Clinical Research

Cardiac manifestations and diagnostic imaging in pediatric inflammatory multisystem syndrome temporally associated with COVID-19: a systematic review

Gilbert Sterling Octavius,[1] Ricardo Tan,[1] Teodorus Alfons Pratama,[1] Charista Lydia Budiputri,[1] Fellisa Meliani,[1] Rivaldo Steven Heriyanto,[1] Rusli Muljadi,[2] Andry Juliansen[3]

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Authors' affiliations:
[1]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia, [2]Department of Radiology, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia, [3]Department of Pediatrics, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

Corresponding author:
Gilbert Sterling Octavius
Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia, Jalan Boulevard Jenderal Sudirman, Lippo Karawaci, Tangerang 15811, Indonesia
Tel/Fax: +62-21-5460901
E-mail: sterlinggilbert613@hotmail.com

ABSTRACT

BACKGROUND Several studies have reported pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) cases with their cardiac manifestations, but only few studies synthesize the cardiovascular characteristics in children with PIMS-TS. However, detecting cardiac abnormalities is crucial in improving patients' outcomes and reducing mortality. This review aimed to summarize the overall symptoms, laboratory, and workup findings in PIMS-TS patients, focusing on cardiovascular manifestations.

METHODS We searched 4 medical databases (PubMed, Science Direct, Medline, and Scielo) and 4 preprint databases (Medrxiv, Research Square, SSRN, and Biorxiv). The literature search was done on November 8, 2021. All case reports, case series, cross-sectional studies, cohort studies, and possible clinical trials published from December 2020 onward that studied PIMS-TS on cardiac manifestation (aged 0–18 years) were included. Studies on multisystem inflammatory syndrome in children, animal studies, and studies without full-text availability were excluded. This review was registered in PROSPERO (CRD42021194468).

RESULTS 59 studies were included with a total of 698 patients. The most common cardiovascular findings were the presence of cardiogenic shock (37%) and hypotension (8.5%). Almost all laboratory values were deranged. Cardiac computed tomography scan mostly showed normal results (56%), followed by cardiomegaly with pericardial effusion (14%). Electrocardiography showed normal findings (46%), ST-segment abnormalities (32%), and abnormal T wave (12%). Echocardiography findings showed left ventricle dysfunction (40.6%), which can be considered most significant, followed by pericardial effusion together with pericarditis (11.4%) and tricuspid regurgitation (6.9%).

CONCLUSIONS This review found various cardiac abnormalities that may develop during PIMS-TS. Due to these findings, we should be more vigilant and not underestimate the consequences in pediatric COVID-19 patients.

KEYWORDS cardiovascular, COVID-19, echocardiography, pediatrics, PIMS-TS

Coronavirus disease 2019 (COVID-19) cases have been increasing globally since first emerged in 2019. As of July 29, 2021, over 195 million cases of COVID-19 have been confirmed, with more than 4 million deaths,[1] including children. In Indonesia, the case fatality rate in children had reached 1.4, which is very high in the pediatric population.[2] Children with COVID-19 have a relatively mild infection compared with adults.[3,4] They also have lower COVID-19 mortality at 0.17 per 100,000 population as of February 2021.[5] Children with COVID-19 may have higher hospitalization and mortality rate up to 10 times greater, called pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS)[6] or multiple

inflammatory syndrome in children (MIS-C).[7,8] These two terms differ in which the latter requires COVID-19 evidence or at least close contact with COVID-19 patients.

PIMS-TS is a rare syndrome that shares standard features with other pediatric inflammatory conditions[9]; this includes the involvement of other organ system dysfunctions such as gastrointestinal, respiratory, nervous, and cardiovascular systems.[10–12] The dysfunction of these organs could still linger, even though PIMS-TS has been treated. The cardiovascular system is one of the most critically affected organ systems, which can cause long-term symptoms such as chronic fatigue, dyspnea, and chest pain. It would indeed affect the quality of life of children that were affected by PIMS-TS.[13,14]

Several studies have reported PIMS-TS cases with their cardiac manifestations, but the results were varied.[15,16] Acute cardiac decompensation due to hyperinflammation in patients with MIS-C results in longer hospital stay and higher mortality.[17,18] Hence, it is crucial to detect cardiovascular abnormalities to improve patients' outcomes. To the best of our knowledge, only few studies have synthesized the cardiology symptoms, laboratory findings, and echocardiography characteristics in children with PIMS-TS. Furthermore, the long-term cardiac sequelae in PIMS-TS patients are still unknown. Thus, this review aimed to summarize the overall symptoms, laboratory, and diagnostic workup findings in PIMS-TS patients, focusing on the cardiovascular manifestations.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses 2020 statement.[19] The protocol has been registered into the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021194468).

The literature search was limited to studies published from December 2020 to October 2021, without language restrictions. All case reports, case series, cross-sectional studies, cohort studies, and possible clinical trials that studied the effects of PIMS-TS in pediatric cardiology patients with COVID-19 (aged 0–18 years) were included in this review. Exclusion criteria comprised MIS-C, animal studies, and studies without full-text references. Abstracts, letters to the editor, and reviews were screened for references to ensure literature saturation before they were excluded.

The literature search was done on November 8, 2021. The authors utilized four distinct databases, including PubMed, Science Direct, Medline, and Scielo and four different preprint databases, including Medrxiv, Research Square, SSRN, and Biorxiv. Differences in databases may be due to different types of studies, population variations, and case severity. PubMed indexed "ahead of print" articles. Therefore, the latest articles sometimes appear in PubMed but not in Medline. The keywords included "pediatric" AND ("PIMS-TS" OR "pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2") AND ("cardiac" OR "cardiology" OR "echocardiography" OR "myocarditis" OR "heart failure"). Data were compiled in a standardized format, including study citations, demographic characteristics of the included participants (age, sex, and comorbidities), severe acute respiratory syndrome coronavirus 2 test results, signs and symptoms, laboratory results, treatments, length of stay, and outcomes. Cardiac-specific examinations such as computed tomography (CT) scan, echocardiography, and electrocardiogram (ECG) were also obtained from each study. If some data were missing, an email would be sent to the corresponding author.

Four independent reviewers (GSO, FM, RSH, and CLB) conducted the initial search and quality assessment of each study. The Joanna Briggs Institute's (JBI)[20] essential evaluation checklist for case reports was used to measure the general consistency of case series and case reports. Meanwhile, the Newcastle-Ottawa quality assessment scale (NOS)[21] was assessed for cross-sectional and longitudinal studies. Any discrepancies between JBI and NOS assessments were discussed until a conclusion was reached. Any unresolved disagreements would be consulted with two expert reviewers (RM and AJ). The included case reports should fulfill most of the JBI criteria and score ≥7 in the NOS score.

Pooled descriptive tests were used to combine all data in this review. Data presented in median and range (or interquartile range) were converted into mean and standard deviation (SD). All the means and

SDs were then combined into a single value using the Cochrane method.[22]

RESULTS

There are 59 studies included in this review, with the selection process is shown in Figure 1. All individual studies achieved good results in JBI and NOS scores, and each study is listed in Table 1. A total of 698 patients were included, with a mean (SD) age of 9.2 (4.1) years and male predominance (58.0%). The demographic characteristics of the patients are shown in Table 2. Most patients had positive polymerase chain reaction tests.

Nutritional problems such as underweight or obesity were the most common comorbidities, followed by respiratory problems and neurologic disorders (Table 2). Many patients experienced a shock. The mean (SD) length of hospital stay was 9.8 (11.3) days. Intravenous immunoglobulin was commonly used for PIMS-TS. Of 600 patients with available data on mortality, 3.33% died.

The mean (SD) of systolic and diastolic blood pressure were 81 (14) and 46 (12), respectively. Almost all laboratory values were deranged in PIMS-TS patients (Table 2). Notably, there was an increase in white blood cells count, neutrophil, C-reactive protein (CRP), ferritin, procalcitonin, creatinine kinase, creatinine, alanine transaminase, aspartate aminotransferase, D-dimer, fibrinogen, and erythrocyte sedimentation rate, and almost all cardiac markers were also elevated. Meanwhile, hemoglobin and lymphocyte values were decreased (Table 2).

The reference range in this table followed the normal values for 9-years-old children (mean age of this study) that were obtained from the Nelson Textbook of Pediatrics[23] and Mosby's Manual of Diagnostic and Laboratory Tests.[24] High sensitivity troponin T values were taken from Calò Carducci et al.[25]

The most common cardiac CT scan result was normal (56%), followed by cardiomegaly with pericardial effusion (14%). Among 121 patients, the ECG evaluation results were mostly normal (46%). ST abnormalities (32%) and abnormal T wave

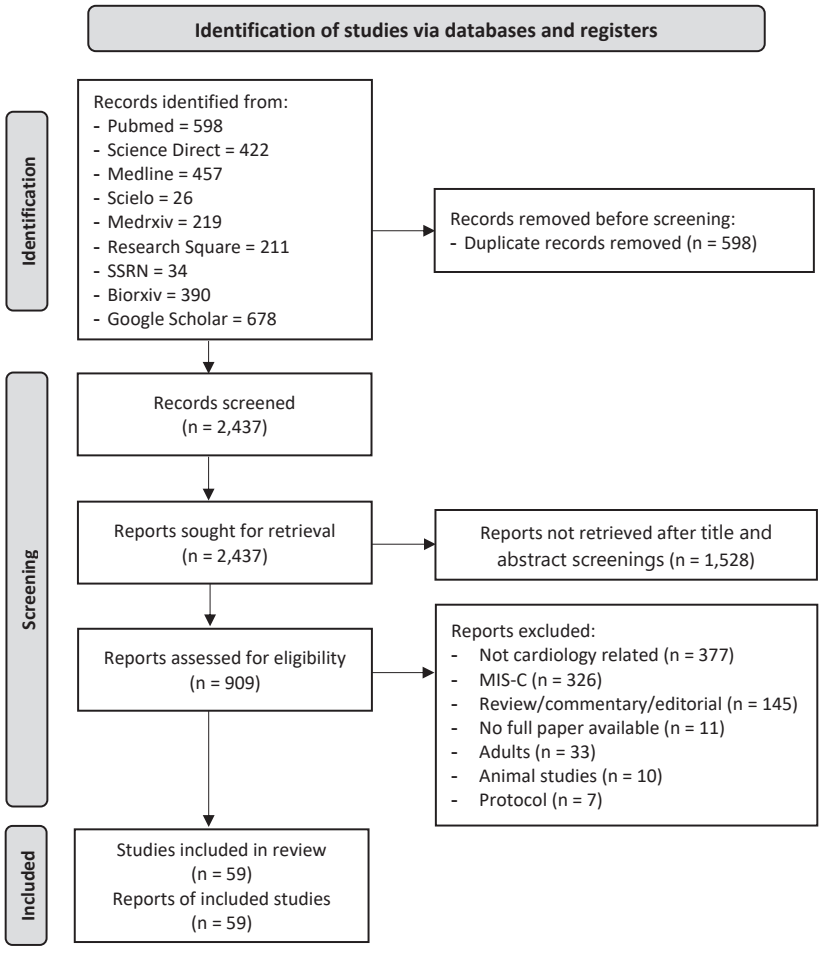

Figure 1. Flow diagram of studies selection

Table 1. List of studies included

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
de Farias,[42] 2020	Prospective observational	11 (81)	4 (0.6–11)	NA	Extreme prematurity, chronic neonatal lung disease, and ischemic hypoxic encephalopathy (1); chronic post-traumatic encephalopathy and chronic respiratory failure did not depend on oxygen, tracheostomy (1); overweight (3); none (3); mild asthma (2); and obesity (3)	Invasive mechanical ventilation (3) and non-invasive mechanical ventilation (4)	Corticosteroid, IVIG single-dose 2 g/kg, ASA, and enoxaparin dose 3 mg/kg	Median (range) = 17 (12–180)	2
Penner,[43] 2021	Retrospective cohort	46 (65)	10.2 (IQR 8.8–13.3)	White (9), South Asian (11), African-Caribbean (16), and others (10)	Autism (4), sickle cell disease (2), asthma (1), type 1 diabetes (1), spina bifida (1), autism, and sickle cell disease (1)	Mechanical ventilation (16)	Inotropic support (22), LMWH (35), methylprednisolone (25), and IVIG (38)	Median (IQR) = 11 (8–16)	0
Ramcharan,[15] 2020	Retrospective observational	15 (73.3)	8.8 (IQR 6.4–11.2)	African Afro-Caribbean (6), South Asian (6), Mixed (2), and other (1)	NA	Mechanical ventilation (4), HFNC (4), and NA (7)	IV fluid bolus, inotrope/ vasopressor, hydrocortisone, methylprednisolone, and broad-spectrum antibiotic	NA	0
Jhaveri,[44] 2020	Retrospective observational	15 (60)	11.5 (3–20)	NA	NA	NA	IVIG, corticosteroid, tocilizumab, anakinra, therapeutic anticoagulant, remdesivir, plasma therapy, aspirin during admission, and vasopressor	NA	1
Kaushik, [45] 2020	Retrospective observational	33 (61)	10 (6–13)	Hispanic (15), Black (13), White (3), Asian (1), and other (1)	Overweight (4), obesity (2), asthma (5), allergic rhinitis/ eczema (3), cardiac comorbid (2), hematologic comorbid (2), and others (3)	Non-invasive mechanical ventilation (12), invasive mechanical ventilation (5), ECMO (1), and intra-aortic balloon pump (1)	IVIG, corticosteroid, tocilizumab, remdesivir, anakinra, convalescent plasma, norepinephrine, dopamine, epinephrine, dobutamine, vasopressin, milrinone, aspirin, diuretics, anticoagulant prophylaxis, anticoagulation therapeutic, antibiotic <48 hours, and antibiotic >48 hours	Median (IQR) = 7.8 (6.0–10.1)	1

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Grimaud,[46] 2020	Retrospective observational	20 (50)	10 (2.9–15)	NA	NA	Non-invasive ventilation (11), invasive ventilation (8), and high-flow nasal oxygen (1)	IVIG, inotropic/vasoactive (epinephrine, milrinone, dopamine, and norepinephrine), corticosteroids, IL-1 receptor antagonist, and IL-6 receptor antagonist	NA	0
Lee,[47] 2020	Retrospective	28 (57)	9 (1 month–17 years)	Hispanic (12), White (10), and Black (6)	None	Non-invasive ventilation (7) and nasal cannula (4)	Vasopressors, IVIG, anankinra, remdesivir, antibiotics, and anticoagulants	NA	0
Biko,[48] 2020	Retrospective	10 (100)	9 (5–15)	NA	Type 2 neuronal ceroid lipofuscinosis (1), prematurity (1), and asthma (1)	Ventilatory support (9)	IVIG, steroids, and plasma antibodies	Range 3–76, remained hospitalized = 1	0
Blumfield,[49] 2020	Retrospective	16 (37.5)	9.2 (SD 4.9), range = 20 months–20 years	NA	Overweight/obesity (4), asthma (1), primary immunodeficiency GATA3 deficiency (1), and prematurity (1)	Intubation and mechanical ventilation (1)	NA	NA	NA
Cheung,[50] 2020	Retrospective	17 (47)	8 (1.8–16)	Ashkenazi Jewish (6), White non-Hispanic (2), White Hispanic (4), Black (4), and Asian (1)	Asthma (3)	NA	Corticosteroid, IVIG, tocilizumab, prophylactic enoxaparin, and aspirin	Median (range) = 7.1 (3–18)	NA
Matsubara,[51] 2020	Retrospective	28 (50)	11.4 (IQR 8.0–13.7)	African American (13), Caucasian (7), Hispanic (4), Asian (1), and NA (3)	Obesity (3), overweight (9), and NA (16)	Invasive ventilation (7), continuous airway pressure (2), BiPAP (5), and NA (14)	Aspirin, IVIG, vasopressor, corticosteroid, and anticoagulants	NA	NA

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Mamishi,[52] 2020	Retrospective	45 (53)	7 (10 month–17 years)	NA	Acute lymphocytic leukemia, chronic kidney disease, underlying seizure disorder, cerebral palsy, cardiovascular disease, and Budd-Chiari syndrome in 6 patients	NA	IVIG and steroid	NA	5
Bartoszek,[53] 2021	Retrospective	19 (73.7)	10 (IQR 10–15)	NA	NA	NA	IVIG in 19 patients and steroid in 12 patients	Median (IQR) = 11 (7–14.5)	0
Pouletty,[54] 2020	Retrospective	16 (50)	10 (IQR 4.7–12.5)	NA	Overweight (4), asthma (2), and NA (10)	Non-invasive ventilation (3) and NA (13)	IVIG, single infusion, double infusion, steroids, anti-IL-1 treatment, anti-IL-6 treatment, HCQ, and aspirin	NA	0
Riollano-Cruz,[55] 2020	Retrospective	12 (66.7)	11.5 (3–17)	Hispanic or Latino (8), non-Hispanic African American (2), non-Hispanic White (1), and NA (1)	Asthma (3), hypothyroidism and NAFLD (1), and NA (8)	Mechanical ventilation (2), non-invasive ventilation (3), SVIA (1), and none (6)	Vancomycin, cefepime, metronidazole, IVIG, tocilizumab, enoxaparin, clindamycin, norepinephrine, vasopressin, amiodarone, lidocaine, meropenem, anakinra, remdesivir, milrinone, cefazolin, ceftriaxone, dopamine, linezolid, and metronidazole	Median (range) = 7.5 (4–13)	1
Belhadjer,[17] 2020	Retrospective	35 (51.4)	10 (1–16)	NA	Asthma (3), lupus (1), overweight (6), and NA (25)	Invasive respiratory support (22) and non-invasive (11)	Inotropic support, IVIG, IV corticosteroids, IL-1 receptor antagonist, and anticoagulant with heparin	5	0
Davies,[56] 2020	Observational	78 (67)	11 (1–17)	NA	None (61), usually expected to require primary care (15), and usually expected to require hospital care (2)	None (12), oxygen only (12), HFNC (13), non-invasive ventilation (5), invasive mechanical ventilation (36), and ECMO (3)	Antibiotics, steroids, IVIG, immunomodulation with biologic agents, anakinra, infliximab, tocilizumab, rituximab, aspirin or other antiplatelet therapy, anticoagulation prophylactic, anticoagulation therapeutic, and antiviral therapy (remdesivir)	Median (IQR) = 5 (3–6.5)	2

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Torres,[57] 2020	Observational	27 (51.8)	6 (0–14)	NA	Overweight/obesity (4), asthma (1), GATA3 deficiency (1), prematurity gestational age of 33 weeks (1), and none (20)	Oxygen (13), invasive mechanical ventilation (12), and NA (2)	Antibiotic treatment, acetylsalicylic acid, anticoagulant therapy, IVIG, and systemic corticosteroid	Median (IQR) = 9 (6–13)	0
Darren,[58] 2021	Observational	18 (55)	8.9 (0.3–14.6)	Black, Asian, and minority ethnic 89%, 16/18	NA	HFNC (5), supplemental oxygen (3), invasive ventilation (3), and none (8)	IVIG, methylprednisolone, tocilizumab, and infliximab	NA	0
Ng,[59] 2020	Case series	3 (67)	16 (13–17)	Asian Indian (1) and Afro-Caribbean (2)	NA	Nasal cannula (2) and mechanical ventilation (1)	Vasopressor, IVIG, steroid, aspirin, and antibiotic	NA	0
Paolino,[60] 2021	Case series	3 (67)	8 (6–9)	African American (2) and NA (1)	NA	NA	NA	NA	0
Prieto,[16] 2020	Case series	5 (60)	7 (IQR 5–12)	Caucasian (2), Hispanic (1), Arab (1), and Sub-saharan African (1)	Psoriasis (1) and post-operative tonsillectomy (1)	Nasal cannula (3) and BiPAP (1)	Dopamine, norepinephrine, ceftriaxone, IVIG (2 g/kg), steroids (2 mg/kg), HCQ, and azithromycin	NA	0
Harwood,[61] 2020	Case series	2 (50)	8.5 (3–14)	NA	None	NA	None	7	0
Lishman,[62] 2020	Case series	4 (50)	8	NA	Perforated appendicitis (2), appendicitis (1), and NA (1)	Mechanical ventilation (1) and nasal cannula (1)	Inotropic support, IVIG, steroid, aspirin, and antibiotics	Median (range) = 8 (4–11)	0
Calò Carducci,[25] 2020	Case series	2 (100)	13.5 (13–14)	Caucasian (2), Hispanic (1), Arab (1), and Sub-saharan African (1)	None	NA	Methylprednisolone, anakinra, lopinavir, and LMWH	Median (range) = 12 (10–14)	0

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Dallan,[63] 2020	Case series	2 (100)	10	Mixed-race (Asian and White) (1) and Black (1)	Obesity (2)	Non-invasive mechanical ventilation (1) and invasive mechanical ventilation (1)	HCQ, azithromycin, and anakinra	12, remained hospitalized = 1	0
Wolfler,[64] 2020	Case series	5 (40)	6 (0.17–14)	NA	NA	Non-invasive mechanical ventilation (1)	IVIG, epinephrine, antibiotic, prophylactic LMWH, steroid, tocilizumab, PDE3 inhibitor, and HCQ	Median (range) = 7.2 (5–10)	NA
Rogo,[65] 2020	Case series	4 (67)	5 (3–17)	NA	NA	ECMO (1)	Vasopressor, IVIG, and tocilizumab	NA	1
Shahbaznejad,[66] 2020	Case series	10 (60)	5.75 (1.1–12)	Iranian (10)	Chronic renal failure (1)	Intubation (1), oxygen hood (1), none (3), and NA (4)	Oseltamivir, meropenem, vancomycin, HCQ, IVIG, packed red cells, ceftriaxone, zinc gluconate, albumin, vasoactive drugs, clindamycin, cefotaxime, vitamin D, and diclofenac	Median (range) = 11.19.5 (3–2417)	1
Nathan,[67] 2020	Case series	2 (0)	8 (5–11)	NA	Overweight (2)	Mechanical ventilation (2)	Appendicectomy, post-operative diagnosis of myopericarditis, inotropic support, and antibiotic	Median (range) = 16.5 (12–21)	0
Wehl,[68] 2021	Case series	3 (33.3)	14 (7–17)	Turkish-German (1) and German (2)	None	NA	Antibiotics, IVIG, and acetylsalicyclic acid	Median (range) = 9 (7–13)	0
Mehta,[69] 2021	Case series	21 (50)	(6–7.5)	NA	NA	None	IVIG and methylprednisolone	Median (range) = 8.5 (5–12)	0
Mukund,[70] 2020	Case series	3 (100)	7 (6.5–12)	NA	AKI stage 2 (1)	Non-invasive ventilator (1) and low-flow oxygen (2)	Adrenaline, IVIG, methyplrednisolone, and azithromycin	Median (range) = 20 (16–32)	0

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Capone,[71] 2020	Case series	33 (61)	8.6 (2.2–17)	Hispanic (9) and non-Hispanic (23)	Obesity (13), asthma or reactive airway disease (5), renal tubular acidosis (1), and hemodynamically insignificant ventricular septal defect (1)	Mechanical ventilation (6) and required oxygen or PPV (17)	IVIG, methylprednisolone, aspirin, anakinra, tocilizumab, infliximab, and enoxaparin	Median (IQR) = 4 (4–8)	0
Whittaker,[72] 2020	Case series	58 (43)	9 (5.7–14)	Black (22), Asian (18), White (12), and others (6)	Asthma (3), neurological disability (1), epilepsy (1), sickle cell trait (1), and alopecia (1)	Mechanical ventilation (23), intubation (25), and ECMO (3)	IVIG, corticosteroids, anakinra, and infliximab	NA	1
Blumfield,[73] 2020	Case series	19 (53)	8 (2 months–18 years)	NA	Severe neurologic impairment (5), morbid obesity (3), congenital heart disease (1), metastatic cancer (1), asthma (1), hypertension (1), sickle cell disease (1), prior thromboembolic events (1), and fragile X syndrome (1)	Intubation (8), HFNC (1), and BiPAP (1)	NA	NA	2
Waltuch,[74] 2020	Case series	3 (100)	5 (5–13)	NA	Hypothyroid (1) and asthma (1)	BiPAP and intubation (1)	Meropenem, linezolid, enoxaparin, IVIG, tocilizumab, anakinra, cefepime, clindamycin, ceftriaxone, and dopamine	NA	NA
Chiotos,[75] 2020	Case series	6 (17)	7.5 (5–14)	Black (2), White (2), and NA (2)	None	Mechanical ventilation (3) and invasive mechanical ventilation (2)	Vasoactive support, IVIG, methylprednisolone 2 mg/kg/day, antibiotic, tocilizumab, and corticosteroid	Median (range) = 11 (8–17); NA = 5	0
Patel,[76] 2021	Case report	1 (100)	16	NA	None	NA	Acyclovir, ceftriaxone, paracetamol, IVIG, and aspirin	NA	0
Gupta,[77] 2020	Case report	1 (100)	1.9	Asian (2)	None	Nasal cannula	Dopamine, norepinephrine, antibiotics, and IVIG (2 g/kg) methylprednisolone	4	0

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Rauf,[78] 2020	Case report	1 (100)	5	Asian	None	Nasal cannula	Adrenaline, IV ceftriaxone, IVIG (2 g/kg), methylprednisolone pulse (30 mg/kg/day), diuretics, and enalapril	6	0
Gupta,[79] 2020	Case report	1 (0)	7	Indian	None	NA	Meropenem, IVIG (2 g/kg), aspirin (3 mg/kg), and methylprednisolone (15 mg/kg/day)	NA	0
Balasubramanian,[80] 2020	Case report	1 (100)	8	Indian	None	Nasal cannula	Ceftriaxone, tocilizumab (8 mg/kg IV over 2 hours), IVIG (2 g/kg), and aspirin (75 mg 1x/day)	14	0
Schneider,[81] 2020	Case report	1 (100)	9	NA	None	NA	Prednisolone	NA	0
Orlanski-Meyer,[82] 2020	Case report	1 (0)	6.5 (0–12)	NA	Inflammatory bowel syndrome	NA	Pulse methylprednisolone theraphy (30 mg/kg/day), prednisolone (2 mg/kg/day), anakinra (3.5 mg/kg/day), and IVIG (2 g/kg)	NA	0
Masih,[83] 2020	Case report	1 (100)	9	Caucasian (2) and Hispanic (1)	Asthma	Face mask	Ceftriaxone, clarithromycin, IVIG, and IV methylprednisolone	7	0
Meredith,[84] 2020	Case report	1 (0)	10	Polynesian/ Caucasian	Ulcerative colitis	NA	IVIG (2 g), high-dose IV methylprednisolone (1 g), aspirin (10 mg/kg), proton-pump inhibitor, adjuvant thromboprophylaxis, IV pipercillin/tazobactam, and IV meropenem	28	0
Ghatasheh,[85] 2021	Case report	1 (100)	0.75	Asian	None	NA	IVIG, anticoagulation, and antiplatelet	21	0
Dasgupta,[86] 2020	Case report	1 (0)	8	NA	None	None	Vasopressor, IVIG, corticosteroid, aspirin, and antibiotic	11	0
Klocperk,[87] 2020	Case report	1 (0)	8	NA	None	Nasal cannula (1)	IV methylprednisolone 2 mg/kg, IVIG, and nadroparin	15	0
Yozgat,[88] 2020	Case report	1 (0)	3	NA	NA	NA	IVIG and aspirin	NA	NA

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Table 1. (continued)

First author, year	Study design	No. of patients (% males)	Age (years), median (range)	Ethnicity (n)	Comorbidities (n)	Oxygen support (n)	Treatment	Length of stay (days)	Death (n)
Regev,[89] 2020	Case report	1 (100)	16	NA	Diffuse brain hemosiderosis	Mechanical ventilation	IVIG, methylprednisolone, and aspirin	NA	0
Hutchison,[90] 2020	Case report	1 (100)	14	NA	NA	HFNC	Vasopressors, IVIG, steroids, anticoagulants, and anankira	NA	0
Rodriguez-Gonzalez,[91] 2020	Case report	1 (100)	0.5	NA	Short bowel syndrome	Mechanical ventilation	Milrinone 0.5 mcg/kg/min, norepinephrine 0.2 mcg/kg/min, meropenem, vancomycin, and fluconazole	21	NA
Niño-Taravilla,[92] 2020	Case report	1 (100)	8	NA	None	Invasive mechanical ventilation (1)	Tocilizumab, methylprednisolone, and enoxaparin	17	0
Bahrami,[93] 2020	Case report	1 (0)	5	NA	NA	None	IVIG (2 g/kg), high-dose acetylsalicylic acid, epinephrine, meropenem, vancomycin and ciprofloxacin, and low-dose aspirin	NA	0
Carraro,[94] 2020	Case report	1 (0)	5	Brazilian	None	None	IVIG and aspirin	NA	0
Buonsenso,[95] 2020	Case report	1 (0)	11	NA	NA	NA	NA	NA	NA
Richardson,[96] 2021	Case report	1 (0)	5 months	NA	NA	HFNC	IVIG 2 g/kg, methylpredinosolone 10 mg/kg, anakinra 4 mg/kg, infliximab 5 mg/kg, aspirin 5 mg/kg, and warfarin	38	0

AKI=acute kidney injury; ASA=acetylsalicylic acid; BiPAP=bilevel positive airway pressure; ECMO=extracorporeal membrane oxygenation, HCQ=hydroxychloroquine; HFNC=high-flow nasal cannula, IL=interleukin; IV=intravenous; IVIG=intravenous immunoglobulin; IQR=interquartile range; LMWH=Low-molecular-weight heparin; NA=not available; NAFLD=non-alcoholic fatty liver disease; PDE3=phosphodiesterase enzyme 3; PPV=positive pressure ventilation; SD=standard deviation; SVIA=self-ventilating in air

Table 2. Demographic and clinical characteristics, supporting examination, and treatment in PIMS-TS patients

Variables	n (%)	Reference range
Age (years), mean (SD) (n = 698)	9.2 (4.1)	-
Male gender (n = 698)	405 (58.0)	-
Ethnicity (n = 404)		-
African American/ Afro-Caribbean/African	135 (33.4)	
White/European/Caucasian	71 (17.6)	
Hispanic/Latino	53 (13.1)	
Asian/Indian/Middle Eastern	81 (20.0)	
Others	64 (15.8)	
Days of fever before admission, mean (SD) (n = 146)	6.27 (2.7)	-
Temperature upon admission (°C), mean (SD) (n = 51)	39 (2)	-
Systolic blood pressure (mmHg), mean (SD) (n = 42)	81 (14)	-
Diastolic blood pressure (mmHg), mean (SD) (n = 36)	46 (12)	-
Signs and symptoms* (n = 698)		-
Fever	563 (80.6)	
Dyspnea	7 (1.0)	
Tachypnea	30 (4.3)	
Cough	85 (12.2)	
Oxygen desaturation	13 (1.9)	
Hypotension	59 (8.5)	
Shock	251 (36.0)	
SARS-CoV-2 test* (n = 654)		-
IgM positive	2 (0.3)	
IgG positive	181 (27.7)	
IgA positive	2 (0.3)	
IgM and IgG positive	11 (1.6)	
IgG and IgA positive	41 (6.3)	
IgM, IgG, and IgA positive	13 (1.9)	
Negative	122 (18.7)	
Polymerase chain reaction test positive	244 (37.3)	
Not specified†	185 (28.3)	
Comorbidities* (n = 319)		-
Respiratory	34 (10.7)	
Neurologic	11 (3.4)	
Endocrine	2 (0.6)	
Gastrointestinal	9 (2.8)	
Cardiovascular	6 (1.8)	
Nephrology	4 (1.2)	
Hemato-oncology	7 (2.1)	
Nutritional issues	62 (19.4)	
Immunology/allergic	8 (2.5)	
Prematurity	3 (0.9)	
Others	23 (7.2)	
Length of stay (days), mean (SD) (n = 328)	9.8 (11.3)	-
Outcome (alive) (n = 529)	509 (96.2)	-
Treatments received* (n = 621)		-
Intravenous immunoglobulin	469 (75.5)	
Vasopressor	119 (19.2)	
Antibiotics	213 (34.3)	
Anticoagulants	206 (33.2)	
Diuretic	22 (3.5)	
Nasal cannula for oxygen delivery	60 (9.7)	
Non-invasive ventilation	88 (14.2)	
Mechanical ventilation	167 (26.9)	
Antiarrhythmics	1 (0.2)	
Remdesivir	17 (2.7)	
Hydroxychloroquine	11 (1.8)	
Corticosteroids	303 (48.8)	
Aspirin	166 (26.7)	
Convalescent plasma	11 (1.8)	
Anakinra	47 (7.6)	
Tocilizumab	47 (7.6)	
Laboratory findings		-
Hematology		
Hemoglobin (g/dl) (n = 204), mean (SD)	9.6 (2.4)	11.5–14.5
White blood cell count (10^3/µl) (n = 187), mean (SD)	13.9 (6.2)	4–12
Lymphocyte (%) (n = 87), mean (SD)	13 (13)	25–33
Neutrophil (%) (n = 67), mean (SD)	74 (19)	57–67
Platelets (10^3/µl) (n = 250), mean (SD)	165.7 (94.3)	150–400
Inflammatory markers		
C-reactive protein (mg/l) (n = 310), mean (SD)	218.3 (119.6)	Male = 0.6–7.9 Female = 0.5–10.0
Ferritin (µg/ml) (n = 244), mean (SD)	918.5 (706.4)	10–60

Table continued on next page

Table 2. (continued)

Variables	n (%)	Reference range
Procalcitonin (µg/ml) (n = 80), mean (SD)	42 (78)	≤0.15
Lactate dehydrogenase (U/l) (n = 120), mean (SD)	663.1 (280.9)	150–500
Creatine kinase (U/l) (n = 42), mean (SD)	145 (221)	5–130
Liver and kidney functions		
Creatinine (mg/dl) (n = 233), mean (SD)	13.15 (25.25)	0.3–0.7
Alanine transaminase (U/l), mean (SD)	103 (217)	5–45
Aspartate aminotransferase (U/l) (n = 83), mean (SD)	95 (161)	15–50
Blood urea nitrogen (mg/dl) (n = 9), mean (SD)	55 (35)	5–18
Coagulation		
D-dimer (mg/l) (n = 158), mean (SD)	2,923.59 (3,170)	<0.4
Fibrinogen (mg/dl) (n = 214), mean (SD)	434.26 (293.77)	220–440
Erythrocyte sedimentation rate (mm/h) (n = 71), mean (SD)	69 (29.0)	0–20
Cardiac		
Troponin I (ng/l) (n = 27), mean (SD)	1,442 (5,693)	<300
Troponin T (ng/l) (n = 94), mean (SD)	98 (182)	<100
High sensitivity troponin I (ng/l) (n = 1), value	29	<100
High sensitivity troponin T (ng/l) (n = 2), mean (SD)	129.75 (43.25)	<14
Unspecified troponin (ng/l) (n = 60), mean (SD)	1,425 (4,260)	<10
BNP (pg/ml) (n = 41), mean (SD)	3,224 (5,038)	0–100
NT-proBNP (pg/ml) (n = 13), mean (SD)	12,323 (12,150)	0–450
Echocardiography findings (n = 490)		-
Mitral regurgitation	31 (6.3)	
Tricuspid regurgitation	34 (6.9)	
Pericardial effusion + pericarditis	56 (11.4)	
Myocarditis	29 (5.9)	
RV dysfunction	5 (1.0)	
Biventricular systolic dysfunction	3 (0.6)	
Coronary echogenicity	18 (3.7)	
Coronary artery dilatation	27 (5.5)	
Coronary artery aneurysm	26 (5.3)	
Aortic regurgitation	4 (0.8)	
Pulmonary regurgitation	2 (0.4)	
Coronary artery dilatation or aneurysm	18 (3.7)	
Ectatic coronary artery	15 (3.1)	
Myocardial dysfunction	5 (1.0)	
Cardiomegaly	10 (2.0)	
Dilated left ventricle	3 (0.6)	
Diastolic dysfunction	5 (1.0)	
Left ventricle dysfunction	199 (40.6)	
LVEF (n = 281)		-
≥55%	82 (29.2)	
<55%	199 (70.8)	
LCA Z-score (n = 12)		-
<2	8 (67)	
2–2.5	0 (0)	
≥2.5	4 (33)	
LAD Z-score (n = 6)		-
<2	4 (67)	
2–2.5	0 (0)	
≥2.5	2 (33)	
RCA Z-score (n = 18)		-
<2	8 (44)	
2–2.5	1 (6)	
≥2.5	9 (50)	

BNP=brain natriuretic peptide; Ig=immunoglobulin; LAD=left anterior descending artery; LCA=left coronary artery; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal-pro hormone BNP; PIMS-TS=pediatric inflammatory multisystem syndrome temporally associated with COVID-19; RCA=right coronary artery; RV=right ventricle; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SD=standard deviation. *Each patient may have more than one test done/symptoms/comorbidities/treatment; †presented as serologies positive without further specifications

(12%) were the most common abnormalities found in ECG (results not shown). Table 2 shows the echocardiographic findings on PIMS-TS patients, with left ventricle dysfunction (40.6%) being the most common abnormality, followed by pericardial effusion together with pericarditis (11.4%) and tricuspid regurgitation (6.9%). Echocardiographic findings showed that abnormalities were resolved in 88 days and ectatic coronary arteries in only 3 days

(results are not shown in the table). Most patients presented with left ventricular ejection fraction (LVEF) of <55% (70.8%), left coronary Z-score of <2 (67%), left anterior descending artery Z-score of <2 (67%), and right coronary artery Z-score of ≥2.5 (50%).

DISCUSSION

We found that PIMS-TS is most prevalent among older children, and other studies have found a similar mean age of 7 to 10 years.[15,26–28] Although they share similar clinical features, Kawasaki disease (KD) primarily affects children under 5 years old, with a median age of 2 years.[27,29–31] Compared with KD, patients with PIMS-TS are more likely to present with gastrointestinal symptoms, such as abdominal symptoms, diarrhea, vomiting, and multiorgan involvement.[28]

Shock and hypotension are the two most common signs of cardiovascular system as ventricular dysfunction is frequently encountered in PIMS-TS patients.[32] Previous studies found cardiovascular symptoms in 71% of patients.[27] Most myocardial involvement is usually moderate to severe, which is higher than in KD.[28]

This review also reported inflammatory markers, particularly CRP as the most notable abnormalities in laboratory measurements. This reflects the hyperinflammatory nature of PIMS-TS,[33] as shown in other studies.[27,34–37] D-dimer and cardiac markers, such as troponin and brain natriuretic peptide, were also found to be elevated across all studies, confirming that myocardial involvement is indeed a hallmark feature of this disease.[34,37,38]

Since PIMS-TS frequently involves the heart,[39] it is imperative to evaluate the patient's cardiac anatomy and function using echocardiography, cardiac CT, magnetic resonance imaging, and electrocardiography. In this systematic review, most patients had some cardiac involvements with a wide range of echocardiographic manifestations of PIMS-TS. The most common echocardiography abnormalities were reduced left ventricular (LV) function, pericardial effusion with pericarditis, myocarditis, and valvular abnormalities, which are similar to other systematic reviews.[36,38,39] Patients with impaired left ventricle function, specifically impaired LV global longitudinal strain and LV apical four-chamber peak longitudinal strain at clinical presentation, are at higher risk for developing adverse acute clinical course. Subclinical left myocardial dysfunction may persist for weeks after recovery in these patients. Thus, LV strain may be used to identify the higher-risk patients.[40] Coronary artery abnormalities were also found in a significant number of patients in this review, with coronary artery dilatation and aneurysms as the most common abnormalities, which also supported by other reviews.[38] Interestingly, most CT scans showed no abnormalities, with only a minority of patients manifesting cardiomegaly and pericardial effusion. Therefore, CT scans must be reconsidered to detect cardiovascular manifestation in children because it increases radiation exposure risk without generating significant findings. ST-segment and T wave abnormalities (32% and 12%, respectively) were most commonly reported in ECG, although most patients displayed normal ECG.

Cardiac abnormalities due to PIMS-TS, as shown in this review, represent a significant medical challenge that warrants more attention. This cardiac involvement may become a long-term health issue, as shown in a previous study that only 28.3% of patients had improved LVEF after hospital discharge.[39] Reduced LVEF may manifest as left-sided heart failure, which may cause fatigue, edema, and fluid retention, leading to a significant impairment on quality of life.[41] Treatments should aim to minimize the long-term impact of PIMS-TS.

There are limitations to this systematic review. Since COVID-19 is still considered an emerging new disease, and the term PIMS-TS is relatively new, the knowledge of COVID-19 and PIMS-TS is constantly evolving and changing rapidly. To date, PIMS-TS has only been described from mid-2020. This review also has minimal cardiovascular clinical findings due to limited data. However, more than half of the patients had one or more cardiac abnormalities on echocardiography, emphasizing that most PIMS-TS patients survived the critical phase, although the long-term complications were not observed. Thus, further research is needed as the delayed complications should not be underestimated. In addition, we could not analyze the clinical and echocardiographic progression of the patients. Many cardiac abnormalities in PIMS-TS patients were lacking proper evaluation and follow-up. Many patients with PIMS-TS were not evaluated with echocardiography or only evaluated once at admission, which leads to difficulty in evaluating the progress of cardiac abnormalities that have developed. Due to the wide variety of data, we suggest future

studies to standardize the echocardiographic finding reports associated with PIMS-TS and assess the disease progression.

In conclusion, numerous organ or system dysfunctions may complicate the clinical course of pediatric patients with COVID-19. This review primarily focused on the possible development of various cardiac abnormalities, which were assessed by laboratory tests and imaging, with echocardiography as the leading modality in detecting and evaluating these patients. We should be more vigilant with cardiac abnormalities in COVID-19 pediatric patients and should not underestimate their consequences in pediatric patients. Thus, the importance of addressing cardiac abnormalities that may occur in PIMS-TS can not be understated.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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