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Clinical Phenotypes of Pediatric Rheumatic and Systemic Inflammatory Manifestations Temporally Associated With SARS-CoV-2: A Retrospective Descriptive Cohort

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ABSTRACT

Background: Rheumatic and systemic inflammatory manifestations temporally associated with SARS-CoV-2 infection or exposure in children range from isolated vascular or articular disease to multisystem inflammation and persistent rheumatic illness, but their phenotypic diversity remains insufficiently characterized.

Objectives: To characterize clinical phenotypes, inflammatory findings, treatment, complications, and short-term outcomes in children in Georgia presenting with rheumatic or systemic inflammatory manifestations temporally associated with SARS-CoV-2 infection or exposure.

Methods: This retrospective single-center descriptive cohort study, conducted from March 2022 to March 2025, included 68 children younger than 18 years with new-onset rheumatic or systemic inflammatory manifestations temporally associated with preceding SARS-CoV-2 infection or epidemiological exposure.

Results: The cohort included 41 females (60.3%) and 27 males (39.7%); the mean age was 6.12±4.71 years. We could interpret the infection/exposure-to-symptom interval for 53/68 children, with a median of 8 weeks (IQR, 5–12). The vascular phenotype occurred in 32 children (47.1%), articular in 20 (29.4%), systemic inflammatory in 9 (13.2%), and mixed in 7 (10.3%). Cutaneous manifestations were documented in 35 children (51.5%), predominantly consisting of vasculitis or vasculopathy (33/35, 94.3%) and arthritis in 23 (33.8%). We administered corticosteroids to 51 children (75.0%), NSAIDs to 26 (38.2%), antibiotics to 22 (32.4%), and IVIG to 4 (5.9%). Complications were documented in 9/68 children (13.2%; 95% CI, 7.1–23.3). Among 41 children with available longitudinal follow-up, 16 (39.0%) had persistent or recurrent inflammatory manifestations, including 9 (22.0% of followed children) who subsequently fulfilled ILAR criteria for JIA.

Conclusions: Children with rheumatic or systemic inflammatory manifestations temporally associated with SARS-CoV-2 infection or exposure showed heterogeneous vascular, articular, systemic inflammatory, and overlapping presentations. The descriptive phenotype framework summarizes predominant clinical presentations but should not be interpreted as a validated disease classification. Longitudinal assessment is particularly important in children with persistent arthritis, recurrent inflammation, or cardiovascular involvement.

Keywords. Arthritis; COVID-19; Juvenile Idiopathic Arthritis; Multisystem Inflammatory Syndrome in Children (MIS-C); Pediatric Rheumatology; SARS-CoV-2; Vasculitis.

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BACKGROUND

SARS-CoV-2 infection is typically asymptomatic or mild in children; however, delayed immune-mediated complications may still occur after infection. These include multisystem inflammatory syndrome in children (MIS-C), vasculitic or vasculopathic lesions, arthritis, arthralgia, myalgia, and occasionally the emergence of chronic rheumatic disease.[1-4] Proposed mechanisms include persistent immune activation, molecular mimicry, endothelial and complement-mediated injury, cytokine dysregulation, and unmasking of pre-existing immune susceptibility.[3-5] Published pediatric evidence remains heterogeneous and is dominated by case reports, small series, and studies focused on individual entities such as MIS-C or vasculitis.[1,6-8] A descriptive phenotype-based framework may provide a practical means of

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organizing the heterogeneous vascular, musculoskeletal, cutaneous, and systemic presentations reported in affected children, while preserving the distinction between individual clinical entities. This study, therefore, aimed to characterize the clinical phenotypes, inflammatory profile, treatment patterns, complications, and short-term outcomes of children presenting with post-COVID rheumatic manifestations in Georgia.

METHODS

This retrospective, single-center descriptive cohort study was conducted at G. Zhvania Pediatric University Clinic, Tbilisi State Medical University, Georgia, from March 2022 to March 2025. The study included 68 children younger than 18 years with new-onset rheumatic or systemic inflammatory manifestations after SARS-CoV-2 infection or exposure. We categorized evidence of preceding SARS-CoV-2 infection or exposure by the certainty of attribution. We classified laboratory-supported cases as children with documented RT-PCR-confirmed infection or positive SARS-CoV-2 serology. In contrast, we classified children with documented close epidemiological exposure but no laboratory confirmation as exposure-only cases. We did not consider these categories equivalent evidence of prior infection. Where available, we reconstructed the interval between SARS-CoV-2 infection or exposure and onset of rheumatic or systemic inflammatory manifestations from the medical record. When documented, we extracted the interval between preceding SARS-CoV-2 infection or exposure and the onset of the first rheumatic or systemic inflammatory manifestation from the medical record and recorded it in weeks. Children were eligible if they had no previously established rheumatic disease and sufficient clinical and laboratory documentation. We excluded patients when an alternative diagnosis fully explained the presentation or when documentation was inadequate for clinical classification.

Phenotype classification

We recorded individual clinical manifestations and established clinical diagnoses documented in the medical records separately. For descriptive purposes only, we then assigned patients to one of four mutually exclusive clinical phenotypes based on the predominant presentation at the initial rheumatology assessment: vascular, articular, systemic inflammatory, or mixed. The vascular phenotype included predominantly vascular or inflammatory cutaneous presentations. Within the vascular phenotype, we additionally reviewed individual cases for a specific vasculitic diagnosis. The 32 children assigned to this phenotype had clinical features consistent with IgA vasculitis (IgAV), including palpable purpura, with gastrointestinal, musculoskeletal, and renal involvement recorded separately. We assessed renal involvement based on documented urinalysis findings, including hematuria and proteinuria. The articular phenotype included arthritis, arthralgia, or inflammatory joint stiffness without dominant vascular or systemic features; and the systemic inflammatory phenotype included MIS-C or other febrile multisystem inflammatory presentations. We categorized patients with clinically important involvement of at least two domains and no clearly predominant presentation as mixed. We used these phenotypes as an organizational framework for descriptive analysis and did not intend them to represent distinct disease entities, shared pathophysiological mechanisms, or a validated classification system. We retained individual diagnoses and manifestations separately wherever available. Two pediatric rheumatologists independently assigned phenotypes using the predefined phenotype definitions and the clinical information available at the initial rheumatology assessment. The reviewers classified all cases independently without access to each other's assignments. We assessed inter-rater agreement using Cohen's κ.

Diagnostic adjudication of MIS-C and JIA

We reviewed specific rheumatic and systemic inflammatory diagnoses separately from the descriptive phenotype classification. We retrospectively reviewed cases documented as MIS-C against the CDC case definition applicable to the corresponding period of illness, including fever, systemic inflammation, multisystem involvement, absence of a more likely alternative diagnosis, and evidence of preceding SARS-CoV-2 infection or epidemiological exposure. We retrospectively reviewed subsequent diagnoses of juvenile idiopathic arthritis (JIA) according to International League of Associations for Rheumatology (ILAR) criteria. We defined JIA as arthritis of unknown etiology beginning before age 16, persisting for at least 6 weeks, with alternative causes of arthritis excluded. We recorded the JIA subtype when sufficient clinical information was available. We adjudicated systemic JIA separately based on documented systemic and articular features.

Data collection and outcomes

We extracted demographic data, previous medical history, presenting manifestations, hospitalization duration, complete blood count, ESR, CRP, ferritin, D-dimer, ANA titer, RF, treatment, complications, relapse or persistent inflammation, and subsequent rheumatologic diagnoses from medical records. We extracted, where available, the interval between

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documented SARS-CoV-2 infection or epidemiological exposure and the onset of the first rheumatic or systemic inflammatory manifestation from the medical record and expressed it in weeks. We restricted timing analyses to patients with a documented, interpretable infection/exposure-to-symptom interval. We performed ANA testing in all patients by indirect immunofluorescence (IIF) using HEp-2 cells as the substrate. The reporting laboratory considered an ANA titer of 1:80 low-positive and of limited clinical significance; therefore, we analyzed titers >1:80 separately as higher-titer ANA reactivity. ANA staining patterns were not consistently available in the retrospective records and were therefore not analyzed. We extracted treatment data from the medical records, including systemic corticosteroids, NSAIDs, IVIG, and antibiotics. Corticosteroid use was recorded according to the documented treatment during the index clinical episode. The retrospective dataset did not uniformly include detailed information on corticosteroid dose, route of administration, or treatment duration, so we did not analyze these variables systematically. Outcomes included hospitalization duration, documented complications, persistent or recurrent inflammation, and subsequent diagnosis of JIA. We categorized longitudinal outcomes by documented clinical course. Persistent or recurrent inflammatory manifestations were distinguished from subsequently diagnosed chronic rheumatic disease. Subsequent JIA, including systemic JIA, was recorded separately and required fulfillment of ILAR criteria, including persistence of arthritis for more than 6 weeks. We descriptively compared baseline characteristics of children with and without available longitudinal follow-up to assess potential attrition bias. We assessed longitudinal follow-up at approximately 2 and/or 6 months after the index clinical presentation, depending on available follow-up data. We recorded antibiotic exposure during the index clinical episode from the medical records. Information regarding the specific indication for antibiotic initiation, microbiological confirmation, agent, and duration of treatment was not systematically available and was therefore not analyzed. We based laboratory analyses on available case data. We report the number of available observations for each laboratory parameter, and we did not impute missing values. Because laboratory investigations were performed according to clinical indication rather than a standardized study protocol, the availability of individual biomarkers may have varied by clinical presentation and disease severity.

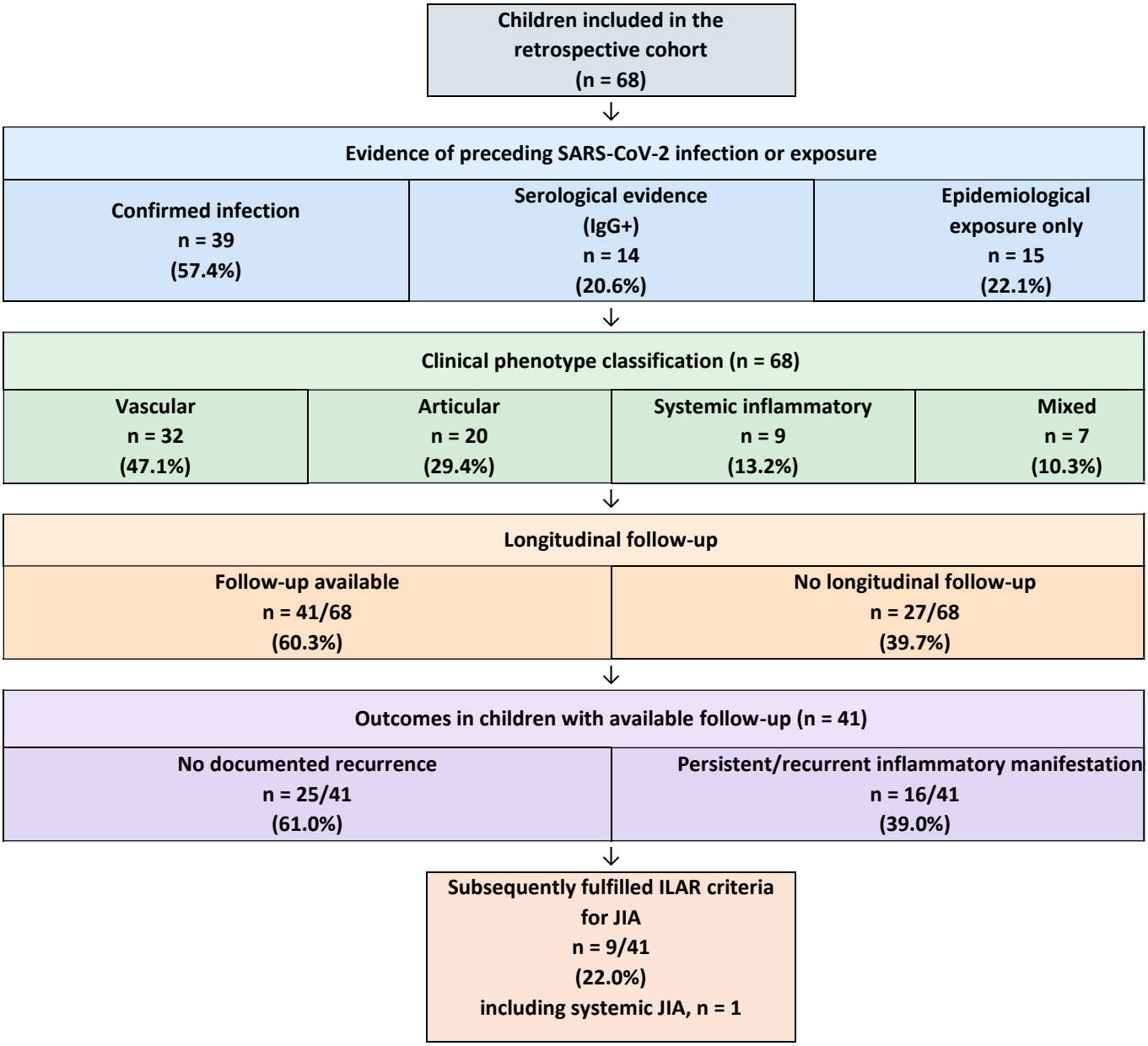
Statistical analysis and ethics

We performed analyses using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± SD or median with IQR and range, as appropriate; categorical variables are shown as frequencies and percentages. To assess potential attrition bias, we descriptively compared baseline characteristics of children with available longitudinal follow-up with those without documented follow-up. Comparisons included age, sex, hospitalization duration, CRP concentration, and treatment exposure. Given the descriptive design, we did not calculate hypothesis-testing P values. We assessed inter-rater agreement for phenotype classification using Cohen's κ. We used available-case denominators for laboratory analyses and did not impute missing values. We present key proportions with 95% confidence intervals (CIs) calculated using the Wilson method. We summarized age and sex distributions descriptively across the four clinical phenotype groups. **Figure 1** summarizes patient inclusion, SARS-CoV-2 evidence categories, clinical phenotype classification, and longitudinal follow-up availability.

The Biomedical Research Ethics Committee of Tbilisi State Medical University approved the study (Protocol No. 8-2022/101), and we conducted the study in accordance with the Declaration of Helsinki. We waived the requirement for written informed consent because we retrospectively analyzed anonymized, routinely collected data.

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FIGURE 1. Patient flow through cohort classification and longitudinal follow-up



Explanations: The diagram summarizes SARS-CoV-2 evidence categories, descriptive clinical phenotype classification, longitudinal follow-up availability, and subsequent inflammatory and rheumatic outcomes. We calculated percentages for longitudinal outcomes using the 41 children with available follow-up as the denominator. We based JIA diagnoses on ILAR criteria.

RESULTS

Study population and phenotypes

Independent phenotype classification by two pediatric rheumatologists showed complete agreement across all 68 cases (68/68, 100%; Cohen's κ=1.00). The cohort comprised 41 females (60.3%) and 27 males (39.7%). The mean age was 6.12±4.71 years, and the median age was 5.5 years (range, 0.25–16 years). Four children (5.9%) had non-rheumatic comorbidities; none had a documented autoimmune or rheumatic disease before SARS-CoV-2 infection. The vascular phenotype was most frequent (32/68, 47.1%; 95% CI, 35.7–58.8), followed by articular (20/68, 29.4%; 95% CI, 19.9–41.1), systemic inflammatory (9/68, 13.2%; 95% CI, 7.1–23.3), and mixed phenotypes (7/68, 10.3%; 95% CI, 5.1–19.8).

SARS-CoV-2 evidence and temporal relationship

Evidence supporting preceding SARS-CoV-2 infection or exposure differed across the cohort. Of 68 children, 39 (57.4%) had documented confirmed infection, 14 (20.6%) had serological evidence based on SARS-CoV-2 IgG, and 15 (22.1%) were classified based on documented close epidemiological exposure without laboratory confirmation. We could determine an interpretable interval between preceding SARS-CoV-2 infection/exposure and onset of the first rheumatic or

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systemic inflammatory manifestation for 53 of 68 children (77.9%). Among these patients, the median interval was 8 weeks (IQR, 5–12; range, 2–12 weeks). Among children with documented confirmed infection and an available interval (n=38), the median interval was 8.5 weeks (IQR, 5.25–12; range, 2–12 weeks). Among exposure-only cases (n=15), the corresponding interval was 8 weeks (IQR, 5–11; range, 3–12 weeks). For the serology-supported group, the dataset recorded dates rather than a consistently reconstructable infection-to-onset interval; these cases were therefore not included in the interval summary.

For serology-supported cases, the available dataset contained dates rather than a consistently reconstructable infection-to-symptom interval; therefore, these observations were not included in the interval summary.

Table 1 presents age and sex distributions by clinical phenotype.

TABLE 1. Age and sex distribution according to clinical phenotype

Clinical phenotype	n (%)	Age, years, median (IQR)	Female, n (%)	Male, n (%)
Vascular	32 (47.1)	5.0 [2.0–9.0]	17 (53.1)	15 (46.9)
Articular	20 (29.4)	4.5 [2.0–8.5]	13 (65.0)	7 (35.0)
Systemic inflammatory	9 (13.2)	12.0 [1.0–14.0]	5 (55.6)	4 (44.4)
Mixed	7 (10.3)	7.0 [1.46–8.5]	6 (85.7)	1 (14.3)
Total	68 (100.0)	5.5 [2.0–10.0]	41 (60.3)	27 (39.7)

Clinical manifestations and hospitalization

When we analyzed manifestations independently of the mutually exclusive phenotype classification, we documented cutaneous manifestations in 35 children (51.5%), predominantly vasculitis or vasculopathy (33/35, 94.3%) and arthritis in 23 (33.8%). Fever was recorded as part of the presenting syndrome in 12 children (17.6%). Manifestations overlapped; therefore, percentages exceed 100%. Median hospitalization was 4 days (IQR, 3.0-6.25; range, 2-19), and mean hospitalization was 5.60±3.44 days. Among the 41 children with available longitudinal follow-up, 25/41 (61.0%) had no documented recurrence, whereas 16/41 (39.0%) had persistent or recurrent inflammatory manifestations during follow-up. Importantly, we further characterized these categories by subsequent clinical course rather than treating them as a single disease entity. Nine of the 41 followed children (22.0%) subsequently fulfilled ILAR criteria for JIA, including one child with systemic JIA; objective arthritis persisted for more than 6 weeks in all nine cases. Of the 16 children with persistent or recurrent manifestations, 9 subsequently fulfilled criteria for JIA, while the remaining 7 experienced.

Clinical characteristics of the vascular phenotype

The vascular phenotype comprised 32 children (47.1% of the total cohort). Among these 32 children, preceding SARS-CoV-2 evidence consisted of documented confirmed infection in 20 (62.5%), serological evidence alone in 5 (15.6%), and epidemiological exposure without laboratory confirmation in 7 (21.9%). On detailed review, these cases were clinically characterized as IgA vasculitis (IgAV), and all 32 children had palpable purpura. Gastrointestinal involvement was common, with abdominal pain documented in 22/32 (68.8%). Renal involvement was documented in 11/32 (34.4%), including hematuria in 11/32 (34.4%) and proteinuria in 5/32 (15.6%). We also observed musculoskeletal manifestations, including arthralgia or arthritis. These findings demonstrate that the original broad “vascular phenotype” predominantly represented a clinically recognizable IgAV presentation rather than an undifferentiated group of vascular disorders.

Subsequent diagnosis of juvenile idiopathic arthritis

Among children with available longitudinal follow-up, 9/41 (22.0%) subsequently fulfilled ILAR criteria for JIA, including cases of systemic JIA. We analyzed these patients separately to characterize their initial presentation, temporal relationship with preceding SARS-CoV-2 infection or exposure, pattern and duration of arthritis, inflammatory and immunological findings, final JIA category, treatment, and follow-up course. **Table 2** presents individual patient characteristics.

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TABLE 2. Characteristics of children subsequently diagnosed with JIA

Patient	Age	Sex	SARS-CoV-2 evidence	Interval to arthritis	Initial presentation	ANA	ESR	CRP	Ferritin	Initial treatment	Final diagnosis
JIA-1	8 m	F	Close contact	3 wk	Arthritis	1:1280	40	44	220	GCs	JIA
JIA-2	10 y	F	Confirmed	12 wk	Arthritis	1:80	32	256	250	GCs	sJIA
JIA-3	5 y	F	Confirmed	6 wk	Arthritis	1:640	30	40	300	NSAIDs + GCs	JIA
JIA-4	4 y	F	Confirmed	12 wk	Arthritis	1:640	20	12	100	GCs	JIA
JIA-5	7 y	M	Confirmed	10 wk	Arthritis	1:640	5	2	80	NSAIDs	JIA
JIA-6	7 y	F	Confirmed	12 wk	Arthritis	1:320	35	33	300	NSAIDs + GCs	JIA
JIA-7	2 y	F	Confirmed	2 wk	Arthritis	1:320	25	12	300	NSAIDs + GCs	JIA
JIA-8	12 y	F	Confirmed	12 wk	Arthritis	1:640	30	36	35	NSAIDs + GCs	JIA
JIA-9	11 m	F	Close contact	3 wk	Arthritis	1:640	38	48	350	GCs	JIA

Laboratory findings

Laboratory data availability varied across the cohort: ESR and CRP were available for 60/68 children (88.2%), ferritin for 39/68 (57.4%), D-dimer for 54/68 (79.4%), and RF for 57/68 (83.8%). We therefore calculated all laboratory summaries using available-case denominators. Mean WBC, absolute neutrophil, and absolute lymphocyte counts were 12.25±5.27 ×10⁹/L, 7.42±4.60 ×10⁹/L, and 3.12±1.40 ×10⁹/L, respectively. Median ESR was 30 mm/h, CRP 40 mg/L, ferritin 320 ng/mL, and D-dimer 1.50. These laboratory findings are reported using available-case denominators.

Laboratory findings by clinical phenotype

We also summarized laboratory findings by the four descriptive clinical phenotypes. The mixed and systemic inflammatory groups showed higher median inflammatory markers, particularly CRP, while the mixed group also had higher median WBC and neutrophil counts. Higher-titer ANA reactivity (>1:80) was observed in 11/32 (34.4%) vascular, 13/20 (65.0%) articular, 7/9 (77.8%) systemic inflammatory, and 5/7 (71.4%) mixed cases. These summaries are descriptive only and should be interpreted cautiously because subgroup sizes were small and laboratory testing was based on clinical indication (**Tab.3**).

TABLE 3. Laboratory findings according to clinical phenotype

Variable	Vascular	Articular	Systemic inflammatory	Mixed
WBC, ×10⁹/L	11.2 [7.9–16.1] (n=32)	10.5 [7.0–13.3] (n=20)	13.0 [9.4–15.0] (n=9)	19.0 [17.5–20.5] (n=7)
Neutrophils, ×10⁹/L	5.65 [3.08–9.15] (n=32)	6.15 [3.60–8.20] (n=20)	8.0 [6.0–8.0] (n=9)	15.0 [13.8–15.5] (n=7)
Lymphocytes, ×10⁹/L	3.55 [2.23–4.30] (n=32)	3.0 [2.25–3.45] (n=19)	2.9 [1.7–5.0] (n=9)	3.0 [2.05–3.25] (n=7)
ESR, mm/h	21.5 [14.8–32.8] (n=32)	27.5 [12.8–39.8] (n=20)	30.0 [20.0–47.0] (n=9)	40.0 [40.0–42.5] (n=7)
CRP, mg/L	17.5 [9.5–42.3] (n=32)	31.5 [8.0–48.8] (n=20)	67.0 [48.0–78.0] (n=9)	67.0 [53.0–84.0] (n=7)
Ferritin, ng/mL	80 [46–320] (n=32)	100 [50–300] (n=19)	250 [150–400] (n=9)	250 [148–438] (n=7)
D-dimer, µg/mL	1.0 [0.5–2.08] (n=32)	0.75 [0.4–1.58] (n=20)	1.5 [0.9–3.8] (n=9)	3.0 [1.0–4.0] (n=7)
ANA >1:80, n (%)	11 (34.4%)	13 (65.0%)	7 (77.8%)	5 (71.4%)

Values are median [IQR] with available n unless otherwise indicated. ANA was measured by HEp-2 indirect immunofluorescence; 1:80 was considered low-positive, and titers >1:80 are shown separately. RF was available in 57 children and was negative in all tested patients. Laboratory testing was performed according to clinical indication; missing values were not imputed.

ANA testing by HEp-2 IIF was available for all 68 children. A titer of 1:80, considered low-positive and of limited clinical significance by the reporting laboratory, was observed in 32/68 children (47.1%). Higher ANA titers (>1:80) were present in 36/68 (52.9%): 1:160 in 16 (23.5%), 1:320 in 14 (20.6%), 1:640 in 5 (7.4%), and 1:1280 in 1 (1.5%).

Among the nine children who subsequently fulfilled ILAR criteria for JIA, 8/9 (88.9%) had ANA titers >1:80. ANA titers were 1:80 in one child, 1:320 in two, 1:640 in five, and 1:1280 in one. All nine children were RF-negative.

Coronary artery abnormalities were documented in 4/68 children (5.9%). Two of these four children had a documented diagnosis of MIS-C. Quantitative echocardiographic data were available for three children. In one infant with a panniculitis/vasculitis presentation, the LMCA Z-score was 1.95, the LAD Z-score was 5.20, and the RCA Z-score was 2.48. In a 9-month-old child with MIS-C, the LAD and RCA Z-scores were 3.80 and 2.22, respectively, and in a 1-year-old child with MIS-C, the corresponding Z-scores were 4.0 and 2.6. The fourth child had echocardiographically documented mild coronary artery dilation, but quantitative Z-scores were not available. Three of the four children received IVIG plus dexamethasone,

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whereas one received NSAIDs plus dexamethasone. Clinical and echocardiographic characteristics of children with coronary artery abnormalities are summarized in **Table 4**.

TABLE 4. Clinical and echocardiographic characteristics of children with coronary artery abnormalities

Age/Sex	SARS-CoV-2 evidence	Clinical presentation	Coronary artery findings	Treatment
3 mo/M	Confirmed infection	Panniculitis/vasculitis	LMCA: 2.5 mm, Z 1.95; LAD: 2.5 mm, Z 5.20; RCA: 2.1 mm, Z 2.48	NSAIDs + dexamethasone
12 y/M	SARS-CoV-2 IgG+	Fever	Mild coronary artery dilation; quantitative Z-scores unavailable	IVIG + dexamethasone
9 mo/F	SARS-CoV-2 IgG+	MIS-C	LAD: 3.0 mm, Z 3.80; RCA: 2.0 mm, Z 2.22	IVIG + dexamethasone
1 y/F	SARS-CoV-2 IgG+	MIS-C	LAD: Z 4.0; RCA: Z 2.6	IVIG + dexamethasone

Treatment and outcomes

We administered systemic corticosteroids to 51 children (75.0%), NSAIDs to 26 (38.2%), antibiotics to 22 (32.4%), and IVIG to 4 (5.9%). Corticosteroid treatment reflected clinical management of the presenting inflammatory manifestations; however, dose, route, and duration were not uniformly available for standardized analysis. All IVIG recipients had systemic inflammatory presentations, including MIS-C. We administered antibiotics to 22/68 children (32.4%) during the index clinical episode. Because the retrospective dataset did not consistently capture the indication for antibiotic therapy or microbiological confirmation, we interpret antibiotic use as treatment exposure rather than evidence of confirmed bacterial infection. Ceftriaxone was the most frequently documented antibiotic; a small number received vancomycin, meropenem, or combination therapy.

Complication status was available for all 68 children. Complications were documented in 9/68 children (13.2%; 95% CI, 7.1–23.3), whereas 59/68 (86.8%) had no documented complication. Documented complications included coronary artery dilatation in 4; anemia or severe anemia in 3; and nephritis, pneumonia, thrombocytosis, and severe pancytopenia in 1 child each. One child had more than one complication.

Follow-up was available for 41 children (60.3%). Sixteen (39.0%; 95% CI, 25.7–54.3) had persistent or recurrent inflammatory manifestations or progression to chronic rheumatic disease, whereas 25 (61.0%) had no documented relapse. Nine children (22.0%; 95% CI, 12.0–36.7) subsequently fulfilled ILAR criteria for JIA. Outcome percentages were calculated using the available-case denominator of 41.

Follow-up availability and assessment of attrition

Longitudinal follow-up data were available for 41/68 children (60.3%), with follow-up assessments documented at approximately 2 and/or 6 months after the index presentation, whereas 27/68 (39.7%) had no documented longitudinal follow-up. We compared baseline characteristics descriptively to assess potential attrition bias. Children with follow-up had a median age of 7.0 years (IQR, 2.0–10.0) versus 4.0 years (IQR, 2.0–9.0) among those without follow-up; females accounted for 27/41 (65.9%) and 14/27 (51.9%), respectively. Median hospitalization duration was 6 days (IQR, 4–8) versus 3 days (IQR, 3–4), and median CRP was 35 mg/L (IQR, 6–67) versus 38 mg/L (IQR, 15.5–48.5). Corticosteroids were administered to 33/41 (80.5%) versus 18/27 (66.7%), NSAIDs to 14/41 (34.1%) versus 13/27 (48.1%), and antibiotics to 16/41 (39.0%) versus 6/27 (22.2%). These descriptive differences indicate that longitudinal outcome estimates may be affected by non-random follow-up and should be interpreted cautiously.

DISCUSSION

In this retrospective cohort, rheumatic and systemic inflammatory manifestations temporally associated with SARS-CoV-2 infection or exposure were heterogeneous. For descriptive purposes, we organized presentations into four predominant clinical phenotypes—vascular, articular, systemic inflammatory, and mixed—with vascular and articular presentations accounting for more than three-quarters of the cohort. These categories should not be interpreted as components of a single biological syndrome or as distinct disease entities; rather, they provide an organizational framework for describing the predominant presentation at initial rheumatology assessment. Vascular and articular phenotypes accounted for more than three-quarters of the cohort, while systemic inflammatory and mixed presentations were less frequent. The observed heterogeneity highlights the importance of reporting individual clinical diagnoses and manifestations alongside broader descriptive phenotype categories.

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Vascular and cutaneous manifestations predominated, consistent with reports of IgA vasculitis, chilblain-like lesions, Kawasaki-like disease, and cutaneous small-vessel vasculitis after SARS-CoV-2 infection.[1,2] Proposed mechanisms include endothelial injury, complement activation, immune complex formation, cytokine-mediated inflammation, and molecular mimicry.[1,3-5] Although these mechanisms are biologically plausible, temporal association does not prove that SARS-CoV-2 caused the vascular disease. Among patients with an interpretable temporal interval, rheumatic or systemic inflammatory manifestations developed a median of 8 weeks after documented SARS-CoV-2 infection or epidemiological exposure. This timing supports a temporal relationship but should not be interpreted as evidence of causality. Moreover, we could not reconstruct precise infection-to-onset intervals for the serology-supported subgroup, further limiting causal attribution. The predominance of vascular presentations in this cohort should be interpreted in the context of the tertiary referral setting. It should not be considered an estimate of the relative frequency of postinfectious rheumatic manifestations in the general pediatric population.

Longitudinal outcomes were heterogeneous. Among the 41 children with available follow-up, 16 (39.0%) had persistent or recurrent inflammatory manifestations; however, this should not be interpreted as a single outcome category. Nine children subsequently met ILAR criteria for JIA, whereas the remaining recurrent or persistent presentations were considered separately based on their documented clinical course.

The articular phenotype was the second most frequent, and arthritis affected approximately one-third of the cohort. Arthralgia, reactive arthritis, and new-onset inflammatory arthritis have been reported after COVID-19, but pediatric evidence remains limited and heterogeneous.[6,7] A clinically important observation was that 9 of the 41 children with available longitudinal follow-up (22.0%) subsequently fulfilled ILAR criteria for JIA. Given the substantial proportion of the original cohort without longitudinal follow-up, interpret this percentage as the proportion among followed patients rather than as an estimate of JIA incidence after SARS-CoV-2 infection. Infection may trigger transient postinfectious arthritis, unmask pre-existing susceptibility, or coincide with the natural onset of JIA. The subsequent JIA diagnoses in nine children are therefore clinically important but should not be interpreted as proof of causation. The temporal association between SARS-CoV-2 infection or exposure and subsequent JIA diagnosis should not be interpreted as evidence of causality. Several explanations may account for the nine JIA/sJIA diagnoses observed during follow-up. SARS-CoV-2 may have acted as an inflammatory trigger in susceptible children or may have immunologically unmasked a pre-existing predisposition to chronic inflammatory disease. Alternatively, increased medical contact following infection may have accelerated recognition of previously evolving disease, and some children initially considered to have postinfectious arthritis may have represented early JIA before the six-week duration criterion was fulfilled. Finally, the observed cases may reflect coincidental JIA onset within the expected background occurrence of the disease. Without a comparator group or population denominator, the present study cannot determine whether JIA incidence increased after SARS-CoV-2 infection.

The systemic inflammatory group included MIS-C and other febrile multisystem presentations. MIS-C remains the best-defined delayed inflammatory syndrome associated with SARS-CoV-2 and may overlap clinically with Kawasaki disease, systemic JIA, macrophage activation syndrome, and severe infection.8-10 The relatively small number of MIS-C cases in this cohort reflects the deliberately broader inclusion of non-MIS-C rheumatic phenotypes.

Inflammatory markers varied, with broad ranges for CRP, ferritin, and D-dimer. Phenotype-specific descriptive summaries showed higher median CRP in the systemic inflammatory and mixed groups, and higher median WBC and neutrophil counts in the mixed group. These findings should not be interpreted as evidence of biologically distinct phenotypes because the subgroup sizes were small, no inferential testing was performed, and laboratory investigations were obtained according to clinical indication rather than a standardized protocol. Values from this mixed cohort should also not be directly compared with cohorts restricted to critically ill MIS-C patients.[8,11]

An ANA titer of more than 1:80 was recorded in 36 children (52.9%), whereas all tested patients were RF-negative. Higher-titer ANA reactivity was frequently observed among children who subsequently fulfilled criteria for JIA; however, given the small number of cases, incomplete follow-up, and absence of a comparator group, this observation is descriptive and should not be interpreted as evidence that ANA predicts subsequent JIA. ANA positivity can occur transiently after infection and in healthy children and is not diagnostic of systemic autoimmune disease. Autoantibodies have been described during and after COVID-19, but their persistence and pathogenic

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relevance remain uncertain.[12] Because pre-infection ANA values, staining patterns, and serial measurements were unavailable, the present findings should be interpreted as an immunologic observation rather than evidence that SARS-CoV-2 induced systemic autoimmunity.

Corticosteroids were used in three-quarters of the cohort, reflecting substantial inflammatory disease among referred or hospitalized patients, but the observational design does not allow conclusions about comparative effectiveness. IVIG was limited to systemic inflammatory presentations, consistent with ACR guidance supporting IVIG and glucocorticoids for MIS-C when immunomodulatory treatment is required.[9] Antibiotics were prescribed to approximately one-third of patients, likely because early inflammatory presentations can resemble bacterial sepsis; this finding also highlights the need for timely reassessment once infection is excluded.

Coronary artery dilatation was the most frequent complication, supporting cardiovascular evaluation in MIS-C or Kawasaki-like presentations. Follow-up findings also warrant caution. Persistent or recurrent inflammation was documented in 39.0% of patients with available follow-up, but 27 children lacked follow-up data. Return visits may have been more likely among symptomatic patients, producing selection bias; conversely, ongoing disease treated elsewhere may have been missed.

The phenotype-based framework is a practical organizational tool rather than a validated classification system. It may nevertheless help clinicians align investigations with presentation: renal and vascular assessment for vascular disease, detailed joint evaluation for articular disease, and cardiac, coagulation, and hyperinflammation screening for systemic presentations. Persistent arthritis, recurrent fever, rising ferritin, coronary involvement, or evolving JIA features should prompt longitudinal rheumatology or cardiology follow-up.

Longitudinal follow-up was available for 60.3% of the cohort. Consequently, estimates of persistent or recurrent inflammatory manifestations and subsequent JIA are restricted to the followed subgroup and may be affected by attrition bias. In particular, the proportion of children subsequently diagnosed with JIA (9/41, 22.0%) should not be interpreted as an incidence estimate among children following SARS-CoV-2 infection or exposure.

Strengths and limitations

To our knowledge, this is the first Georgian cohort describing post-COVID pediatric rheumatic manifestations using a phenotype-based framework. The principal strength of this study is the inclusion of a broad post-COVID rheumatic spectrum within a single clinical framework. Limitations include its retrospective, single-center design; referral and selection bias; nonstandardized testing; no control group; and incomplete or nonuniform follow-up. The temporal relationship with SARS-CoV-2 cannot establish causality, and the operational phenotypes require external validation. The infection-to-manifestation interval could not be reconstructed uniformly for all participants, particularly in children identified through serological evidence, for whom the timing of the preceding infection could not be established reliably. Histopathologic confirmation, serum IgA concentrations, and complement measurements were not systematically available in this retrospective dataset because these investigations were performed according to clinical indication rather than a standardized research protocol. The single-center tertiary-care setting may have introduced referral and severity bias, as children with more prominent, persistent, or clinically complex inflammatory manifestations may have been more likely to undergo rheumatologic evaluation. Consequently, the distribution of clinical phenotypes, treatment patterns, and complication rates in this cohort may not represent the broader pediatric population with SARS-CoV-2 infection or exposure. We could not systematically evaluate the indication and microbiological basis for antibiotic treatment, limiting interpretation of the relatively frequent antibiotic exposure observed in the cohort. The lack of standardized information on corticosteroid indication, dose, route, and duration limited treatment-related analyses. Follow-up echocardiographic measurements were not systematically available, limiting assessment of the subsequent course and resolution of coronary artery abnormalities. An important limitation of this study is the absence of a contemporaneous or historical comparator group. Consequently, the observed clinical phenotype distribution and the proportion of children who subsequently fulfilled criteria for chronic rheumatic disease cannot be interpreted as excess risk attributable to SARS-CoV-2. In particular, the study cannot determine whether the occurrence of JIA among children with available follow-up exceeded the expected background occurrence of JIA in the pediatric population. Future controlled studies comparing children with and without documented SARS-CoV-2 infection, as well as analyses using historical rheumatology cohorts, are needed to clarify whether SARS-CoV-2 exposure is associated with

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an increased risk of subsequent chronic rheumatic disease. Laboratory testing was not standardized across the cohort and was performed according to clinical indication. In particular, biomarkers such as ferritin and D-dimer may have been preferentially measured in children with more severe or systemic inflammatory presentations. Consequently, available-case laboratory summaries may be affected by testing-indication bias and should not be interpreted as representative of the entire cohort. Prospective multicenter studies with standardized definitions and long-term follow-up are needed. Follow-up was recorded at approximately 2 and/or 6 months rather than as a uniform continuous duration for every patient; therefore, median follow-up duration and phenotype-specific follow-up duration could not be calculated reliably.

CONCLUSIONS

In this retrospective Georgian pediatric cohort, rheumatic and systemic inflammatory manifestations temporally associated with SARS-CoV-2 infection or exposure showed a heterogeneous spectrum, with vascular and articular presentations predominating. Among children with available longitudinal follow-up, persistent or recurrent inflammatory manifestations were clinically relevant, and a subset subsequently fulfilled ILAR criteria for JIA; however, these observations do not establish causality or an increased post-SARS-CoV-2 incidence of chronic rheumatic disease. The findings support phenotype-directed assessment and longitudinal follow-up, particularly for children with persistent arthritis, recurrent inflammation, or cardiovascular involvement. Prospective multicenter studies with standardized evaluation, comparator groups, and longer follow-up are needed to clarify the long-term rheumatologic implications of SARS-CoV-2 in children.

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