Review Article

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Multisystem Inflammatory Syndrome in Children (MIS-C): A Review of Short- and Long-Term Complications

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but serious post-infection disorder associated with SARS-CoV-2 infection, typically occurring 2-6 weeks after acute COVID-19. The syndrome is characterized by persistent fever, multisystem organ impairment, and laboratory evidence of inflammation. The affected individuals require prompt diagnosis and treatment to avoid morbidity. The short-term complications are widespread during the acute phase of the disease, often requiring intensive care. Cardiovascular symptoms occur in up to 80% of the cases. Gastrointestinal presentations are common along with respiratory, neurologic, renal and mucocutaneous complications.

Hematologic complications are one of the most frequent organ system presentations of MIS-C. They occur in over 50% of patients and pose significant thrombotic risks. Thrombocytopenia is observed in approximately 40-60% of patients, frequently with coagulopathy and elevated D-dimer, indicating a hypercoagulable state. There is a heightened prevalence of thromboembolic events in the form of deep vein thrombosis or pulmonary embolism due to endothelial injury and cytokine storms. These features point to the prothrombotic profile of MIS-C, which is distinct from other pediatric inflammatory syndromes. Also, late sequelae, an inadequately researched subject, include chronic cardiac defects, such as dilatation of coronary arteries or reduced ventricular function in 10-20% of survivors, who require ongoing echocardiography. Respiratory, gastrointestinal, and neurocognitive dysfunctions have been reported in follow-up observations, although most children return to normal after a few months. Hematological recovery is typically excellent, but chronic thrombotic risks exist in only some serious cases of the disease. While the short-term prognosis of MIS-C is generally favorable, uncertainties persist regarding its long-term complications. Standardized follow-up protocols for the complications of MIS-C are warranted to detect subclinical abnormalities and guide ongoing management. Continued surveillance and longitudinal research are essential to fully elucidate the natural history of the disease and optimize the outcomes for the survivors.

Keywords: Cardiovascular Diseases, Hematologic Diseases, Multisystem Inflammatory Syndrome in Children, Post-Acute COVID-19 Syndrome, Sequelae

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Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare and severe post-infection immune-mediated condition linked to severe and acute coronavirus 2 (SARS-CoV-2) infection in children (1). Typically, MIS-C emerges two to six weeks after the initial COVID-19 infection and is characterized by fever, generalized inflammation, and dysfunction of multiple organ systems in the presence of a positive SARS-CoV-2 test (2).

According to the U.S. Centers for Disease Control and Prevention (CDC), the incidence of MIS-C is estimated to be approximately 2 per 100,000 persons younger than 21 and about 316 cases per 1,000,000 SARS-CoV-2 infections, with a reported mortality rate of 1-2% among the confirmed cases (3). However, the mortality would be even higher if six or more organ systems are involved (4). Diagnosing MIS-C can be challenging due to the broad case definitions and its overlap with other conditions, such as Kawasaki disease, toxic shock syndrome (TSS), and macrophage activation syndrome (MAS) (5, 6). The diagnosis is based on a combination of clinical, laboratory, and epidemiologic criteria (7).

The new definition of MIS-C, established by the Council of State and Territorial Epidemiologists (CSTE) and the CDC for cases with an onset after January 1, 2023, addresses certain criteria including age of less than 21 years, documented fever of > 38°C, required hospitalization, occurrence of death, systemic inflammation with C-reactive protein (CRP) ≥ 3 mg/dL, and multisystem involvement with at least two of the five organ systems affected. The organ involvements include shock, cardiac Involvement (low ventricular ejection fraction ≤ 55%, coronary artery abnormalities, or elevated troponin), mucocutaneous involvement (rash, oral mucosa inflammation, conjunctival injection, or extremity findings), gastrointestinal involvement (abdominal pain, vomiting, or diarrhea), and hematologic involvement (thrombocytopenia).

In addition, the diagnosis does not require an alternative plausible method, a positive SARS-CoV-2 RNA polymerase chain reaction (PCR), an antigen test within 60 days of illness, or positive SARS-CoV-2 serology (with antigen specificity not required) if associated with a current illness. If there is no positive laboratory test result for SARS-CoV-2, the case must also meet the epidemiologic link criterion, defined as a close contact with a probable or confirmed COVID-19 case within 60 days of the disease, in addition to the required clinical criteria (8, 9).

Although different studies use varying timeframes to define short-term and long-term outcomes, most define short-term outcomes as those occurring during hospitalization and within the first month after discharge, while long-term outcomes are typically considered those developing beyond one month after discharge (10). Understanding both the short-term and long-term complications of MIS-C is crucial for early recognition and timely intervention. Prompt management of MIS-C can significantly reduce its associated morbidity and mortality while improving long-term health outcomes (11, 12). Although many acute issues may resolve, persistent subtle organ dysfunction or new complications can occur over time (13). The complications of MIS-C, both short-term and long-term, include cardiovascular complications, gastrointestinal manifestations, neurological symptoms, psychologic effects, respiratory complications, renal problems, endocrine disturbances, and hematologic concerns (10). There also long-term outcomes of MIS-C to evolve (12-14).

In the present review the existing literature on both short- and long-term MIS-C complications was evaluated, and the data on treatment and follow-up care of MIS-C patients were extracted. The literature was explored by retrieving databases such as PubMed and Google Scholar for the articles published since 2020, using the search key words "MIS-C", "multisystem inflammatory syndrome in children", "COVID-19 complications", "short-term outcomes", and "long-term outcomes".

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The articles were selected based on their relevance to the subject of this study. Ethics approval was also given by the Research Ethics Committee of Shahid Sadoughi University of Medical Sciences (Approval code: IR.SSU.REC.1404.077).

2. Short-term complications of MIS-C

Short-term complications are seen during the acute phase of the illness, more frequently within days to weeks of the onset of symptoms that include cardiovascular dysfunction, respiratory, gastrointestinal and neurological complications, renal impairment, hematological complications, shock, and multi-organ failure (Table I).

2.1. Cardiovascular complications

Myocardial dysfunction

Myocardial dysfunction is one of the most common cardiac manifestations of MIS-C, occurring in approximately 33-65% of affected children (15-17). Left ventricular systolic dysfunction is the predominant finding, with ejection fraction (EF) less than 55% reported in 27.3-58% of patients (17, 18). Several studies have found that myocardial involvement in MIS-C is more common and typically more severe than in Kawasaki disease (19). In a large European cohort of 286 children with MIS-C, 52% demonstrated reduced ejection fraction, and 9% had severely reduced function with EF < 40% (20). The pathophysiology of myocardial dysfunction in MIS-C appears to be multifactorial, involving direct viral injury, dysregulated inflammatory responses, microangiopathy, and endothelial dysfunction (15, 16). Elevated cardiac biomarkers, including troponin and brain natriuretic peptide (BNP), are common laboratory findings. They correlate with the severity of myocardial dysfunction. Troponin elevation is reported in 50-95% of MIS-C patients, while BNP elevation occurs in 73-100% (15, 18). Cardiac magnetic resonance imaging (CMR) studies have shown evidence of myocardial inflammation with T1 and T2 abnormalities during the acute phase (21). A recent multicenter experience found late gadolinium enhancement (LGE) indicative of myocardial scarring in 50% of MIS-C patients who underwent CMR in the follow-up period (21). Despite the initial severity, myocardial function typically improves rapidly with appropriate treatment, with the majority of patients experiencing normalized ventricular function before discharge or within weeks of presentation (15).

Coronary artery abnormalities

Coronary artery abnormalities are reported in 8-35% of MIS-C patients (17, 18, 20). These abnormalities include coronary ectasia, dilation, and aneurysm formation. In the largest case study to date, Valverde et al. (20)found coronary artery involvement in 24% of 286 MIS-C patients, with 56 children developing small aneurysms (z-score 2.5-5), 15 developing moderate aneurysms (z-score 5-10), and one patient developing a giant aneurysm (z-score > 100).

Coronary artery involvement in MIS-C differs somewhat from that in Kawasaki disease, with milder coronary dilation being more common in MIS-C. Many cases show coronary hyperechogenicity on echocardiography, which may represent coronary arteritis (ibid). The pathophysiology of the dilation of coronary arteries is unknown, but it probably involves vasculitis or pansystemic hyperinflammation (16). Most coronary abnormalities in MIS-C children resolve by 30 days to six months, with the vast majority having resolution in a 1-year follow-up (22, 23). Progression of coronary artery dilation on convalescence has been reported, which emphasizes the importance of follow-up (24).

Arrhythmias and cardiogenic shock

Arrhythmias and conduction defects are observed in 9-67% of patients with MIS-C (20, 25). The corresponding ECG abnormalities include the prolongation of QT interval, ST changes, T-wave abnormality, and all forms of heart block. First-degree atrioventricular blocks are common (in 6.3-25% of cases), but second- and third-degree blocks are uncommon (7%) (26). All forms of tachyarrhythmias, including ventricular tachycardia and atrial fibrillation, have also been reported (27). Cardiogenic shock is the most serious presentation of MIS-C,

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occurring in about 50% of hospitalized patients (15, 28). In the largest US case series, 40% of MIS-C patients received inotropic support, and 50-80% were admitted to intensive care units (17). In some other studies, approximately 4.4% of the MIS-C patients required mechanical circulatory support through ECMO (29, 30). Even where there were severe shocks, the patients tended to recover rapidly with supportive management and immunomodulatory therapy.

Pericardial effusion

Pericardial effusion occurs in 14-66% of patients with MIS-C (23, 31). In a multicenter comparative study, pericardial disease was more common in children with MIS-C (66%) than in those with acute COVID-19 (31.8%) (17). Pericardial effusions are usually mild to moderate and rarely lead to cardiac tamponade (17). Also, a majority of pericardial effusions resolve after treatment, with only 8% remaining at discharge. In multiple cohort studies, six months after discharge, pericardial effusions typically resolved completely, with no cases identified in the 1-year follow-up (23).

Gastrointestinal findings

Gastrointestinal symptoms are reported as the most common clinical presentation of MIS-C (10, 32, 33). In a short-term follow-up, the most frequently reported patient complaints are usually gastrointestinal involvement including abdominal pain, vomiting, and subsequently diarrhea (10, 32, 33).Elevated liver enzymes are observed in approximately 50% of patients, while abdominal ultrasonography commonly reveals ascites and lymphadenopathy. Some studies have noted that MIS-C may mimic acute appendicitis or other surgical abdominal emergencies (10, 34). Importantly, these findings typically improve with immunomodulatory therapy (10).

2.2. Dermatologic and mucocutaneous complications

Rash, conjunctivitis, mucositis

Dermatologic and mucocutaneous manifestations are the hallmark features of MIS-C, occurring in approximately 57% of affected children (35). These manifestations are often similar to those in Kawasaki disease, but they may have distinct characteristics.Cutaneous eruptions are present in the majority of MIS-C patients, though detailed descriptions are frequently lacking in the literature, with “rash” being the sole descriptor in nearly half of reported cases. More specifically, rash is the most commonly polymorphic, maculopapular morbilliform, or diffusely erythrodermic complication (35, 36). Other reported morphologies include urticarial, reticular, petechial, and purpuric eruptions (35).

The distribution of rash can be generalized or localized to specific areas such as the face, trunk, extremities, or acral regions. Palm and sole involvement, including erythema and edema, have been observed in some patients (37). Rashes typically appear from days 2 to 6 of the disease. Symptomatology is variable, with rashes described as non-pruritic in most cases, though occasionally pruritic or painful (35).

Conjunctival injection (non-purulent) is reported in 32-45% of patients with MIS-C (24). Mucositis, including cheilitis and oral mucosa hyperemia, occurs in 19-29% of cases (24, 28). Extremity changes (edema, erythema, induration) and periungual desquamation are also reported in some patients. Specific dermatologic diagnoses in MIS-C include erythema multiforme-like target lesions and leukocytoclastic vasculitis, though histopathologic confirmation is rarely obtained (35). The timing of mucocutaneous findings in relation to other manifestations and their response to therapy remains incompletely characterized.

Neurological involvement

Neurological involvement in MIS-C has been reported at varying percentages (12-66%) across studies (32, 38-40). The differences in the percentages may be due to the differences in the study populations and the definitions of neurological involvement. MIS-C may cause persistent neurological and psychosocial complications. Symptoms such as altered mental status, seizure, irritability, severe encephalopathy, encephalitis, and non-specific symptoms (e.g., lack of appetite, asthenia,

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apathy, changes in the sleep/wake rhythm, headache, paresthesia, anesthesia, trunk or limb pain) are usually common during short-term follow-ups. However, the involvement of cranial nerves and delirium as complications of MIS-C are rarely reported in studies (38, 39, 41).

In a prospective cohort study, acute encephalopathy (76.0%), delirium (11.6%), dysautonomia (10.9%), and seizures or status epilepticus (9.6%) were the most common severe neurological manifestations (41). The pathophysiology of neurological involvement in MIS-C appears to be related to vascular and cerebral inflammatory responses with damage of blood-brain barrier caused by an immune system hyperactivation after SARS-COV-2 infection. Furthermore, hypoxia resulting from cardiovascular or pulmonary involvement, hyper coagulopathy, hyperviscosity, venous stasis, myocardial dysfunction and shock can lead to neurological manifestations (38, 42). In various studies, EEG, MRI and cerebrospinal fluid analysis, along with physical examinations, have been helpful in diagnosing neurological involvement during both short- and long- term follow–ups (38, 39, 41). Most cases of neurological dysfunction have been successfully managed with IVIG and corticosteroids in the acute phase and over a long-term follow-up (38, 42).

Neurological involvement in MIS-C is generally frequent, though typically not severe. More than half of the affected patients have mild and transient symptoms, and neurological assessments at discharge time are usually normal. EEG abnormalities tend to improve within first week and typically normalize within 2 to 3 weeks during a short- term follow-up (42).

2.3. Renal complications

Acute kidney complications are a significant problem in patients with MIS-C. Acute kidney injury (AKI) has been frequently reported, particularly in patients with more severe disease phenotypes such as Kawasaki-like disease (KD) and shock, both of which are extremely associated with ICU admission (43). A case report explained AKI in a 13-year-old female MIS-C patient caused by presumed thrombotic events in the setting of extreme inflammation (44). Moreover, in a cohort study, increased adiposity in MIS-C patients was linked with more critical outcomes, including higher creatinine levels, which may indicate renal involvement (45). In the majority of studies, AKI attributed to MIS-C seems to resolve. For instance, in a study conducted at Great Ormond Street Hospital (London, UK), it was shown that most of the renal abnormalities were resolved within six months from hospital admission (32). These findings highlight the reversible but potentially profound impact of MIS-C on renal function, emphasizing the value of careful follow-up and supportive care for affected patient

2.4. Respiratory complications

Respiratory presentation is common during the acute phase of MIS-C, with a prevalence of 21% to 70% in different reports (46). These symptoms often include tachypnea, cough, hypoxia, and sore throat (7). Frequently, there are radiological findings including pulmonary edema, basilar opacities suggestive of atelectasis, pleural effusion, and pulmonary infiltrates, as well as less common pneumothorax, pulmonary hemorrhage, and bronchospasm. Acute respiratory distress syndrome (ARDS), asa more severe pulmonary complication, appears to be rare (46). Although most children with MIS-C do not require respiratory support for a pulmonary disease, some may need intubation and ECMO due to cardiovascular collapse (47).

In a systematic review (47), respiratory symptoms occurred in 50% of the patients, including problems with the upper respiratory tract (23.9%), difficulty breathing (26.7%), and radiological infiltrates (35.5%). In MIS-C, shortness of breath is a predictor for ICU admission (6). ARDS is uncommon in children who require a ventilator or oxygen support (46). The pathophysiology of pulmonary involvement in MIS-C is mainly the result of an exaggerated systemic inflammatory response rather than the direct viral infection of the lungs. Pulmonary symptoms in MIS-C are typically secondary to more general systemic processes such as fluid

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overload and sedation, rather than primary pulmonary disease (32).

2.5. Hematologic complications

In addition to hypercoagulability and thromboembolic events, hematologic complications in MIS-C include thrombocytopenia, anemia of inflammation, lymphopenia, and coagulation abnormalities that may resemble disseminated intravascular coagulation (DIC) (Table II).

Hypercoagulability and thromboembolic events

COVID-19 and MIS-C have been linked to an increased risk of hypercoagulability and thromboembolic events (TEs), even in pediatric populations, contributing to significant morbidity and mortality. Although understanding of these complications in children remains limited, the data from 62 studies involving 138 patients revealed a total of 157 TEs, as 16 patients experienced multiple events. Venous TEs were the most common complications (54%) (49).

Thrombosis

Clinically evident thrombosis has been observed in children with COVID-19-associated MIS-C, ranging in age from infancy to adolescence (50). The key risk factors associated with thrombosis in MIS-C include elevated D-dimer levels, thrombocytopenia, intensive care unit (ICU) admission, and the presence of noncardiogenic pulmonary edema. The reported thrombotic events involved the deep vein thrombosis (DVT) of the lower limbs, large-vessel cerebral artery thrombosis, and secondary thrombotic microangiopathy (50). Several studies have also demonstrated an increased rate of thrombosis in these hospitalized pediatric patients (51).

2.6. Systemic complications

Hyperinflammatory shock or multi-organ failure

During the COVID-19 pandemic, MIS-C was first reported as a case of hyperinflammatory shock in eight children in the UK in April 2020. Most patients with MIS-C present with Kawasaki disease-related features, gastrointestinal symptoms, and hypotension (52). In addition, children with MIS-C can present multi-organ failure. Early identification and treatment are essential to prevent clinical deterioration, shock, cardiac complications, and further organ damage. Therefore, early recognition and prompt management are critical for achieving optimal patient outcome (53).

3. Long-term complications of MIS-C

Long-term complications of MISC can persist for months after the initial recovery and may affect multiple aspects of a child's health. Cardiac issues remain among the most concerning, while neurological and psychological effects, chronic respiratory problems, gastrointestinal disturbances, and renal and endocrine abnormalities may also develop during recovery. Although nearly all of them ultimately recover, these long-standing complications underscore the need for greater understanding of the disease and persistent medical follow-ups even after apparently complete clinical recovery, as detailed in Table III.

Distinguishing between long-standing sequelae of MIS-C and Long COVID (also known as post-acute sequelae of SARS-CoV-2 infection) is important, as the latter can involve residual viral effects or milder, chronic symptoms that are not typically marked by acute hyperinflammation in the case of MIS-C. While there exit some overlapping symptoms like fatigue and anxiety, sequelae of MIS-C tend to be secondary to primary multisystem inflammation, and Long COVID may occur due to viral persistence or immune dysregulation (13, 54, 55). Direct comparisons are limited due to differing definitions and populations, and the corresponding studies are inconsistent regarding this issue.

3.1. Cardiovascular sequelae

Chronic myocardial dysfunction

While acute myocardial dysfunction spontaneously recovers with treatment in most cases, concern exists about potential long-term cardiac complications for MIS-C survivors. Follow-up assessments every three months to once a year have provided data regarding the long-term cardiovascular function of MIS-C. In an Italian multicenter study, 67 MIS-C patients

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were followed for a mean of nine months. All those who had initial left ventricular dysfunction experienced complete recovery of systolic function by three months. Cantarutti et al. (23) reported that the mean ejection fraction in a 1-year follow-up was 61 ± 3%, with no cases of persistent LV dysfunction. Similarly, Penner et al. (32) found normalized cardiac functions in all the MIS-C patients in a 6-month follow-up.

However, despite a normal ejection fraction, subtler abnormalities in myocardial function may persist. Studies using more sensitive techniques such as myocardial strain imaging have detected abnormal strain values in some patients with normalized EF (56, 57). Evidence of diastolic dysfunction has also been reported to persist after the normalization of systolic function (31). Due to inconsistent findings regarding persistent abnormalities despite preserved EF, the potential limitations of echocardiography to detect mild fibrosis were recognized, as compared to cardiac magnetic resonance (CMR) imaging (58). This suggests a need for more uniform long-term follow-ups to resolve the discrepancies.

Coronary artery abnormalities and long-term risk of coronary artery diseases

The long-term evolution of coronary artery abnormalities in MIS-C is still being investigated. Most studies report complete resolution of coronary artery dilation by 6-12 months (22, 23). In a multicenter experience in Italy, coronary involvement decreased from 35% during the acute phase to 0% within a 1-year follow-up (21). However, the CMR performed during the follow-up revealed concerning findings. In a study of 20 MIS-C patients who underwent CMR over a median of 9.4 months after an acute illness, 50% showed evidence of myocardial scarring with late gadolinium enhancement (LGE) despite having normal ventricular function on echocardiography (22, 23). Similar findings were reported by Bermejo et al. (58) who found LGE in a small number of patients in the follow-up CMR. The long-term implications of these persistent myocardial scars remain unknown. Given the experience with other inflammatory heart diseases, there are concerns about potential arrhythmogenic substrate, persistent subclinical inflammation, and increased risk of future heart failure (36). Current guidelines recommend at least one year of cardiac follow-up for all patients with MIS-C, with more frequent and extended monitoring for those who experienced significant cardiac involvement during the acute phase (59).

Overall, while the immediate outcomes for MIS-C patients are generally favorable, with survival rates exceeding 98%, the potential for long-term cardiovascular sequelae necessitates ongoing surveillance and research (29, 30). Analysis of discordant data shows that, while resolution is common, small-sample CMR studies report 50% or higher scarring, indicating biases in larger cohorts based solely on echocardiography and a need for broader CMR utilization to tackle long-term risk (60).

3.2. Long-term gastrointestinal complications

During a long-term follow-up, the most common reasons for the readmission and hospitalization of children following MIS-C are recurrent abdominal pain and cardiac abnormalities. This was reported in approximately 14.2% of cases (10). The majority of patients become asymptomatic over time, decreasing from 98% at the onset of symptoms to 13% in a 6-month follow-up (32). Gastrointestinal symptoms have also been identified as markers of severe MIS-C (33, 34, 61), and they are probably attributable to an exaggerated inflammatory response, which may be more frequent or severe in the gastrointestinal tract.

Since short-term GI symptoms resolve quickly, long-term follow-up studies are spare and conflicting; some studies report persistence symptoms only in 13-14% of the cases within six months. Thus, more inclusive cohorts are needed to decide whether this is evidence of true sequelae or unrelated pediatric GI pathology (10, 32).

3.3. Chronic respiratory complications

Abnormalities may take longer time to resolve in lungs than in other organs (54). Respiratory symptoms such as difficulties in

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breathing, cough, tachypnea, hypoxia, chest pain and tightness have been reported as the long-term complications of MIS-C (46). While these symptoms may suggest a worsening of chronic lung conditions or central nervous system respiratory control issues, there is no definitive proof yet that they are caused by localized, low-grade inflammation in the respiratory system (55). According to a meta-analysis, three months after having COVID-19, 32% of patients experience shortness of breath, 8.6% have a cough, and 6.6% report chest pain (62). In a study by Sezer (10), pulmonary symptoms were reported in 8% of the patients in a follow-up longer than six months. In a cohort study, 33 children hospitalized with MIS-C were followed for nearly six months. Of them, 21% reported shortness of breath during exercise that might have been due to the initial cytokine storm but not by lasting physicaldamage to the lungs (39). Other potential long-term respiratory complications of MIS-C rather than respiratory symptoms include persistent oxygen requirements and cough, lung tissue collapse, pulmonary thromboembolism, lung infiltration, and lung fibrosis (54, 63). It is worth noting that respiratory involvement is less frequent in children with MIS-C than in adults with severe COVID-19 (64).

However, differentiating the chronic respiratory complications of MIS-c from those of Long COVID is a key issue. In this regard, meta-analyses have shown higher prevalence in Long COVID (e.g., 32% dyspnea) than in MIS-C (8-21%); of course, MIS-C studies have limitations like small cohorts and benefit from no background condition control (10, 62). This suggests that MIS-C respiratory sequelae may be less severe but require follow-up in specific cases.

3.4. Neurologic sequels

In long-term follow-ups, minor neurological and neuropsychiatric abnormalities are significantly more common in patients who have experienced severe neurological involvement during the acute-phase or severe MIS-C (10, 41, 42). Various studies show that most neurological complications are mild and nonspecific, while fewer patients experience moderate or severe symptoms (10, 41, 65).

Although the relationship between neuropsychiatric findings and severe MIS-C is not completely clear, the degree of multi-organ involvement and inflammation may be related. In contrast to more recent studies, older studies showed only an association with age (10, 42). Over a 6-month follow-up, neuropsychiatric sequelae include dysmetria, anxiety, emotional lability, impaired memory, motor coordination, gait abnormalities, ADHD, anxiety, depression, psychosomatic symptoms like headaches, chest pain, back pain and nausea(32, 42, 65, 66). In a systematic review, there were neuropsychiatric findings in 6.2% of children during a long-term follow-up. Most patients with neurological involvement achieve recovery in a long-term follow-up (10, 67). A retrospective cohort study showed minor abnormalities in around 50% of the patients within six weeks, 39% within six months, and emotional difficulties in 18% in six months (32). Other studies indicate that neurological involvement can lead to significant sequelae including cognitive, psychological and behavioral difficulties in around 30% of patients within a six-month follow-up after MIS-C presentation.

Severe neurological manifestations are linked to a higher risk of long-term morbidity (28% compared to 15%) (41). Persistent neurological sequelae may include ischemic cerebrovascular and peripheral neuropathy (67). Therefore, long term follow-up is necessary to assess the effect of MIS-C on persistent neurological and psychosocial complications as well as to evaluate complete recovery (41).

Although the prevalence is highly unpredictable (6-50% in follow-up), with differences most reasonably attributed to inconsistent assessment tools (e.g., PedsQL vs. PI-ED) and study designs, acute severe impairment predicts worse outcomes, but overall recovery is good, emphasizing the value of early treatment (41). Unlike in fatigue predominance without acute encephalopathy in Long COVID, MIS-C neuropsychiatric issues are more significantly associated with early inflammation.

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3.5. Long-term renal complication

The long-term outcomes of AKI following MIS-C remain unclear and represent a critical area for future research (31, 47). AKI is known to have lasting consequences, including an increased risk of hypertension and a twofold greater likelihood of developing chronic kidney disease (CKD), even after mild episodes (68). Some studies have shown reassuring results, with one reporting the normalization of renal parameters by six months (12) and another indicating that most abnormalities, including renal manifestations, resolve within the first few weeks, with no significant dysfunction observed in a six-month follow-up (39).

Nontheless, these findings are not entirely consistent. Differences among studies might be explained by differences in sample size, length of follow-up, or diagnostic criteria for AKI and CKD. Pre-existing renal diseases have occasionally been omitted from cohorts, potentially underestimating the true prevalence of chronic renal dysfunction. However, clinical evidence related to Long COVID (LC) suggests that nephrological monitoring may still be warranted, as the persistence of SARS-CoV-2 in renal tissue could influence immune function and potentially contribute to the recurrence of kidney diseases (55).

SARS-CoV-2 has the capacity to directly infect renal cells, including tubular epithelial cells, glomerular endothelial cells, and podocytes, potentially leading to glomerular damage and subsequent fibrosis. This viral-induced cellular injury occurs independently of immune system involvement. The extent to which these mechanisms affect post-MIS-C renal outcomes is speculative, as most of the evidence available is either from adult populations or animal studies. These findings help to explain the occurrence of AKI in COVID-19 patients, as well as its progression to chronic kidney disease (CKD) observed in cases of LC (69, 70).

3.6. Endocrine complications

Beyond obesity, metabolic dysfunction, including insulin resistance and dyslipidemia, is frequently observed in children with MIS-C. One study found that 72.7% of the affected children exhibited at least two abnormal metabolic parameters at admission, including hypertriglyceridemia (51.5%), low HDL cholesterol (87.9%), and elevated fasting blood glucose (63.6%). Also, 94.7% of the tested children demonstrated insulin resistance, which persisted in 21.2% of the patients even after six months (39). Although these reports emphasize the prevalence of endocrine abnormalities, pathophysiological mechanisms showing chronic metabolic dysfunction remain insufficiently addressed. Whether these abnormalities reflect a primary consequence of systemic inflammation or a secondary consequence of corticosteroid therapy is unclear. Additionally, metabolic and endocrinological abnormalities, such as insulin resistance and non-thyroidal illness syndrome (NTIS), were observed in a significant proportion of children, with persistent effects over six months after hospitalization (15, 28). Notably, some studies suggest that such abnormalities resolve spontaneously, while others report persistence, indicating a need for standardized follow-up protocols and more rigorous longitudinal studies. These findings highlight the role of metabolic disorders in MIS-C pathophysiology and suggest that underlying insulin resistance may exacerbate systemic inflammation and organ dysfunction.

3.7. Quality of life

Emerging evidence highlights a significant and multifaceted impact of MIS-C on long-term quality of life (QoL) (12). A study utilizing the Pediatric Quality of Life Inventory (PedsQL) in a one-year follow-up reported severe physical functioning impairment in up to 13% of the participants (60). Emotional challenges were also notable, with emotional lability observed in 26% of the children in six weeks and persisting in 15% for six months. The Pediatric Index of Emotional Distress (PI-ED) identified that 7% of the patients remained at high risk for significant emotional distress even for a year (54). Nevertheless, heterogeneity of study designs and parent reporting limit comparability of QoL outcomes among cohorts. The lack of baseline

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pre-infection QoL data also makes causality interpretation harder. In six months after diagnosis, children with MIS-C exhibited more emotional and behavioral problems and worse overall QoL compared to the normal population (ibid). These differences highlight the need for multicenter prospective studies and standardized assessment tools in order to account for the true burden of long-term psychosocial sequelae.

MIS-C has been linked to significant long-term health impacts, particularly in sleep disorders, mental health, and overall well-being. Sleep disturbances, including increased sleep duration (28%) and disrupted sleep (7.7%), have been commonly reported among MIS-C patients, persisting for over 120 days after infection in some cases (10, 45). Cognitive impairments such as difficulties with thinking, memory, and concentration affect approximately 15.4% of MIS-C children, potentially influencing their academic performance and daily functioning (45). Moreover, emotional and psychological consequences are prominent, with increased prevalence of anxiety (11.5%), depression, and emotional liability (12, 71). These neuropsychiatric symptoms are more pronounced in children with severe MIS-C and those who require ICU admission, suggesting a potential link between the disease severity and long-term psychological outcomes (45). In this regard, a review of MIS-C cases revealed that children with a severe disease were more likely to experience persistent neuropsychiatric symptoms, including difficulty with concentration, memory problems, and emotional instability, particularly in long-term follow-ups. The persistence of endocrine abnormalities, such as insulin resistance and non-thyroidal illness syndrome (NTIS), may further contribute to sleep disruptions and mood instability (39).

4. Factors influencing the outcomes

Age and demographic factors play a significant role in the clinical presentation, severity, and outcomes of MIS-C. Studies indicate that MIS-C is more frequently observed in children aged 5-12 years, with a higher prevalence in males and non-Hispanic black patients than in non-Hispanic white ones (10, 22, 23, 34). Older age is associated with an increased risk of severe outcomes (8, 9, 34). Additionally, sex differences determine disease progression and long-term outcomes; while MIS-C is more common in males, pre-pandemic risk factors are more strongly associated with MIS-C in females, potentially due to variations in immune response and hormonal influences (15, 16, 18). However, the existing literature does not often account for confounding variables such as socioeconomic status, diet history, or healthcare access, which may robustly mediate such observed population differences. Long-term follow-up studies indicate that older children and females are more likely to experience prolonged complications, including fatigue, cognitive difficulties, and anxiety (20, 25-27).

Considering the role of ethnic disparities in MIS-C outcomes, it is suggest that non-Hispanic black children may experience more severe disease courses, including higher rates of ICU admission and decreased cardiac function, potentially influenced by social determinants of health, limited healthcare access, and higher prevalence of pre-existing conditions (8, 9, 22, 23, 34). In spite of it, very few studies have controlled for the potential genetic vs. environmental sources of these differences. The causal inference is still dubious.

Approximately 25-33% of children diagnosed with MIS-C have preexisting conditions, with obesity and asthma being the most commonly reported (8, 9, 21-23). There is a significant correlation between higher adiposity and increased severity, including greater likelihood of shock, ICU admission, need for inotropic support, along with elevated inflammatory markers as well as creatinine and alanine aminotransferase (ALT) levels (8, 9, 24). Despite these associations, obesity has not been directly linked to coronary artery abnormalities in MIS-C patients (24). This inconsistency suggests that obesity may modulate systemic inflammation rather than directly affecting cardiac pathology. Future studies are necessary

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to differentiate the metabolic and inflammatory components of obesity contribution to MIS-C pathogenesis.

A review of nearly 2,000 children with MIS-C reported asthma as one of the most frequently observed comorbidities (21-23). Although asthma itself is not a direct cause of MIS-C, it may predispose affected children to respiratory complications and heightened systemic inflammation. However, the data regarding severity of asthma, drug use (e.g., corticosteroids), and environmental exposure are often missing, undermining the interpretability of such associations. Additionally, children with pre-existing metabolic or atopic conditions may experience prolonged hospitalization and an increased risk of long-term complications, such as fatigue, cognitive difficulties, and neuropsychiatric symptoms, which are more pronounced in those with severe MIS-C (20, 25, 26).

The severity of initial symptoms in children diagnosed with MIS-C plays a crucial role in disease progression, clinical outcomes, and long-term complications. Studies have indicated that children presenting with more severe initial symptoms, including shock, impaired cardiac function as indicated by elevated concentrations of biomarkers such as troponin, BNP, proBNP, ferritin, CRP and D-dimer, and multi-organ involvement, are more likely to require ICU admission; such children exhibit significant short- and long-term sequelae (8, 9, 20, 25, 34).

5. Management and follow up

MIS-C presents with a variety of clinical manifestations. Problems arise when conventional therapy fails and patients rapidly deteriorate. Most patients can be diagnosed immediately, but sometimes it can be a diagnostic puzzle even for specialists. Early diagnosis and rapid initiation of treatment have a significant impact on the prognosis of the patient's clinical course (61).

Initial treatment strategies in the first phase of MIS-C include IVIG, pulse steroids, and both or either of IVIG and low doses steroids (34, 65). In refractory cases, biological drugs like tocilizumab, and anakinra are recommended. The use of aspirin or anticoagulants is advised in special circumstances or even recently for everyone. Starting antibiotics is recommended if an infection is suspected (33, 34, 65, 67). Patients usually recover with immunomodulation and supportive care (e.g., hydration and effective ventilation). Early recognition and rapid initiation of treatment can change the prognosis of MIS-C, so starting appropriate treatment quickly is of great clinical importance (34).

Despite these therapeutic successes, the optimal timing, dosage, and sequencing of immunomodulatory agents remain unclear. Most current recommendations are based on retrospective studies or expert consensus rather than randomized controlled trials. Moreover, the heterogeneity of treatment protocols among institutions makes it difficult to establish universal guidelines or predict long-term outcomes reliably.

With its short-term outcomes, MIS-C can be a serious and life-threatening disease. It has many complications by involving various organs in long-term follow-ups. (10, 34, 42, 66). Therefore, it is recommended that, in addition to cardiac monitoring with echocardiography, long-term complication and outcomes be followed and monitored by neuropsychiatric findings (emotional difficulties, educational problems, and functional impairment on clinical examination), gastrointestinal symptoms, inflammation markers, fever, and pulmonary manifestations in MIS-C patients in collaboration with a team of subspecialists in cardiology, pulmonary diseases, infectious diseases, gastrointestinal disorders, and neurology.

However, the lack of standardized follow-up intervals and outcome measures across studies limits comparability. Some centers perform extensive assessments up to 12 months after discharge, while others cease monitoring after clinical recovery. Future work should prioritize timely follow-up protocols to clarify the natural history of post-MIS-C sequelae.

Recent studies cannot completely determine the possibility of future complications and

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sequelae after MIS-C. Therefore in addition to a short-term follow-up, a long-term follow-up is needed to evaluate these effects on multiple organs with regular assessments (i.e., at discharg time, after two weeks, 6 - 8 weeks, 12 months, and >12 months) (34, 40, 65).

A critical gap exists in defining which patients require extended monitoring versus those who can safely discontinue a follow-up. Risk stratification models integrating demographic, immunologic, and clinical parameters would improve individualized care. To achieve this goal, appropriate guidelines should be designed for the care of children with diagnosis of MIS-C, and a subset requires ongoing care with both short-term and long-term follow-ups. Moreover, mass vaccination of children is a strong recommendation.

Table I: Short-term complications of MIS-C

Organ/System	Common complications	Duration/Outcome
Cardiovascular	Myocardial dysfunction, coronary dilation, shock, arrhythmia, pericardial effusion	Usually improve with treatment, some persistent
Gastrointestinal	Abdominal pain, vomiting, diarrhea, hepatitis	Mostly resolve with therapy
Neurological	Headache, seizures, altered mental status, encephalopathy	Often transient, may persist
Renal	Acute kidney injury	Mostly reversible
Respiratory	Tachypnea, hypoxia, infiltrates, rare ARDS	Usually supportive recovery
Hematologic	Hypercoagulability, thrombosis	Requires monitoring
Systemic	Hyperinflammatory shock, multiorgan failure	Critical care required

*Abbreviations: ARDS (acute respiratory distress syndrome)

Table II. Hematologic complications of MIS-C

Category	Complications	Notes / Follow-up
Cytopenias	Thrombocytopenia, anemia of inflammation, lymphopenia	Often transient but may correlate with disease severity
Coagulation abnormalities	Elevated D-dimer, PT/aPTT prolongation, hypofibrinogenemia	Can mimic DIC, requires coagulation monitoring
Thromboembolic events	DVT, pulmonary embolism, cerebral arterial thrombosis	Reported even in children, associated with ICU stay
HLH/MAS-like features	Hyperferritinemia, cytopenias, organomegaly	Overlap with hyperinflammatory syndromes
Long-term risks	Potential risk of recurrent thrombosis, late effects of endothelial dysfunction	Long-term hematology follow-up may be warranted, especially in oncology patients

*Abbreviations: PT (prothrombin time), aPTT (activated partial thromboplastin time), DIC (disseminated intravascular coagulation), DVT (deep vein thrombosis), ICU (intensive care unit), HLH (hemophagocytic lymphohistiocytosis), MAS (macrophage activation syndrome)

Table III. Long-term complications of MIS-C

Organ/System	Long-term complications	Follow-up findings
Cardiovascular	Persistent myocardial strain changes, coronary artery scarring, diastolic dysfunction	Require long-term echo/CMR
Gastrointestinal	Recurrent abdominal pain, persistent GI symptoms	Limited data, often decrease over time
Neurological	Neurocognitive issues, anxiety, ADHD, memory impairment	Up to 30% with mild–moderate deficits
Renal	Risk of CKD, hypertension after AKI	Mostly normalize by 6 months but monitoring needed
Respiratory	Persistent dyspnea, cough, rare fibrosis	Symptoms in 8–21% up to 6 months
Endocrine/Metabolic	Insulin resistance, dyslipidemia, NTIS	Persist in some up to 12 months
Quality of Life	Emotional lability, fatigue, sleep disturbance	Reduced QoL up to 1 year

*Abbreviations: CMR (cardiac magnetic resonance imaging), CKD (chronic kidney disease), AKI (acute kidney injury), NTIS (non-thyroidal illness syndrome), QoL (quality of life)

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Discussion

From a hematology-oncology perspective, it is crucial to note that MIS-C can significantly impact blood and coagulation parameters, which is particularly relevant for children with pre-existing hematologic disorders or malignancies. In children undergoing chemotherapy for oncology, suppression of bone marrow and MIS-C-associated cytopenias can aggravate prognosis. Furthermore, MIS-C hyperinflammatory conditions may mimic or exaggerate HLH/MAS, which are conditions in the field of hematology. An interaction between pediatric hematologists and oncologists is, therefore, important in both acute management and long-term monitoring of patients with MIS-C, allowing for the early recognition of hematologic sequelae and modification of interventions accordingly.

Multisystem Inflammatory Syndrome in Children (MIS-C) represents a post-infection hyperinflammatory response following SARS-CoV-2 infection that may affect multiple organs. Although the acute phase can be life-threatening, early immunomodulatory therapy has led to favorable short-term outcomes in most patients (10, 15, 28, 41, 65). The majority recover ventricular function and systemic stability within weeks, yet the long-term sequelae of MIS-C remain incompletely understood (23, 32, 42, 65, 66).

Cardiac involvement remains the most frequent and clinically significant complication. Despite the normalization of ejection fraction in nearly all survivors within three to six months, subclinical myocardial strain abnormalities and the CMR evidence of fibrosis persist in up to half of patients (23, 58). These findings suggest that echocardiography alone may underestimate subtle myocardial injury, supporting recommendations for at least one year of structured cardiac follow-up (32, 42, 59, 65, 66). The implications of such myocardial scarring for arrhythmia risk and long-term ventricular remodeling require longitudinal evaluation.

Non-cardiac sequelae, including neurological, renal, endocrine and psychosocial effects, have gained increasing recognition. Neuropsychiatric manifestations such as fatigue, attention difficulties, anxiety, and emotional lability occur in up to 30% of patients at six to twelve months, particularly among those with a severe acute disease (32, 41, 42, 65, 66). Renal abnormalities generally resolve within months, but the potential for future hypertension or a chronic kidney disease warrants ongoing nephrological monitoring (47, 68). Endocrine and metabolic disturbances, notably insulin resistance and dyslipidemia, may persist for months, reflecting the metabolic consequences of systemic inflammation or corticosteroid therapy (39). These findings highlight the multi-systemic nature of MIS-C and emphasize the importance of a coordinated follow-up after hospital discharge.

Demographic factors including age, sex, obesity, and ethnicity also appear to influence the disease severity and long-term outcomes (8, 9, 22, 23, 34). Obesity has been correlated with more severe systemic inflammation and prolonged recovery, whereas older children and females show a higher prevalence of persistent fatigue and emotional symptoms (20, 25, 26). Ethnic disparities in MIS-C incidence and severity may be partly explained by social determinants of health rather than biological factors (22, 23). Such observations underscore the need for standardized and inclusive research frameworks that control for confounders and reflect global diversity.

Conclusion

According to these findings, although MIS-C generally has a favorable prognosis, the potential for subclinical organ injury, neuropsychiatric morbidity, and metabolic dysfunction supports the need for a structured multidisciplinary follow-up involving cardiology, neurology, nephrology, respirology and psychology. Long-term prospective studies using harmonized assessment protocols are essential to define the true natural history of MIS-C and to identify children at the risk of chronic complications. Preventive strategies, including widespread vaccination and early disease recognition, remain pivotal in reducing the incidence and severity of this syndrome.

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Availability of Data

None

Ethical Considerations

This review article was approved by the Research Ethics Committee of Shahid Sadoughi University of Medical Sciences (approval code: IR.SSU.REC.1404.077).

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Authors' Contributions

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Sh.S: Methodology, investigation, data curation, writing the original draft, review, and editing.

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S.T: Conceptualization, supervision, project administration, review, and editing.

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Conflict of Interest

The authors have no conflict of interests to declare regarding this study.

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