Convergence and divergence in Kawasaki disease and multisystem inflammatory syndrome in children: the results from the COVASAKI survey

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Abstract

Objective

To compare Kawasaki disease (KD) and multisystem inflammatory syndrome (MIS-C) in children.

Methods

Prospective collection of demographics, clinical and treatment data. Assessment of type 1 interferon (IFN) score, CXCL9, CXCL10, Interleukin (IL)18, IFNγ, IL6, IL1b at disease onset and at recovery.

Results

87 patients (43 KD, 44 MIS-C) were included. Age was higher in MIS-C compared to KD group (mean 31±23 vs. 94±50 months, p<0.001). Extremities abnormalities (p=0.027), mucosal involvement (p<0.001), irritability (p<0.001), gallbladder hydrops (p=0.01) and lymphadenopathy (p=0.07) were more often recorded in KD. Neurological findings (p=0.002), gastrointestinal symptoms (p=0.013), respiratory involvement (p=0.019) and splenomegaly (p=0.026) were more frequently observed in MIS-C. Cardiac manifestations were higher in MIS-C (p<0.001), although coronary aneurisms were more frequent in KD (p=0.012). In the MIS-C group, the multiple linear regression analysis revealed that a higher IFN score at onset was related to myocardial disfunction (p<0.001), lymphadenopathy (p=<0.001) and need of ventilation (p=0.024). Both CXCL9 and CXCL10 were related to myocardial disfunction (p<0.001 and p=0.029). IL18 was positively associated to PICU admission (0.030) and ventilation (p=004) and negatively associated to lymphadenopathy (0.004). IFNγ values were related to neurological involvement and lymphadenopathy (p<0.001), IL1b to hearth involvement (0.006). A negative correlation has been observed between IL6 values, heart involvement (p=0.013) and PICU admission (p<0.001).

Conclusion

The demographic and clinical differences between KD e MIS-C cohorts confirm previous reported data. The assessment of biomarkers levels at MIS-C onset could be useful to predict a more severe disease course and the development of cardiac complications.

Key words

Kawasaki disease, MIS-C, biomarkers, cytokines

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Introduction

In the early phases of the pandemic, multisystem inflammatory syndrome in children (MIS-C) was associated with Kawasaki disease (KD) due to the sharing of several clinical findings as prolonged fever, conjunctivitis, rash, mucositis, extremities changes and frequent cardiac involvement. Subsequent data from epidemiological and clinical observation suggested that the two conditions differ in ethnicity, age of onset, clinical spectrum, laboratory findings and type of cardiac manifestations (1-7). In addition, the comparison of KD and MIS-C immune cell profiles, cytokines and autoantibodies levels has detected several differences in terms of inflammatory proteins values, lymphocyte subsets, and autoantibodies (8-12). The main aim of this study was to compare clinical, biochemical, treatment and outcome data of two cohorts of KD and MIS-C patients. Moreover, an assessment of specific serum biomarkers levels in the two groups has been carried out and their potential association with clinical features and outcomes has been investigated.

Methods

Data collection

The COVASAKI survey is a prospective multicentre comparative study including KD and MIS-C patients diagnosed between November 1st 2020 to February 28th 2023 belonging to 8 Paediatric Tuscany units. Medical charts of KD and MIS-C group were reviewed for age, gender, ethnicity and comorbidities. In addition, data on clinical manifestations, biochemical values, treatment and disease outcome were retrieved (13).

The fulfilment of the American Heart Association criteria for Kawasaki disease (14) and the World Health Organization criteria for the Multisystem Inflammatory syndrome in children (15) was assessed in KD and MIS-C groups, respectively.

Of note, the relationship of KD and MIS-C with exposure to SARS-CoV2 has been assessed according to current criteria during the first and the second pandemic waves (14, 15). Considering the increase in the vaccination rate as well as in the SARS CoV-2 infection incidence during the subsequent COVID-19 waves, the dosage of anti-nucleocapsid antibodies together with anti-spike antibodies and the history of recent infection was considered to select MIS-C patients.

For each patient a blood sample at disease onset (T0), and at recovery (T1) was collected to assess type 1 interferon score (IFN score), serum cytokines and chemokines: Interleukin (IL) 1 beta, IL6, IL18, chemokine ligand (CXCL) 9, CXCL10 and IFNγ in both groups.

For the IFN signature, total RNA was extracted from whole blood with a PAX gene RNA isolation kit. Six target gene transcripts were analysed (IFI27, IFI44L, IFIT1, ISG15, RSAD2 and SIGLEC1). For each of the six probes, patients' data were expressed relative to a pool of 20 healthy individuals. The median fold change of the six genes compared to the median of the pool of healthy controls was used to create an IFN score, with an abnormal score being defined as greater than +2 standard deviations above the mean of the control group. For the simultaneous dosages of pro-inflammatory cytokines and chemokines, Luminex Multiplex assay was used.

The COVASAKI study complies with the Declaration of Helsinki and was approved by the Paediatric Ethical Committee of Meyer Children's Hospital IRCCS (N 03/2021I) and by the institutional review board of all centres participating to the study. Written informed consent was obtained from each patient's parent or legal representative.

Statistical analysis

Continuous variables were reported as median values and related interquartile range (IQR) and mean and related range and were compared between groups using the Mann-Whitney test for unpaired data. Data distribution was assessed by the Shapiro-Wilk test. Categorical variables were reported as absolute frequencies and percentages and were compared between the two groups using Chi-square test, with Fisher exact test correction when appropriate. Spearman's analysis was used to explore the correlation between serum biomarkers

values and clinical signs in both groups. A multiple linear regression analysis was performed to assess the correlation between the biomarkers' values at onset and the main clinical manifestations in the MIS-C group. Regression analysis was limited to variables resulted associated in univariate analysis and/or judged as clinically relevant. Results were presented as correlation coefficients of the independent variables, a $p<0.05$ was considered statistically significant. Data analysis was performed using SPSS v. 28 (IBM Corp., Armonk, NY, USA).

Results

Eighty-seven patients (43 KD, 44 MIS-C) were included in the study. The demographic features of the two cohorts are detailed in Table I, along with the detected significances by the reciprocal comparisons. Age at onset was significantly higher in MIS-C compared to KD patients (mean 31±23 *vs*. 94±50 months, $p<0.001$). No differences in gender and ethnicity were observed.

The length of stay was longer in MIS-C patients (mean 8.6±4.1 *vs*. 14.5±6.9 days, $p=0.002$) and paediatric intensive care unit (PICU) admission was significantly higher ($p<0.001$) together with the need for inotropes ($p=0.048$). As regards clinical manifestations, neurological findings, in particular headache ($p=0.002$) and meningism ($p=0.035$), were significantly more frequent in MIS-C patients ($p=0.002$). Extremities abnormalities and mucosal involvement were more often recorded in KD patients ($p=0.027$; $p<0.001$). Irritability was a typical clinical feature in the KD cohort ($p<0.001$). Gastrointestinal symptoms were more frequently observed in MIS-C group ($p=0.013$) as well as respiratory involvement ($p=0.019$) and splenomegaly ($p=0.026$). Conversely, gallbladder hydrops ($p=0.01$) and lymphadenopathy ($p=0.07$) more often occurred in KD patients. The frequency of cardiac manifestations overall was significantly higher in MIS-C group ($p<0.001$), although coronary arteries aneurisms were more frequently observed in KD patients ($p=0.012$).

The comparison of biochemical parameters (Table II) reported that the lym-

Table I. Comparison between demographic and clinical data of KD and MIS-C patients.

	MIS-C (n=44)	KD (n=43)	*p* value
Demographic data			
Age (months)	94 ± 50	31 ± 23	**<0.001**
Sex			
Male	32 (72.7)	28 (65.1)	0.443
Female	12 (27.3)	15 (34.9)	
Ethnicity			
Caucasian	35 (79.5)	39 (90.7)	
Hispanic	/	/	0.360
Asian	4 (9.1)	2 (4.7)	
African	5 (11.4)	2 (4.7)	
Clinical symptoms			
Skin	29/44 (65.9)	35/43 (81.4)	0.115
Rash	28/29 (96.6)	32/35 (91.4)	0.620
Extremities abnormalities	9/29 (20.5)	20/35 (57.1)	**0.027**
Mucosa	16/44 (36.4)	33/43 (76.7)	**<0.001**
Cheilitis	12/16 (75.0)	21/33 (63.6)	0.426
Enanthema	5/16 (31.3)	24/33 (72.7)	**0.006**
Strawberry tongue	2/16 (12.5)	7/33 (21.2)	0.698
Eye	30/44 (68.2)	29/43 (67.4)	0.941
Conjunctivitis	30/30 (100)	28/29 (96.6)	0.492
Uveitis	1/30 (3.3)	/	1.000
Papilledema	5/30 (16.7)	1/29 (3.5)	0.194
CNS	19/44 (43.2)	23/43 (53.5)	0.275
Headache	9/19 (47.4)	1/23 (4.3)	**0.002**
Impaired consciousness	4/19 (9.1)	2/23 (8.7)	0.384
Meningism	4/19 (9.1)	/	**0.035**
Irritability	7/19 (36.8)	21/23 (91.3)	**<0.001**
GI	32/44 (72.7)	21/43 (48.8)	**0.013**
Diarrhoea	21/32 (65.6)	9/21 (42.9)	0.102
Vomiting	24/32 (75.0)	16/21 (76.2)	0.922
Abdominal pain	20/32 (62.5)	4/21 (19.0)	**0.002**
Gallbladder hydrops	/	4/21 (19.0)	**0.020**
Pancreatitis	/	/	/
Peritoneal effusion	1/32 (3.1)	/	1.000
Lung	16/44 (36.4)	7/43 (16.3)	**0.019**
Dyspnoea	6/16 (37.5)	/	0.124
Cough	5/16 (31.3)	3/7 (42.9)	0.657
Rhinitis	3/16 (18.8)	2/7 (28.6)	1.000
Pneumonia	2/16 (12.5)	1/7 (14.3)	1.000
Pleural effusion	4/16 (25)	2/7 (28.6)	1.000
Heart	19/44 (43.2)	4/43 (9.3)	**<0.001**
Myocarditis	3/19 (15.8)	/	0.578
Pericarditis	1/19 (5.3)	1/4 (25.0)	0.380
Valve insufficiency	5/19 (26.3)	/	0.539
LVSD	10/19 (52.6)	/	0.104
Coronary aneurism	2/19 (10.5)	3/4 (75.0)	**0.021**
Hypotension	6/19 (31.69)	/	0.309
Cardiac arrest	1/19 /5.3)	/	1.000
Arrythmia	2/19 (10.5)	/	1.000
MSK	4/44 (9.1)	6/43 (14)	0.521
Arthritis/ Arthralgia	4/4 (100)	5/6 (83.3)	1.000
Myositis	0	1/6 (16.7)	1.000
Lymphadenopathy	15/44 (34.1)	27/43 (62.8)	**0.007**
Hepatomegaly	3/44 (6.8)	4/43 (9.3)	0.713
Splenomegaly	6/44 (13.6)	/	**0.026**
Treatment			
IVIG	44 (100)	43 (100)	.
Glucocorticoids	41 (93.2)	8 (18.6)	<0.001
Methylprednisolone	35 (79.5)	5 (11.6)	0.127
Dexamethasone	5 (11.4)	0 (0)	0.297
Prednisone	1 (2.3)	3 (7.0)	0.188
Anakinra	24 (54.5)	7 (16.3)	<0.001
ASA	10 (22.7)	39 (90.7)	<0.001
Heparin	15 (34.1)	0 (0)	<0.001
PICU Admission	21/44 (47.4)	2/43 (4.7)	**<0.001**
Amine support	16/21 (76.2)	/	**0.048**
Ventilatory support	8/21 (38.1)	/	0.505

Extremity abnormalities: erythema of the palms and soles and firm and sometimes painful induration of the hands or feet in the acute KD phase.
Irritability: extreme irritability exceeding that observed in other febrile illnesses.
Myocarditis: biventricular cardiac dysfunction.
Coronary artery abnormalities according with the Z-score system: Dilation: 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥1, Aneurysm: ≥2.5 Z scores (14).
CNS: central nervous system; GI: gastrointestinal; LVSD: left ventricle systolic disfunction; MSK: musculoskeletal; PICU: paediatric intensive care unit; IVIG: intravenous immunoglobulins; ASA: acetylsalicylic acid.

Table II. Comparison between biochemical data of KD and MIS-C patients at disease onset.

	MIS-C	no. of pts	KD	no. of pts	*p*-value
WBC (cells/mcL)	11,085 (3,350-37,070)	44	15,973 (4,750-30,600)	42	0.701
N (cells/mcL)	9,218 (2,077-34,475)	42	10,361 (1756-21880)	42	0.716
L (cells/mcL)	1,202 (247-5,407)	43	3,926 (570-15,630)	38	**<0.001**
Hb (g/dL)	11.2 (8.5-14.2)	44	10.9 (8.7-19.0)	41	0.999
PLT (cells/mcL)	207,180 (17,600-518,000)	42	427,317 (184,000-892,000)	41	0.122
ESR (mm/h)	63 (9-120)	25	75 (20-120)	29	0.096
CRP (mg/dL)	18 (1-51)	43	10 (1-27)	39	**0.001**
AST (IU/L)	46 (13-319)	38	83 (14-1,483)	34	0.188
ALT (IU/L)	38 (10-190)	38	84 (7-737)	36	**<0.001**
Ferritin (ng/mL)	1,316 (179-10,058)	27	268 (18-494)	16	**0.019**
pro-BNP (pg/mL)	10,794 (36-103,476)	31	821 (53-2,567)	5	0.114
IFN Score	13.58 (0.29-87.57)	26	5.27 (0.21-34,01)	14	0.114
CXCL9 (pg/mL)	7,828 (417-29,162)	23	3,976 (741-12,571)	9	0.143
CXCL10 (pg/mL)	9,697 (39-82,724)	23	537 (22-2,075)	9	**0.010**
IL-18 (pg/mL)	634 (215-1512)	23	1,158 (239-6,250)	9	**0.008**
IFN-γ (pg/mL)	6.47 (0.15-70.44)	23	4.07 (1.27-8.51)	9	0.322
IL-1β (pg/mL)	4.98 (0.57-14.41)	23	5.40 (1.60-12.37)	9	0.388
1L-6 (pg/mL)	161.18 (0.17-3230.45)	23	84.18 (1.92-254.65)	9	0.380

WBC: white blood cells; N: neutrophils; L: lymphocytes; Hb: haemoglobin; PLT: platelets; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine transaminase; BNP: brain natriuretic peptide; IFN SCORE: type 1 interferon score; CXCL9: chemokine (C-X-C motif) ligand 9; CXCL10: chemokine (C-X-C motif) ligand 10; 1L-18: interleukin 18: IFN-γ: interferon gamma: IL-1β: interleukin 1 beta; IL-6: interleukin-6.

Table III. Multiple regression analysis between biomarkers values and clinical symptoms in MIS-C patient at onset.

	IFN Score R^2=0.997		CXCL9 R^2=0.791		CXCL10 R^2=0.400		IL-18 R^2=0.918		IFN-γ R^2=0.975		IL-1 ß R^2=0.795		IL-6 R^2=0.999	
	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*
Skin	0.046	0.278	0.025	0.903	-0.304	0.366	-0.038	0.906	0.042	0.704	0.227	0.562	0.007	0.478
Mucosa	/	/	-0.056	0.766	-0.128	0.686	-0.754	**0.04**	-0.043	0.586	-0.227	0.553	-0.007	0.547
Eye	0.013	0.799	0.084	0.725	0.004	0.991	/	/	0.060	0.460	-0.320	0.506	/	/
CNS	0.033	0.723	-0.041	0.858	-0.448	0.219	0.231	0.159	0.203	**0.010**	0.483	0.077	0.003	0.786
GI	-0.100	0.160	0.084	0.725	0.004	0.991	/	/	0.060	0.460	-0.320	0.506	/	/
Lung	0.013	0.638	-0.251	0.129	-0.262	0.377	0.019	0.895	0.03	0.957	-0.069	0.801	-0.009	0.364
Hearth	0.014	0.799	0.120	0.644	0.167	0.616	-0.095	0.716	-0.012	0.876	0.795	**0.006**	-0.30	**0.13**
LVSD	0.178	**<0.001**	0.903	**<0.001**	0.683	**0.029**	0.197	0.186	0.101	0.229	0.410	0.106	0.006	0.597
CAA	0.015	0.889	0.019	0.920	0.137	0.665	-0.27	0.861	0.022	0.746	0.140	0.717	-0.003	0.799
MSK	-0.071	0.192	-0.971	0.364	-0.172	0.555	0.091	0.708	-0.020	0.766	-0.443	0.155	0.016	0.301
Lymphadenopathy	0.938	**<0.001**	0.100	0.547	0.007	0.981	0.160	0.332	0.883	**<0.001**	0.354	0.128	-0.008	0.554
Splenomegaly	-0.025	0.532	0.081	0.627	0.005	0.985	0.048	0.733	0.019	0.815	0.060	0.828	-0.008	0.554
PICU admission	0.013	0.799	0.084	0.725	0.004	0.991	0.588	**0.030**	0.060	0.460	-0.320	0.506	-0.999	**<0.001**
Amines	-0.016	0.615	-0.251	0.129	-0.262	0.377	0.019	0.895	0.003	0.957	-0.069	0.801	-0.009	0.364
Ventilation	0.084	**0.024**	0.027	0.893	-0.268	0.415	0.941	**0.004**	0.066	0.482	0.047	0.923	0.003	0.742

IFN SCORE: type 1 interferon score; CXCL9: chemokine (C-X-C motif) ligand 9; CXCL10: chemokine (C-X-C motif) ligand 10; 1L-18: interleukin 18; IFN-γ: interferon gamma; IL-1β: interleukin 1 beta; CNS: central nervous system; GI: gastrointestinal; LVSD: left ventricular systolic disfunction; CAA: coronary arteries abnormalities; MSK: musculoskeletal; PICU: paediatric intensive care unit.

phocyte count was significantly lower in MIS-C group (p<0.001), while the C reactive protein (CRP) and ferritin values were higher compared to those of KD patients (p=0.001 and p=0.018). Higher alanine transaminase (ALT) values were more frequently observed in the KD group.

Considering treatment, steroids and intravenous anakinra were more frequently administered in MIS-C (p<0.001). Aspirin antiplatelet treatment was more often adopted in KD (p<0.001) while anticoagulant prophylaxis with heparin in MIS-C (p<0.001) (Table I).

Focusing on biomarkers, IL18 values at T0 were higher in KD patients (p=0.008), CXCL10 was more elevated in the MIS-C cohort (p=0.010). No other significant differences in the biomarkers' values were detected at the different timepoints (T0-T1 interval median 6 days IQR 8.25) between the two groups. A significant decrease of CXCL9 and CXCL10 values from T0 to T1 in both KD (p=0.02; p=0.015) and MIS-C patients (p=0.004; p<0.001) was reported.

The multiple linear regression analysis revealed that at T0, in MIS-C group, high IFN score values were significantly related to left ventricular systolic disfunction (LVSD) (p<0.001), lymphadenopathy (p=<0.001) and ventilatory support (p=0.024). Both CXCL9 and CXCL10 were related to LVSD (p<0.001 and p=0.029). IL18 higher

values were positively associated to PICU admission (0.030) and mechanical ventilation (p=004) and negatively associated to lymphadenopathy (0.004). Higher IFNγ values were related to neurological involvement and lymphadenopathy (p<0.001), while IL1b to hearth involvement (0.006). A negative correlation was observed between IL6 values, heart involvement and PICU admission (Table III).

Discussion

Our results confirm the previously reported demographic and clinical differences between KD e MIS-C. A higher age at onset, the predominance of gastrointestinal, neurological and respiratory symptoms as well as the higher frequency of cardiac disfunction and PICU admission, the higher CRP and ferritin values, the lower lymphocyte count were widely described in MIS-C group by previous comparative studies (1-8).

Focusing on biomarkers, we observed that, at onset, IL18 values were higher in KD while CXCL10 was more elevated in MIS-C. A study by Rodriguez-Smith *et al*. comparing KD and MIS-C children's biomarkers values, reported that the two groups had similar biochemical profiles with respect to S100A8/A9, S100A12, and IL18. However, MIS-C patients had significantly higher CXCL9 concentrations (12). Since CXCL9 and CXCL10 are closely related as IFNγ-induced protein and their genes are both located on chromosome 4, it is reasonable to consider this result as similar to that observed in our cohorts. Notably, CXCL9 mean value in our MIS-C group was almost double than that assessed in KD, even if a statistically significant difference was not reached.

At this regard, it has been previously reported that MIS-C is characterised by a disproportionate response to IFNγ compared to paediatric COVID-19 patients and MIS-C patients show a higher CXCL9 response to IFNγ compared to COVID-19 patients and healthy controls (9, 10). This inappropriate CXCL9 production induced by IFN-γ stimulation could be explained by the presence of lower levels of Tripartite motif-containing protein 21 (TRIM21), a protein involved in IFNγ signalling repression through degradation of interferon response factors (9).

Furthermore, CXCL9 represent a sensible biomarker of macrophage activation syndrome (MAS) and a subset of MIS-C patients, including 6/44 MIS-C patients from our cohort, fulfilled the 2016 MAS criteria at disease onset, suggesting a connection between IFNγ-high MIS-C and MAS features (9, 12).

Higher CXCL9 levels have been related to an increased risk of mortality in adult patients with severe COVID-19 maybe contributing to cytokine storm in that clinical setting (9). Rodriguez-Smith *et al*. study reported that MIS-C patients with higher CXCL9 values more often reported organ dysfunction including acute kidney injury; shock, LVSD and altered mental status (12). In our MIS-C cohort, the multiple linear regression analysis revealed that higher CXCL9 and CXCL10 values positively correlated with the development of LVSD.

The observation that certain chemokines levels may act as disease severity biomarkers, predicting cardiac involvement and a consequent life-threating disease course, could represent a valuable tool in clinical practice to precociously identify patients at risk to develop organ dysfunction who may require a more aggressive treatment at disease onset. A specific biochemical fingerprint might be able to differentiate KD from MIS-C and timely customize a combined step-down therapy rather than a step-up one for high-risk patients. Further studies are required to better define the correlation between biomarkers and clinical outcome as well as response to treatment in MIS-C.

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