 doi:10.20944/preprints202009.0435.v1

Article

Pediatric Inflammatory Multisystem Syndrome (PIMS) Did Occur in Poland during Months with Low COVID-19 Prevalence. Preliminary Results of a Nationwide Register.

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Abstract: Pediatric inflammatory multisystem syndrome (PIMS) is a new entity in children, likely associated with previous coronavirus disease 19 (COVID-19). Most of reports about PIMS come from countries particularly hit by the COVID-19 pandemic. Our aim was to investigate the nature of inflammatory syndromes in Poland (country with low COVID-19 prevalence) and to perceive the emergence of PIMS in our country. On May 25th 2020 we have launched a nationwide survey of inflammatory syndromes in children for retrospective (since 4th March 2020) and prospective data collection. Up to 28th July 39 reported children met inclusion criteria. We stratified them according to age (<5 and ≥ 5 years old) and COVID-19 status. Majority of children had clinical and laboratory features of Kawasaki disease, probably non-associated with COVID-19. However, children ≥5 years of age had PIMS characteristics, and 9 children had COVID-19 confirmation. This is the first to our knowledge report of PIMS register from the country with low COVID-19 prevalence, and it proves that PIMS may emerge in any area involved in the COVID-19 pandemic. In a context of limited COVID-19 testing availability other risk factors of PIMS, e.g. older age should be considered in differential diagnosis of inflammatory syndromes in children.

Keywords: PIMS; MIS-C; SARS-CoV-2; COVID-19; Kawasaki disease; survey

1. Introduction

Since late April 2020, a growing set of articles has been published describing Pediatric Inflammatory Multisystem Syndrome (PIMS) - a new inflammatory entity in children, temporally and geographically associated with the coronavirus disease 2019 (COVID-19) pandemic [1-9]. The first definition of PIMS had been announced by the Royal College of Paediatrics and Child Health (RCPCH) on 1st May [10]. Multisystem Inflammatory Syndrome in Children (MIS-C) is an alternative name proposed in the United States of America (USA) [11] and adopted by the World Health Organization (WHO) [12]. Unlike PIMS, MIS-C definition requires confirmed SARS-CoV-2 infection or COVID-19 exposure. Approximately 1000 cases of PIMS and MIS-C have been reported as of July 2020, with the vast majority of reports from countries particularly hit by COVID-19 pandemic. Epidemiological studies revealed that an abrupt increase in PIMS incidence occurs about 4-5 weeks after the peak of local COVID-19 cases [5, 7].

If a connection with COVID-19 is real, unusual clusters of severely ill children observed in the United Kingdom (UK), France, or the USA, may not occur in countries where COVID-19 is not as prevalent. Moreover, there are concerns that remarkably severe clinical course of PIMS emerging from reports published so far, with 50-80% of children requiring intensive care unit (ICU) admission, may represent an extreme point of the broader spectrum of the post-infectious inflammatory response to COVID-19 [3, 13]. Thus, in countries with lower COVID-19 prevalence, we may expect PIMS to be more scattered in distribution and more diverse in the clinical picture, which needs to be investigated.

Poland (population over 37.5 M citizens, highly homogeneous society with predominant Caucasian race) had a relatively low COVID-19 prevalence. As of 28th June, nearly 44,000 confirmed COVID-19 cases had been registered [14]. The incidence rate in Poland was approx. 1,000/1 M, almost 3-fold less than in France, over 4-fold less than in the UK or Italy and 12-fold less than in the USA

[15] (**Error! Reference source not found.**) The lower infectious rate might partially result from a lower testing rate (Poland, 52,101 / 1 M citizens). Thus, the discrepancy in testing didn't correspond to the incidence rate (testing rate was similar in France, only 2-fold higher in Italy, 3-fold higher in the USA and 4-fold higher in the UK). In Poland, children accounted for 0.8-2.8% of all laboratory-confirmed cases, similar to other countries [16].

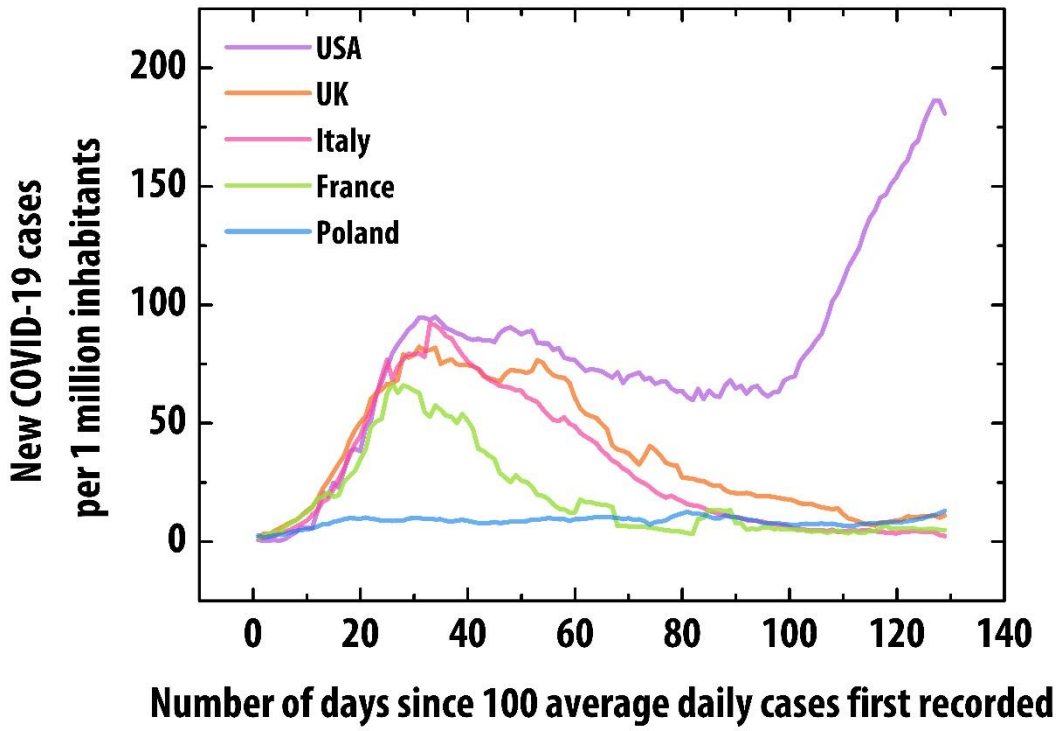

Figure 1. New COVID-19 cases per 1 million inhabitants in Poland compared with France, Italy, the United Kingdom (UK) and the United States of America (USA) – countries with reported cases of Pediatric Inflammatory Multisystem Syndrome (PIMS) [15].

Our aims were: to investigate the nature of inflammatory syndromes in Poland during the COVID-19 epidemic and perceive the emergence of PIMS in our country. On 25 May, we launched nationwide surveillance of pediatric inflammatory syndromes: the MOIS-CoR Study (MultiOrgan Inflammatory Syndromes COVID Related). In this report, we present clinical and laboratory characteristics of the first 39 children with inflammatory conditions, including confirmed PIMS, diagnosed over a period from 4th March (when the first case of COVID-19 in Poland was diagnosed), to 28th July 2020.

2. Experimental Section

The voluntary surveillance for retrospective (since 4th March) and prospective data collection was initiated under the National Consultant of Pediatrics auspices. Anonymized patient data from 34 pediatric hospitals from all over the country (**Error! Reference source not found.**) were extracted from electronic and paper records and collected through online form developed for that purpose. Before the surveillance was launched, reporting clinicians underwent an online training, which included the current state of knowledge about PIMS and unified diagnostic approach to such patients recommended by the study's expert committee. Patient management was at the discretion of the relevant treating clinicians.

 doi:10.20944/preprints202009.0435.v1

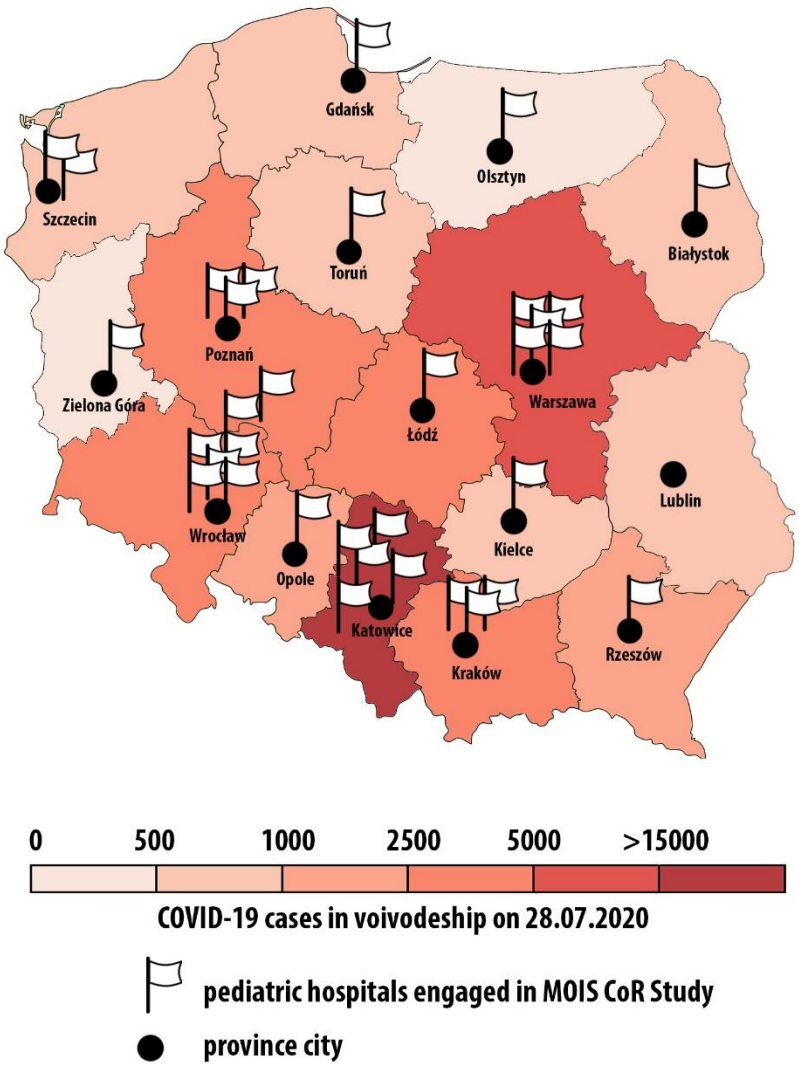

Figure 2. Pediatric hospitals engaged in MOIS CoR Study - Polish register of pediatric inflammatory syndromes during COVID-19 pandemic.

Ethical approval was obtained from the Bioethics Committee at Wroclaw Medical University (CWN UMW BW: 39/2020).

Inclusion criteria were:

1. patients who required hospitalization since 4th March;
2. 0-18 years old;
3. diagnosed Kawasaki disease (KD) or incomplete (atypical) Kawasaki disease (aKD) or toxic shock syndrome (TSS) or macrophage activation syndrome (MAS) or unspecified inflammatory syndrome;
4. exclusion of other infectious and non-infectious causes that could be responsible for the disease;
5. SARS-CoV-2 polymerase chain reaction (PCR) or serology result could have been positive or negative. Due to limited availability and reliability of serologic testing, proven or likely COVID-19 criterion was not a condition determining inclusion to the registry.

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KD and aKD were defined following the American Heart Association (AHA) guidelines [17]. TSS was established based on modified criteria by the Centers for Disease Control and Prevention (CDC) [18,19]. MAS was diagnosed based on the Paediatric Rheumatology International Trials Organization (PRINTO) criteria for MAS classification in systemic juvenile idiopathic arthritis [20]. The definition of the inflammatory syndrome was based on the WHO MIS-C definition with the exclusion of SARS-CoV-2 confirmation [12]. Detailed inclusion criteria and case definitions are presented in Table 1.

Table 1. Polish register of pediatric inflammatory syndromes (MOIS CoR Study): Inclusion criteria.

Study inclusion criteria: age, disease severity, timing, diagnosis criterion and exclusion of other causes must be fulfilled.
Age: 0-18 years
Disease severity: requiring hospitalization
Time frame: since March 4th 2020 (ongoing)
Diagnosis: Kawasaki disease (KD) OR incomplete (atypical) Kawasaki disease (aKD) OR toxic shock syndrome (TSS) OR macrophage activation syndrome (MAS) OR unspecified inflammatory syndrome
Kawasaki disease (KD) case definition Fever for at least 5 days and 4 from the following symptoms: a) Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa b) Bilateral bulbar conjunctival injection without exudate c) Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like d) Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase e) Cervical lymphadenopathy (≥1.5 cm diameter) **Incomplete (atypical) Kawasaki disease (aKD) case definition:** Fever for at least 5 days and 2 or 3 from the above symptoms OR infant with unexplained fever for at least 7 days AND CRP ≥ 3 mg/dl and/or ESR ≥ 40 mm/hr AND 1) at least 3 of the following: a) Anemia for age b) PLT ≥ 450 000 ×10^9/L after the 7th day of fever c) Albumin ≤ 3 g/dL d) Elevated ALT e) WBC count of ≥15 000×10^9/L f) Urine ≥ 10 WBC/hpf OR 2) Changes in echocardiogram suggesting KD **Toxic shock syndrome (TSS) case definition:** 1) Fever AND 2) hypotension AND 3) at least two of the following organ systems involvement: a) Gastrointestinal (vomiting, diarrhea, abdominal pain); b) Muscular (severe myalgia, elevated creatine phosphokinase level); c) Renal (sterile pyuria, elevated creatinine or urea); d) Hepatic (elevated liver enzymes and/or bilirubin level); e) Hematologic (decrease in PLT < 100×10^9/L); f) Disseminated intravascular coagulation; g) Acute onset of diffuse pulmonary infiltrates and hypoxemia;

 doi:10.20944/preprints202009.0435.v1

h) Acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia;
i) Central nervous system (alterations in consciousness in absence of fever and hypotension)

Macrophage activation syndrome (MAS) case definition:

Febrile patient with:
1) Ferritin > 684 ng/mL AND
2) Any two of the following:
a) PLT ≤ 181 000×10^9/L
b) AST > 48 U/L
c) Triglycerides >156 mg/dL
d) Fibrinogen ≤360 mg/dL

Inflammatory syndrome case definition:

1) Fever for at least 3 days AND
2) high inflammatory markers (neutrophil count, CRP, ESR, procalcitonin) AND
3) features of at least one organ dysfunction AND
4) at least two of the following symptoms:
a) Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet).
b) Hypotension or shock.
c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated Troponin/NT-proBNP),
d) Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
e) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain);

Exclusion of other infectious and non-infectious causes that could be responsible for the disease

SARS-CoV-2 testing may be positive or negative.

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLT: platelets; ALT: alanine transaminase; WBC: white blood cells; hpf: high power field; AST: aspartate transaminase; NT-proBNP: N-terminal pro B natriuretic peptide; PT: prothrombin time; PTT: partial thromboplastin time; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

For patients who met the inclusion criteria, we collected demographic data, past medical history, data on COVID-19 exposure, clinical symptoms, physical examination findings, laboratory, imaging, and cardiologic tests results, treatment, and outcome. Three independent, experienced researchers verified the fulfilment of inclusion criteria and the diagnoses.

Most of the findings were interpreted as descriptive and exploratory. Results are presented as counts and percentages for categorical data and medians and interquartile ranges (IQRs) for continuous data, according to COVID-19 evidence and age groups (below or at least five years of age). Groups were compared with Mann-Whitney, and ANOVA Kruskal-Wallis tests were appropriate. Data statistical analyses were done with the use of Excel 2016 and Statistica 12 (Stat Soft). Results with p-value <0.05 were considered statistically significant.

3. Results

39 from 41 reported patients fulfilled the study inclusion criteria (Table 1). Among them: 29 (74%) were male; all 39 were Caucasian. The median age was 3.1 years (IQR 1.4-6.6), median body mass index (BMI) was 15.7 kg/m2 (IQR 14.6-17.4). Six patients (15%) had coexisting chronic diseases – two patients had chronic heart disease, one of them also had asplenia, two others had acquired immunodeficiencies, and two were obese (Table 2). Overall, nine patients (23%) had evidence of SARS-CoV-2 infection or exposure in a household setting. In 18 (46%) cases, SARS-CoV-2 status was unknown, and in the remaining 12 (31%) cases, exposure history and SARS-CoV-2 tests (PCR and serology) were all negative. Overall 34 patients (87%) had KD diagnosed: 20 (51%) classic KD, 14 (36%) aKD. 10 (26%) patients developed MAS. Median 8 days (IQR 6-10.5) of fever of 39.0°C (IQR

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39.0-40.0) were reported, and children were admitted to the hospital after median four days (IQR 2.0-7.5) from the onset of symptoms (Table 3). Reported symptoms and signs included: dermatological in 37 (95%), mucocutaneous in 30 (77%), neurological in 30 (77%), gastrointestinal in 24 (62%), respiratory in 16 (41%) and musculoskeletal in 15 (39%) patients. Clinical presentation differed depending on age group (<5 years of age vs. ≥five years of age) and SARS-CoV-2 status (Table 2). The majority of patients (27; 69%) underwent chest imaging – chest X-ray (CXR) or computed tomography (CT). Of this group, 10 (26%) had no abnormalities. Lung infiltrates were found in 12 (44%), interstitial changes in 4 (15%), and pleural effusion in 4 (15%) cases. 37 (95%) children had an echocardiogram performed. 6 (16%) patients had coronary arteries dilations or aneurysms, including one with giant aneurysms. Coronary artery abnormalities persisted until discharge from the hospital in 4 of them. Four (10%) patients had pericardial effusion, and two (5%) had decreased contractility of the left ventricle with values of shortening fraction (SF) of 27% and 30% and ejection fraction (EF) 52% and 59%, respectively. Laboratory findings according to age group and SARS-CoV-2 status are presented in Table 4. Only one child required treatment in ICU and mechanical ventilation, 4 (10%) other children needed oxygen supply. 35 (90%) children were treated with intravenous immunoglobulin (IVIG), 15 (39%) with steroids, 4 (10%) with cyclosporine A and 1 (3%) with etoposide. 33 (85%) children received acetylsalicylic acid (ASA), 2 (5%) – heparin and 1 (3%) – warfarin. 30 (77%) children were discharged home without any complications thus far. No deaths were reported.

Table 2. Demographic and Clinical Characteristics of the Patients, According to Age Group and SARS-CoV-2 Status.

Characteristics	Overall (N=39)		<5 years (N=25)		≥5 years (N=14)		SARS-CoV-2 history positive (N=9)		SARS-CoV-2 history unknown (N=18)		SARS-CoV-2 history and results negative (N=12)	
	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR
Age [years]	3.1	1.4-6.6	1.8	0.85-2.8	9.15	6.4-12.15	10.5	7-13.4	3.3	1.9-5.4	1.2	0.5-1.6
Male sex	29	74	21	84	8	57	4	44	13	72	12	100
Caucasian race	39	100	25	100	14	100	9	100	1	100	12	100
BMI [kg/m^2]	15.7	14.6-17.4	15.8	14.5-17.3	15.4	14.6-19.1	15.8	15.3-19.1	15.6	14.4-16.5	15.6	14.5-18.1
Comorbidities												
Any	6/39	15	3/25	12	3/14	21	2/9	22	3/18	17	1/12	8
Acquired immunodeficiency	4/39	10	3/25	12	1/14	7	1/9	11	2/18	11	1/12	8
Chronic heart disease	2/39	5	2/25	8	0/14	0	0/9	0	1/18	6	1/12	8
Obesity	2/36	6	0/23	0	2/13	15	1/9	11	1/16	6	0/11	0
Clinical features												
Temperature [°C]	39.0	39.0-40.0	39.0	39.0-40.0	39.0	39.0-40.0	40.0	39.0-40.0	39.5	39.0-40.0	39.0	39.0-40.0

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Length of fever [days]	8	6.0-10.5	8	6.0-10.0	6.5	6.0-12.5	6	6.0-11.0	8	6.0-12.25	8	6.75-9.0
Any dermatologic	**37**	**94**	**20**	**80**	**13**	**93**	**7**	**78**	**17**	**94**	**11**	**97**
Rash	34	87	22	88	12	86	6	67	17	94	11	97
Hands and feet erythema or swelling	23	59	13	52	10	71	7	78	11	61	5	42
Peeling	17	46	10	40	6	44	3	33	10	56	4	33
BCG injection site erythema	1	3	1	4	0	0	0	0	1	6	0	0
Any mucocutaneous	**30**	**77**	**23**	**92**	**10**	**71**	**5**	**56**	**15**	**83**	**10**	**83**
Conjunctivitis	26	67	17	68	9	64	4	44	13	72	9	75
Mucosal changes	27	69	18	72	9	64	4	44	15	83	8	67
Lymphadenopathy	20	51	15	60	5	36	3	33	9	50	8	67
Any musculoskeletal	**15**	**39**	**6**	**24**	**9**	**64**	**5**	**56**	**6**	**33**	**4**	**33**
Arthritis (swollen joints)	8	21	2	8	6	43	4	44	3	17	1	8
Arthralgia (without swelling)	9	23	2	8	7	50	3	33	5	28	1	8
Myalgia	7	18	3	12	4	29	3	33	1	6	3	25
Any gastrointestinal	**24**	**62**	**13**	**52**	**11**	**79**	**7**	**78**	**10**	**56**	**7**	**58**
Nausea or vomiting	15	40	6	24	9	64	5	56	6	33	4	33
Abdominal pain	16	42	6	24	10	71	5	56	7	39	4	33
Diarrhea	13	33	8	32	5	36	5	56	4	22	4	33
Any neurologic	**30**	**77**	**21**	**84**	**10**	**71**	**5**	**56**	**13**	**72**	**11**	**92**
Neck stiffness	3	8	2	8	1	7	1	11	0	0	2	17
Somnolence	17	44	12	48	5	36	4	44	6	33	7	58
Headache	6	15	0	0	6	43	5	56	1	6	0	0
Seizures	1	3	0	0	1	7	1	11	0	0	0	0
Anosmia or aguesia	1	3	0	0	1	7	1	11	0	0	0	0
Partial paralysis	1	3	0	0	1	7	1	11	0	0	0	0
Cutaneous hyperalgesia	8	21	6	24	2	14	1	11	3	17	4	33
Irritability	20	51	15	60	5	36	3	33	10	56	7	58
Photophobia	1	3	1	4	0	0	0	0	1	6	0	0
Any respiratory	**16**	**41**	**14**	**56**	**4**	**29**	**4**	**44**	**5**	**28**	**7**	**58**
Cough	6	15	4	16	2	14	2	22	2	11	2	17
Chest pain	1	3	0	0	1	7	1	11	0	0	0	0
Dyspnea	4	10	2	8	2	14	2	22	0	0	2	17
Coriz	6	15	6	24	0	0	0	0	1	6	5	42
Sore throat	8	21	7	28	1	7	1	11	3	17	4	33

BCG: Bacillus Calmette–Guérin vaccine; BMI: body mass index; IQR: interquartile range, med: median.

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Table 3. Clinical Course and Outcomes, According to Age Group and SARS-CoV-2 Status.

Characteristics	Overall (N=39)		<5 years (N=25)		≥5 years (N=14)		SARS-CoV-2 history positive (N=9)		SARS-CoV-2 history unknown (N=18)		SARS-CoV-2 history and results negative (N=12)	
	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR	n, n/N or med	% or IQR
Time from symptom onset to hospital admission [days]	4.0	2.0-7.5	5.0	2.0-9.0	4.0	2.5-6.0	4.0	2.0-6.0	5.0	2.25-9.0	4.5	2.75-5.25
SARS-CoV-2 epidemiological data												
Confirmed contact with COVID-19	6/29	21	0/17	0	6/12	50	7/8	88	0/12	0	0/9	0
SARS CoV2 RT-PCR test positive	1/34	3	0/21	0	1/13	8	1/9	11	0/13	0	0/12	0
SARS CoV-2 serology test positive[a]	6/21	29	1/13	8	5/8	63	6/9	67	0/0	0	0/12	0
Previous symptoms of respiratory tract infection among household members	9/36	25	4/22	18	5/14	36	6/9	67	0/15	0	3/12	25
Previous symptoms of respiratory tract infection	14/38	37	9/24	38	3	21	4/9	44	8/16	50	2/12	17
Diagnosis												
Classic KD	20	51	13	33	7	50	4	44	10	56	6	50
Incomplete (atypical) KD	14	36	10	26	4	29	3	33	6	33	5	42
MAS	10	26	3	8	7	50	5	56	4	22	1	8
Shock	1	3	0	0	1	7	1	11	0	0	0	0
Coronary arteries dilations or aneurysms[b]	6	15	3	12	3	21	3	33	2	11	1	8
Therapy												
Intensive care treatment	1	3	0	0	1	7	1	11	0	0	0	0
High-flow nasal cannula	5	13	3	12	2	14	3	33	0	0	2	17
IVIG	35	90	24	96	11	79	7	78	16	89	12	100
GCS	15	39	5	20	10	71	7	78	6	33	2	17
GCS and IVIG	14	36	5	20	9	64	6	67	6	33	2	17
Cyclosporine A	4	10	1	4	3	21	2	22	2	11	0	0
Etoposide	1	3	0	0	1	7	0	0	1	6	0	0
ASA	33	85	24	96	9	64	6	67	15	83	12	100
Heparin	2	5	1	4	1	7	1	11	1	6	0	0
Warfarin	1	3	1	4	0	0	1	11	0	0	0	0
Outcome												
Discharged without complications[c]	30	77	19	76	11	79	4	44	15	78	11	92

ASA: acetylsalicylic acid; GCS: systemic glucocorticoids; IQR: interquartile range; IVIG: intravenous immunoglobulins; KD: Kawasaki disease; MAS: macrophage activation syndrome, med: median.

[a] Serology test was considered positive if any result of IgG or IgM was positive; there were 5 IgG positive results (one of them had also IgA antibodies against SARS-CoV-2) and one IgM and IgA positive results

[b] Coronary arteries dilations or aneurysms were defined on the basis of the American Heart Association recommendations for KD [17]

[c] No deaths were reported; 4 children remain under cardiologic care due to persistent dilations or aneurysms of coronary arteries; one patient was unable to walk for 4 weeks due to lower extremities pain, but returned to normal functioning; 1 patient with neurological complications had right side paresis, 1 remains under control due to cholestatic hepatitis and 2 are still treated for MAS.

Table 4. Laboratory Results, According to Age Group and SARS-CoV-2 Status.

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Characteristics[a]		Overall (N=39)		<5 years (N=25)		≥5 years (N=14)		p-value	SARS-CoV-2 history positive (N=9)		SARS-CoV-2 history unknown (N=18)		SARS-CoV-2 history and results negative (N=12)		p-value
		med	IQR	med	IQR	med	IQR		med	IQR	med	IQR	med	IQR	
White-cell count [×10⁹/L]	Min	8.0	5.4-10.6	8.2	6.5-11.0	5.5	4.1-8.6	**<0.01***	6.5	4.0-10.4	7.0	5.6-9.3	9.2	7.0-11.1	0.77
	Max	18.0	4.6-22.6	17.8	15.2-22.6	18.1	10.9-23.2	0.96	18.0	14.8-23.9	17.9	13.0-20.4	18.4	15.3-23.2	0.89
Neutrophil count [×10⁹/L]		10.8	7.5-15.1	10.1	7.5-14.6	11.1	7.1-19.4	0.51	13.5	9.3-20.0	9.8	6.4-12.6	10.8	9.8-14.7	0.49
Lymphocytes count [×10⁹/L]		2.0	1.05-3.5	3.1	2.0-4.94	0.0	0.6-1.1	**<0.01***	0.8	0.6-1.1	2.0	1.1-2.8	4.5	2.8-5.7	**<0.01***
Platelet count [×10⁹/L]	Min	236.0	150.0-465.0	306.0	203.0-530.0	175.5	125.5-298.0	0.07	164.0	124.0-180.0	296.0	195.3-455.8	359.5	225.5-549.0	0.15
	Max	637.0	495.0-830.5	693.0	530.0-862.0	558.0	413.0-727.6	0.16	488.0	328.0-522.0	668.5	541.6-769.5	768.5	616.3-980.6	**0.04***
Hemoglobin [g/dL]		9.7	8.3 10.6	9.4	8.1-10.6	10.0	9.7-10.6	0.19	9.8	7.8-10.6	10.2	9.6-10.9	8.65	7.8-9.6	0.11
CRP [mg/dL]		129.2	76.7-177.9	128.4	100.9-161.5	132.0	74.3-202.0	0.53	190.0	131.0-246.9	107.0	72.5-134.5	128.8	89.9-175.8	**0.03***
Procalcitonin [ng/dL]		1.0	0.3-4.0	1.1	0.3-2.0	1.0	0.4-14.9	0.64	9.3	0.5-18.0	1.0	0.4-1.9	0.8	0.3-12.4	0.37
ESR [mm/hr]		63.0	42.5-93.5	70.0	45.0-92.0	54.0	29.5-89.75	0.37	61.0	43.5-93.5	44.5	23.0-71.0	83.5	58.5-107.5	0.12
Ferritin [ng/mL]		352.6	156.2-1867.8	164.0	90.7-565.0	1335.0	352.6-9230.5	**0.02***	1314.0	330.0-3097.0	1458.0	133.9-27908.0	175.5	119.0-355.8	0.37
BNP [pg/mL]		295.4	89.3-868.8	269.0	68.3-321.0	568.1	102.0-1764.0	0.18	768.6	126.7-2054.3	321.0	269.0-456.0	147.0	60.0-295.7	0.07
Troponin [ng/L]		4.0	2.5-24.6	3.2	2.3-16.5	11.3	2.9-109.2	0.24	16.6	4.7 153.4	2.9	2.5-11.6	3.2	2.2-13.6	0.19
Fibrinogen [mg/dL]	Min	309.5	232.0-391.5	313.0	255.5-353.5	304.0	198.0-471.0	0.81	198.0	53.2-270.0	313.0	273.0-369.0	297.0	230.0-349.0	0.63
	Max	567.0	501.0-650.0	567.0	391.0-693.0	588.0	506.3-648.5	0.91	596.0	567.0-648.0	571.0	368.5-661.5	564.0	530.0-567.0	0.71
D-dimer [mg/L]		3.6	2.3-7.8	3.5	1.6-4.9	2.9	2.3-23.4	0.36	2.9	2.5-48.3	2.3	1.4-5.6	4.2	3.4-5.2	0.38
INR		1.3	1.1-1.4	1.3	1.1-1.3	1.3	1.2-1.5	0.37	1.4	1.2-1.5	1.3	1.1-1.3	1.2	1.1-1.2	0.42
Albumin [g/dL]		3.1	2.6-3.5	3.1	2.8-3.4	3.3	2.5-3.5	0.87	2.9	2.4-3.5	3.3	3.1-3.6	3.0	2.7-3.2	0.09
LDH [U/L]		269.0	232.0-393.0	274.5	244.8-443.8	244.0	212.0-307.0	0.29	232.0	160.0-307.0	278.0	244.5-694.5	263.0	244.0-341.0	0.38
ALT [U/L]		32.0	16.0-96.0	19.0	15.0-55.0	69.5	27.5-214.8	**0.04***	32.0	16.0-178.0	51.5	19.0-100.5	23.0	14.5-57.7	0.27
Sodium [mmol/L]		135.0	132.0-136.0	135.3	132.0-136.0	134.5	129.5-138.3	0.43	131.0	129.0-134.0	136.0	132.3-139.0	135.5	133.0-136.0	**0.01***

ALT: alanine transaminase; BNP: brain natriuretic peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; IQR: interquartile range; LDH: lactate dehydrogenase; med: median.
[a] For neutrophil count, CRP, ESR, procalcytonin, ferritin, troponin, BNP, D-dimer, LDH and ALT levels – highest results were obtained; for lymphocytes count, hemoglobin, albumin and sodium levels – lowest results were obtained
***statistically significant (p<0.05)**

4. Discussion

Our study is the first to our knowledge report of pediatric inflammatory diseases surveillance, from the country of low COVID-19 prevalence. The number of laboratory-confirmed cases of PIMS in our cohort proves that PIMS may emerge in any pandemic area.

The vast majority of children registered in our survey fulfilled KD or aKD diagnostic criteria. Their clinical characteristics and laboratory results were typical for this well-known inflammatory disease of childhood [3, 17]. A substantial proportion of children in our cohort probably had KD non-associated with SARS-CoV-2 infection.

 doi:10.20944/preprints202009.0435.v1

Because of unknown SARS-CoV-2 status in nearly half of the patients, we performed stratification by age (Table 2-4). We found that children over five years of age presented with several distinct features consistent with PIMS from previous reports [3, 5, 6]. Older children had more frequently gastrointestinal symptoms (79% vs. 52%), with a predominance of abdominal pain, nausea, and vomiting. Musculoskeletal symptoms were also more prevalent in the older age group. Lymphadenopathy was observed more commonly in younger children. Children over five years of age had significantly lower lymphocyte count (mean value in the range of lymphopenia) and much higher ferritin values than younger group. We found the distribution of symptoms in separate age groups to be similar to described for PIMS by Dufort et al. and Feldstein et al. [5, 6].

The features characteristic of PIMS were even more definite when comparing COVID-19 positive versus negative patients (Table 4). Clinical presentation of the nine patients who had confirmed SARS-CoV-2 infection or exposure history was consistent with findings described in current reports [3, 5, 6, 21, 22]. These patients were older, with more common gastrointestinal involvement and headaches. Furthermore, compared to SARS-CoV-2 negative patients - they developed lower lymphocyte count, platelet count, and hyponatremia, higher CRP, and ferritin level (all of them statistically significant) tended higher BNP and troponin concentrations (not statistically significant).

The exact incidence and risk of developing PIMS are challenging to assess. The estimated incidence of confirmed PIMS in Poland as of July is approximately 0.1 per 100,000 children and adolescents, which is 20 times lower than that reported in the New York State by Dufort et al. [5]. The small number of COVID-19-related PIMS cases in Poland is another argument supporting that PIMS is a post-infectious complication of COVID-19 in children. Simultaneously, children in our cohort had a milder clinical course than those registered in other countries. One of the possible explanations is specific homogeneous racial and genetic background. However, given the small number of cases, this should be interpreted with caution. On the other hand, the clinical presentation of children with confirmed PIMS in our group supports the broader range of PIMS manifestations. Higher vigilance of PIMS among clinicians involved in our register at the early stage of the pandemic may explain a higher number of benign cases.

Limitations

The lack of historical data about the incidence and clinical characteristics of pediatric inflammatory diseases in Poland makes it impossible to compare our findings to pre-pandemic data. A relatively small group of patients in our register necessitates further surveillance to obtain more data and perform reliable statistical analyses. The number of health centers involved in the study is limited, but new units are still recruiting.

5. Conclusions

PIMS may emerge in any country involved in the COVID-19 pandemic. Distribution of PIMS may be more scattered and clinical presentation milder in a context of low background COVID-19 prevalence. Rising awareness of this new pediatric condition among clinicians is essential for prompt diagnosis and appropriate approach to such patients. In context of limited SARS-CoV-2 testing availability other risk factors of PIMS, e.g. older age, should be considered in differential diagnosis of inflammatory syndromes in children.

Author Contributions: Conceptualization, M.O.-N., K.M.L., L.S. and E.K.; methodology, M.O.-N., K.M.L. and P.B.; validation, M.O.-N., K.M.L., L.S. and E.K.; formal analysis, M.O.-N., K.M.L., N.D., A.M., P.B., M.S., B.W., B.K., L.S.; investigation, N.D., A.M., P.B., K.M.-M., M.S., B.K., L.S., A.C., E.B.-S., P.O., A.M., D.J.-L., C.N., and MOIS CoR Study Group; resources, L.S., E.K., J.K., M.F., B.W., A.G., A.M., D.J.-L., T.J., J.W..; data curation, K.L.; writing—original draft preparation, M.O.-N., K.L., N.D., A.M., K.M.-M., M.F., M.S., B.K., B.W., L.S.; writing—review and editing, M.O.-N., K.L., L.S., A.M., E.K.; visualization, M.O.-N., K.L., N.D..; supervision, M.O.-N., K.L., L.S., E.K..; project administration, M.O.-N and K.L. All authors have read and agreed to the published version of the manuscript

Funding: None.

Acknowledgments: We thank all Polish pediatricians that have contributed to the national surveillance: Jacek Zeckei, Katarzyna Sznurowska, Grzegorz Kmak, Marta Burkietowicz, Karolina Rząsa-Tercjak, Joanna Zadrożna, Malwina Szalkowska, Paweł Dzieński, Małgorzata Kałwak-Baran, Katarzyna Wielgos, Magda Żwirska, Marta Fiedorowicz-Kaźmierczak, Ewelina Gowin, Sara Śliwińska, Krzysztof Orczyk, Anna Obuchowicz, Agnieszka Szlagatys, Ryszard Konior, Hanna Czajka, Mirosława Choińska, Józef Rudnicki, Henryk Szymański, Edyta Machura, Marcin Zaniew, Elżbieta Babicz-Noga, Aneta Górska-Kot, Elżbieta Smolewska

Conflicts of Interest: The authors declare no conflict of interest.

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