to infect and spread within the body. ACE2 expression varies across tissues and can be modulated by factors such as age, sex, and medical conditions like hypertension and diabetes, which may play a role in the severity of COVID-19 in infected individuals. [4]

2.6.3. The Mechanism of SARS-CoV-2 Entry

SARS-CoV-2 employs two primary pathways for host cell entry: the cell surface-dependent pathway and the endosomal pathway. In the cell surface-dependent pathway, the virus's spike protein undergoes cleavage by furin within virus-producing cells and subsequently by the host cell surface enzyme TMPRSS2. This process exposes the fusion peptide, facilitating direct fusion with the host cell membrane and the release of viral RNA into the cytoplasm. In the endosomal pathway, the virus is internalized via endocytosis and enclosed within an endosome. Here, the spike protein is cleaved by cathepsin L, also exposing the fusion peptide and releasing viral RNA into the cytoplasm. ACE2 expression varies across tissues, influencing viral tropism and disease severity. Comorbidities such as asthma, obesity, and specific genetic conditions may modulate ACE2 expression, potentially impacting COVID-19 outcomes. [14, 15]

The virus can adapt to different ACE2 variants, potentially originating from animal reservoirs like Rhinolophus bats via intermediate hosts such as civets. The severity of infection can vary based on these viral adaptations. Beyond ACE2, molecules like lectins (DC-SIGN and L-SIGN), TIM1, AXL, and CD147 are potential alternative receptors, yet their precise roles in SARS-CoV-2 infection require further investigation in medical research. [14, 15]

The viral entry process of SARS-CoV-2 into host cells involves several crucial steps. Initially, the viral spike protein interacts with the cellular ACE2 receptor, facilitating membrane fusion. This interaction can be aided by the cell surface protease TMPRSS2, which cleaves and activates the spike protein. In the absence of TMPRSS2, endosomal cathepsins can similarly cleave the spike protein. Once activated, the spike protein enables SARS-CoV-2 to fuse with the cellular membrane, releasing its RNA into the cytoplasm to initiate viral replication. Cellular proteins like Toll-like receptors (TLRs) and IFITM proteins can limit this viral entry by triggering innate immune responses. Evolutionarily, SARS-CoV-2 has developed mutations in its spike protein, such as D614G, which can influence its transmissibility and interaction with the host. These mutations reflect adaptation to humans and potential reservoir species like bats and pangolins, which share genetic homology with the virus. This ongoing adaptability underscores the need for constant genomic surveillance to assess emerging risks and adapt strategies to combat the virus, especially against immune escape mutations in the spike protein that may compromise the efficacy of vaccines and antibody-based therapies. SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE2) receptor to enter host cells. This receptor is expressed in cardiopulmonary tissues and some hematopoietic cells. [14, 15]

2.6.4. PIMS-TS and SRAS-COV-2

PIMS-TS typically develops weeks after an acute COVID-19 infection, suggesting an immune-mediated mechanism. SARS-CoV-2 infect dendritic cells, leading to apoptosis and depletion of T lymphocytes due to faulty activation caused by dendritic cell dysfunction, contributing to COVID-19 immunopathology. [1]

Clinical features of MIS-C include persistent fever, gastrointestinal symptoms, rash, conjunctivitis, and mucocutaneous inflammation. Cardiac involvement is common, with many children presenting with myocardial dysfunction, elevated cardiac biomarkers, and, in severe cases, shock. [21, 33]

Laboratory findings often reveal elevated inflammatory markers such as CRP, ferritin, and D-dimer, reflecting the hyperinflammatory state. [1, 2]

A significant feature of severe COVID-19 is cytokine release syndrome, marked by elevated levels of interleukin-6 (IL-6), which correlates with respiratory failure, acute respiratory distress syndrome and adverse clinical outcomes. High CRP levels, driven by IL-6, are also biomarkers of severe beta-coronavirus infection. [33]

Infection of monocytes, macrophages and dendritic cells by SARS-CoV-2 leads to their activation and secretion of IL-6 and other inflammatory cytokines, resulting in a "cytokine storm" responsible for a distinctive cardiogenic shock state characterized by vasoplegia and diastolic arterial hypotension. The management of MIS-C involves a multidisciplinary approach with prompt administration of IVIG and corticosteroids as the mainstay of treatment. Adjunctive therapies such as anakinra or tocilizumab, targeting specific inflammatory pathways, may be used in refractory cases. Supportive care, including fluid resuscitation, inotropic support, and anticoagulation, is critical for managing severe cases with cardiac involvement. [1, 2, 33]

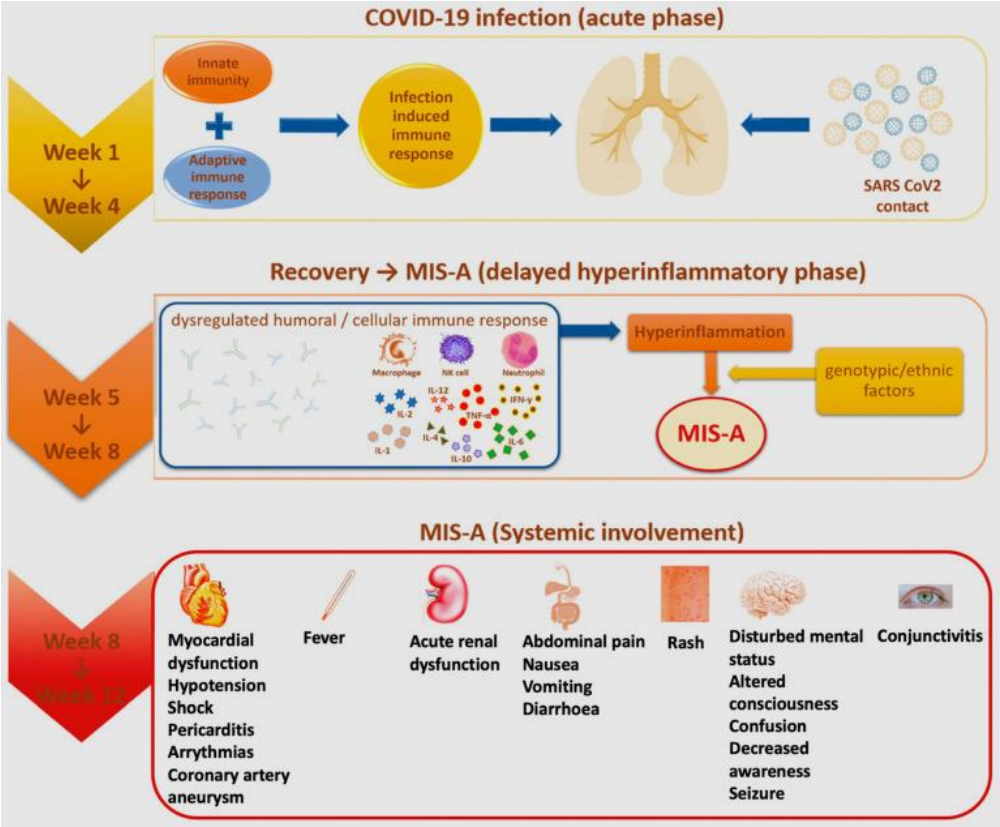

Figure 1. *Pathways leading to cytokine PIMS-TS.*

3. Kawasaki Syndrome

Kawasaki syndrome (KS) is characterized by systemic vasculitis primarily affecting medium-sized arteries, particularly the coronary arteries, in children, which can lead to coronary artery aneurysms if not treated promptly. [1, 17]

Kawasaki disease (KD) was first described by Japanese pediatrician Dr. Tomisaku Kawasaki in 1967 in a Japanese-language journal, and later in 1974 in an English-language journal. He observed a 4-year-old boy who exhibited a range of clinical symptoms, including a persistent high-grade fever and a skin rash. Initially, he referred to this condition as “acute febrile mucocutaneous lymph node syndrome” (MCLS). Despite initial skepticism towards the new diagnosis, Dr. Kawasaki remained persistent. After collecting

a series of 50 cases, he published his findings, accompanied by meticulous hand-drawn diagrams, in a Japanese medical journal. Dr. Kawasaki outlined the key features of this newly discovered disease, which included persistent fever, bilateral non-purulent conjunctivitis, diffuse oral fissures, a distinctive skin rash, edema of the hands and feet, and lymphadenopathy of the neck. [28]

The pathophysiology of Kawasaki syndrome involves a complex interplay of genetic predisposition, immune dysregulation, and potential infectious triggers, although the exact etiology remains elusive. Recent studies have highlighted the role of superantigens and immune complexes in the disease process, contributing to the hyperinflammatory state observed in affected individuals. [16, 17]

According to the American Heart Association (AHA) Guidelines and the Japanese Committee of Kawasaki Disease Research [29-31], there is 5 principal criteria of KD:

1) Strawberry tongue, fissured lips, injected pharynx, and other signs of oropharyngeal mucosa inflammation.
2) Bilateral conjunctivitis (without discharge).
3) Cervical lymph node enlargement of >1.5 cm in diameter of at least one lymph node.
4) Erythema of the palms and soles, edema of the hands and feet in the acute phase, or periungual desquamation after the acute phase.
5) Fever for more than 5 days and a polymorphous skin rash.

Advancements in imaging techniques, particularly echocardiography, have improved the detection and monitoring of coronary artery lesions in KD patients. New biomarkers are also being investigated to aid in early diagnosis and risk stratification. [29-31]

The treatment for Kawasaki disease (KD) primarily involves high-dose intravenous immunoglobulin (IVIG) and aspirin, which significantly reduce the risk of coronary artery complications. Early administration of IVIG within the first 10 days of illness is crucial for optimal outcomes. In resistant cases, additional treatments such as corticosteroids, infliximab, or cyclosporine may be necessary to control inflammation. [29-31]

Despite these advancements, ongoing research is essential to fully elucidate the disease mechanisms and improve therapeutic strategies.

3.1. Physiopathology of Kawasaki Syndrome

3.1.1. Immune Activation and Cytokine Release

The initiation of Kawasaki Disease is often hypothesized to involve an infectious trigger, which sets off an exaggerated immune response in genetically susceptible individuals. This immune dysregulation is marked by the activation of T lymphocytes and macrophages within the arterial walls and circulating immune cells. These activated immune cells release a cascade of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8). During the acute phase of KD, a "cytokine storm" occurs, characterized by high levels of circulating inflammatory mediators. IL-1, IL-6, and TNF-α play pivotal roles, contributing to systemic inflammation, fever, and endothelial dysfunction. These cytokines drive the widespread inflammation observed in KD and are central to its pathogenesis. [17, 18]

3.1.2. Endothelial Cell Dysfunction

Endothelial cells lining the blood vessels play a critical role in the pathogenesis of Kawasaki Disease. The inflammatory cytokines released during the acute phase of the disease lead to endothelial cell activation and dysfunction. This activation results in increased expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). These molecules facilitate the recruitment and adhesion of leukocytes to the vascular endothelium, contributing to local inflammation and vascular injury. Activated endothelial cells become dysfunctional, increasing vascular permeability and allowing immune cells to infiltrate the vascular walls. This endothelial activation and subsequent immune cell recruitment lead to further inflammation and damage to the vascular tissue, playing a crucial role in the development of coronary artery aneurysms (CAA). [19, 20]

3.1.3. Formation of Coronary Artery Aneurysms

One of the most serious complications of Kawasaki Disease is the development of coronary artery aneurysms (CAA). The mechanisms underlying CAA formation are multifactorial and likely involve direct vascular injury from inflammatory cells, cytokine-mediated smooth muscle cell proliferation, and impaired endothelial repair mechanisms. Persistent inflammation and ongoing immune activation can further exacerbate vascular remodeling, leading to the dilation and formation of CAA. Matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix, are upregulated in KD and contribute to the weakening of the vascular walls. This degradation facilitates the formation of aneurysms, underscoring the importance of controlling inflammation to prevent these severe vascular complications. [16, 17]

3.1.4. Genetic and Environmental Factors

While the exact genetic factors predisposing individuals to Kawasaki Disease are not fully understood, studies suggest a genetic component influencing susceptibility and disease severity. Certain genetic polymorphisms, particularly in genes related to immune regulation and inflammatory responses, may contribute to an exaggerated immune reaction to environmental triggers. Polymorphisms in genes such as ITPKC (inositol 1,4,5-trisphosphate 3-kinase C) and CASP3 (caspase 3) have been associated with an increased risk of developing KD. These genetic variations can influence the intensity and regulation of the immune response, potentially leading to

more severe disease manifestations. [23, 22]

3.2. Kawasaki Disease (KD) and Multisystem Inflammatory Syndrome in Children (MIS-C)

COVID-19 has been associated with the emergence of a KD-like condition known as multisystem inflammatory syndrome in children (MIS-C), representing a novel syndrome linked to SARS-CoV-2 infection in pediatric populations.

Kawasaki disease (KD) and Pediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS-TS) share several key clinical and pathophysiological similarities despite their distinct etiologies. Both conditions primarily affect children, with KD typically seen in younger children under the age of 5 years, while PIMS-TS tends to occur in older children and adolescents following recent or concurrent SARS-CoV-2 infection. [34]

Clinically, both KD and PIMS-TS present with systemic inflammation characterized by prolonged fever, mucocutaneous manifestations (such as rash and conjunctivitis), and systemic involvement that can include cardiovascular, gastrointestinal, and respiratory systems. Elevated inflammatory markers, such as CRP and ferritin, are common in both conditions, reflecting the intense inflammatory response. [22, 24, 34]

Furthermore, both KD and PIMS-TS can lead to significant cardiovascular complications, including myocarditis and coronary artery abnormalities, although the incidence and severity may vary. Treatment for both conditions often involve immunomodulatory therapies aimed at reducing systemic inflammation and preventing complications, highlighting their shared approach to management despite differences in specific treatment protocols. [22, 24, 32, 34]

Pathophysiologically, while KD's exact cause remains unclear, both KD and PIMS-TS involve dysregulated immune responses triggered by infectious agents, with PIMS-TS specifically linked temporally to SARS-CoV-2 infection. This association underscores the role of viral-triggered immune dysregulation in both conditions, contributing to their overlapping clinical presentations and systemic manifestations. [34]

4. Materials and Methods

To evaluate the hypothesis of the similarity between post-COVID-19 MIS-C and Kawasaki syndrome, we conducted a qualitative, retrospective study involving 10 pediatric patients who presented with PIMS-TS complicating a COVID-19 infection.

The patients included in our study were those hospitalized at the Mohammed VI International University Hospital (HUIM6) in Bouskoura between January 2021 and October 2023. Patients excluded from our study were those older than 17 years.

The medical records from the pediatric and pediatric intensive care units were collected through the secure electronic system of HUIM6. Data were recorded on an extraction form, entered into a computer, and subjected to statistical analysis using Microsoft Excel. All ethical standards were strictly adhered to.

5. Results

The ages of the patients ranged from 2 to 13 years, with an average age of 6 years, and a sex ratio of 9M/1F. The clinical manifestations were presented as follows (Table 1):

Table 1. *The clinical manifestations of MIS-C post SARS-CoV-2.*

Clinical presentation	Number of cases	Percentage
Complete Kawasaki syndrome	8	80%
Incomplete Kawasaki syndrome	2	20%
Gastrointestinal signs	5	50%

All patients had negative COVID-19 IgM serology and positive COVID-19 IgG serology. The biological examinations revealed the following (Table 2 below):

Table 2. *Biological values and results.*

Biological assessment	Value	Median
C-reactive protein	Positive	117
Sedimentation Rate	Elevated	79,6
Ferritinemia	Elevated	421
D-Dimer	Positive	1 902

All patients received immunoglobulins, aspirin, and corticosteroid therapy. Three patients were treated with antibiotics, and two required oxygen therapy.

The clinical outcomes were favorable for all patients, with improvement in systemic involvement and reduction in inflammatory markers, with no relapses. The overall short- and medium-term survival rate was 100%.

6. Discussion

The diagnostic criteria established by the American Heart Association categorize Kawasaki-like syndrome into two distinct forms: the complete form, characterized by a high fever lasting at least 5 days and the presence of at least four

of the five principal specific clinical signs. Conversely, the incomplete form is characterized by an unexplained fever lasting 5 days or more, accompanied by two to three of the principal clinical signs, supported by laboratory results or cardiac abnormalities. [22]

Post-SARS-CoV-2 PIMS-TS (Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2) or Kawasaki-like syndrome is defined as complete or incomplete Kawasaki syndrome complicated by hemodynamic instability, necessitating intensive care. [24]

The initial reports of a multisystem inflammatory syndrome affecting children emerged from the United Kingdom, Spain, and New York in April 2020. [36]

In the following weeks, Italian pediatric rheumatologists observed a significant rise in Kawasaki disease (KD) cases in Italy. Upon evaluation, these cases were similar to Kawasaki disease but occurred in an older pediatric population. [38]

There were evident similarities between KD and these MIS-C (Multisystem Inflammatory Syndrome in Children) cases. Some patients developed hemodynamic shock resembling Kawasaki shock syndrome. However, more pronounced differences were noted between these extreme presentations of Kawasaki shock and MIS-C shock. [39]

Laboratory abnormalities in MIS-C shock cases were significantly more pronounced compared to Kawasaki shock. Both groups exhibited elevated CRP and ferritin levels, but these elevations were less pronounced in Kawasaki disease shock. [36]

Additionally, the ethnic background of patients differed, with MIS-C patients predominantly being African American/Hispanic, while Kawasaki disease patients who developed shock were more often of Asian descent. [40]

Distinct differences included lymphopenia, low platelet count, and low albumin levels in COVID-19 patients, whereas Kawasaki shock patients did not develop lymphopenia, had less severe thrombocytopenia that reversed within 10 to 14 days and transformed into prolonged thrombocytosis.

In MIS-C patients, platelet counts normalized after the acute phase. The most distinct clinical feature of MIS-C compared to Kawasaki was significant myocardial dysfunction with elevated troponin and BNP markers. In contrast, coronary artery involvement and secondary cardiac dysfunction were predominant in severe Kawasaki cases, with slightly elevated BNP and troponin levels.

To identify differences in immune activation between MIS-C and Kawasaki disease, Consiglio et al. conducted an analysis of immune cell systems, cytokines, and antibodies in patients with Kawasaki disease, MIS-C, SARS-CoV-2 infection, and healthy children. [35]

Their primary analysis revealed that MIS-C overlapped to some extent with Kawasaki hyperimmune syndrome and adult hyperimmune syndrome post-COVID-19.

However, most cytokine profiles were distinct across these subgroups. Principal component analysis showed more similarities in cytokine profiles between MIS-C and SARS-CoV-2 infected children, differing from Kawasaki patients.

Notable differences included IL-6, IL-17, CXCL10, ADA, and SCF. In Kawasaki disease, IL-6, IL-17, and CXCL10 were uniformly expressed at higher levels than in MIS-C and SARS-CoV-2 positive patients. However, between MIS-C and SARS-CoV-2 positive patients, levels were more heterogeneous, suggesting a spectrum rather than two distinct diseases. [40]

Most importantly, the proteome profiling study indicated the presence of immunity against known coronaviruses (human coronavirus 1 and bovine beta coronavirus) in healthy children, SARS-CoV-2 infected patients, and Kawasaki patients, which was surprisingly negative in all MIS-C cohorts. [35]

Before discussing the implications of this finding and relevant immune activation pathways related to coronavirus infections, it would be safer to replicate these data in larger series.

The study also found Endoglin antibodies in both MIS-C and Kawasaki patients, indicating endothelial and cardiac muscle damage. However, MAP2K2 and casein kinase family members were exclusively found in MIS-C. Silmitasertib (CX-4945), a potent antiviral known to inhibit these kinases, is suggested for adjunctive treatment in COVID-19 patients and is currently in clinical trials. Additionally, Kawasaki patients showed more plasma markers of arterial damage than MIS-C, with specific antibodies playing roles in vascular wall regeneration and angiogenesis, highlighting distinct pathogenic mechanisms. [42]

Only 15% of MIS-C patients met KD criteria, emphasizing distinct clinical and immunological profiles between the two conditions. Efforts to identify gene activations during Kawasaki and MIS-C revealed overlapping pathways but distinct transcriptional signatures, providing further insights into the unique pathophysiology of MIS-C and pediatric COVID-19. [41]

In summary, proteomic analysis suggests that while there is overlap, MIS-C and Kawasaki disease involve different pathway activations, targeted structural anomalies, and distinct markers of damage such as endothelial versus myocardial involvement. International data from a large series of MIS-C patients indicated a more severe presentation with higher BNP, D-dimer, CRP, and ferritin levels, and greater cardiac complications compared to Kawasaki patients. [37]

The results of our study align with previous findings that also identified an overlap between the diagnostic criteria for Kawasaki syndrome and MIS-C post-COVID 19. syndrome [25-27]

7. Conclusions

Children exhibit a lower prevalence of severe forms of COVID-19 infection compared to adults.

Nevertheless, some have developed MIS-C following SARS-CoV-2 infection, mimicking Kawasaki syndrome and rapidly regressing after treatment with intravenous immunoglobulins, with or without associated corticosteroid therapy.

This particular progression in children raises numerous pathophysiological questions regarding the connections between myocardial function, endothelial involvement, and immunology. Therefore, evaluating the host's immunological and genetic factors remains necessary to better understand these severe forms.

Abbreviations

WHO	World Health Organization
PIMS-TS	Pediatric Inflammatory Multisystem Syndrome
CRP	C-reactive Protein
PCT	Procalcitonin
MIS-C	Multisystem Inflammatory Syndrome in Children

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Author Contributions

Sanae Ahchouch: Writing – original draft, Writing – Review & editing, Resources

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Data Availability Statement

The data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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